California State Board of Pharmacy
1625 N. Market Blvd, N219, Sacramento, CA 95834
Phone: (916) 574-7900
Fax: (916) 574-8618
www.pharmacy.ca.gov

BUSINESS, CONSUMER SERVICES AND HOUSING AGENCY
DEPARTMENT OF CONSUMER AFFAIRS
GOVERNOR EDMUND G. BROWN JR.

ENFORCEMENT COMMITTEE REPORT

Amy Gutierrez, PharmD, Chair, Professional Member
Rosalyn Hackworth, Public Member
Randy Kajioka, PharmD, Professional Member
Victor Law, RPh, Professional Member
Gregg Lippe, Public Member

Report of the Meeting Held June 4, 2013.

a. ENFORCEMENT MATTERS

1. FOR INFORMATION: Future Enforcement and Compounding Committee Meeting Dates

Future Enforcement and Compounding Committee meetings are scheduled for September 10, 2013 and December 3, 2013. These dates are subject to change. The locations have yet to be determined.

2. FOR DISCUSSION: Request from Sharp Hospital and UCSD on a Waiver of 16 California Code of Regulations Section 1713(d) to Permit Expanded Use of Automated Prescription Dispensing Machines

Attachment I & 2

Relevant Regulation:
California Code of Regulations Section 1713 establishes the requirements for use of an automated prescription delivery device and provides the condition under which it can be used. Under the current regulation the device can be used to furnish refill medications in specified circumstances. These circumstances include, that the patient must opt in to use the machine, the medication to be refilled through the machine is appropriate.

California Code of Regulations Section 1706.5 allows the board to waive particular regulation requirements to allow for experimental plans or programs for drug handling, teaching, and research or to develop better moths involving the ethical practice of pharmacy.

Background:

In 2009-10, Pharmacist Consultant Philip Burgess, on behalf of a manufacturer of one of these machines (Asteres), sought an exemption to permit the use of these machines in areas away from adjacent to the licensed pharmacy premises. The board did not

approve the request, and requested more information about how and where the kiosks would be used. One concern was that the board considered that it lacked the ability to provide the exemption sought (which would have required a regulation change). There was no further interest pursued by Asteres after the January 2010 meeting. (Additional information on this prior discussion is included in **Attachment 2**.)

Further, at the Committee's March 14, 2013 meeting, Mr. Carter, representing Walgreens, discussed a request that would allow for Walgreens to place kiosks in workplace clinics. Mr. Carter provided an overview of the types of services that are provided at the clinic and how Walgreens would provide medication. Mr. Carter highlighted that the kiosk would not be stored in the clinic, but would be housed across the street in a separate building. The Board did not approve the request, indicating there was insufficient evidence to act.

Committee Discussion and Action:

During the meeting, the committee heard a presentation from representatives from Asteres and Sharp HealthCare discussing the need to revise CCR section 1713 to expand the use of automated delivery devices. The presentation included a request to allow three separate pilot studies on the campuses of Sharp, UCSD Health System and USC Hospital to review the use of automated delivery devices. The committee was reminded the Board that section 1713(b) already allows the delivery of prescriptions to employees at their worksite.

Specifically the proposal would revise section 1713(d)(6) to allow for the placement of automated devices in a secure building controlled by a Board licensee at an alternate location readily accessible for Board inspection, but not adjacent to a secure pharmacy area.

In response to questions by the committee members about the location of the devices, members were advised that the devices would not have to be on the premises of a licensee but could be at corporate offices, for example, a non-licensed facility.

In addition, the proposal seeks to revise section 1713(d) to also allow the dispensing of new prescriptions delivered from automated devices as the delivery system allows the ability to load filled prescriptions in the device. The committee was advised that this would only occur after a pharmacist provided consultation and proper documentation has been reviewed and saved. The prescriptions would not be released to the patients until the patients had been counseled by a pharmacist via telephone (adjacent to the device).

The committee heard information on the uses of these devices and was provided pictures. It was noted that in one location employee utilization of the device had grown from 13 percent to 44 percent.

The committee was provided information about the security measures of the device including a camera which takes a photo of every patient as well as the requirement to collect signatures. The device also weighs over 1,350 pounds and is bolted to the ground. The committee was advised that more than 700,000 prescriptions have been delivered without incident.

The committee was provided with information about Sharp's current structure including seven hospitals, seven retail pharmacies and 22 clinics in San Diego serving 200,000 patients. Representatives stated that use of the automated devices align with their vision of providing patient/employee-centered care to the 3000 employees who work in their corporate offices and noted that although their pharmacy is only two miles away, getting to the pharmacy can be difficult due to work schedules and heavy traffic. The committee was provided photos of the proposed location of the device and advised that that the building in which the device would be placed has 24-hour security and requires a badge for entry.

The committee discussed the logistics from the patient's perspective including that a patient could drop off a paper prescription through a slot in the device which would subsequently be picked up and delivered to the pharmacy the following day when the device is serviced.

Counsel discussed if the board could act on the request because current law does not allow for the storage of dangerous drugs at a location not licensed by the Board. In response proponents of the proposal argued that current law allows for the delivery of prescription medications to a patient at his or her office and that the Board should focus on delivery of medications as opposed to the storage of medications.

In response to committee questions, the committee was advised that Sharp planned to have only one pharmacy responsible for filling and delivering prescriptions to an automated device.

The committee heard a second proposal in which Sharp would use the same pharmacy to deliver prescriptions an automated device located at Sharp Memorial Hospital Campus to dispense discharge medications. Sharp envisions a patient being counseled by a Pharmacist at the bedside or over the phone, obtaining an access code, then being discharged and obtaining their prescription from the automated device. The device allows for the use of a credit or debit card for payment. The committee was advised that Sharp does provide next-day home delivery via mails, but prefers delivery via an automated device because the device is secure in that it allows for the tracking of who picks up their medications and who does not.

The board was advised that delivery transaction date is kept forever and there is not purge criteria. Further, the committee was advised that the data includes a full audit

trail which includes a photo of the person picking up the prescription and the signature log.

The committee was advised that representatives from UC San Diego and USC couldn't appear at the meeting, but would like to appear at the full Board meeting in July to discuss proposed changes to section 1713.

The presenters were advised to create a formal proposal for the Board to review including specifying some parameters from the school explaining parts such as what measurements they would take and how long the pilot study would last. It was also suggested that two separate proposal may be appropriate based on the proposed locations being licensed.

The committee was reminded that the Board has limited authority to waive a regulation based on an experimental program pursuant to the requirements listed in section CCR 1706.5. The results of the experimental program would have to demonstrate to the Board that the automated device is safe and that a regulation revision would be advantageous.

Committee Recommendation: Recommend to Board that it consider moving forward with an experimental program/research study once UC San Diego and USC can develop and submit a specific proposal.

During this Meeting:

During this meeting the board will hear a formal presentation on the waiver request to allow for new prescriptions to be delivered from an automated kiosk after consultation and proposed documentation have taken place.

Attachment 1 includes copies of the relevant regulations as well as the written proposal and supporting materials submitted by Asteres, Sharp HealthCare and UCSD.

Attachment 2 includes information on prior board discussions on the use of these devices.

3. **FOR DISCUSSION: Request from California Society of Health-System Pharmacists to Discuss Drug Shortages**

Background:

At the March 13, 2013, Committee meeting, Jonathon Nelson, representing the California Society of Health-System Pharmacists (CSHP), addressed the Committee to discuss the drug shortages and requested the topic be discussed at a future meeting.

Committee Discussion:

The committee heard information on the issue of drug shortages and was provided with an article from the Washingtonian Magazine which detailed rationing, hoarding and bartering of medications in Washington area hospitals.

The committee heard a presentation from a pharmacist sharing her experiences with drug shortages and how they are impacting patients' every day. The committee heard the practices currently employed to manage drug shortage issues which include monitoring and anticipating drug shortages, constantly look for alternative drug sources and medications, creating back orders with wholesalers, and when necessary, rationing of drugs. The committee was advised that shortages have created an informal bartering system where healthcare centers share drugs with each other. The committee learned that results are being reviewed of alternative equivalent therapies being used in the treatment of cancer patients revealed that patients have a significant increase in cancer recurrence.

The committee asked about why shortages are occurring and was advised there are multiple reasons including financial decisions which result in a dropped product line; drugs dropped from the market due to regulatory issues; and short supplies of raw product used in drug production.

The committee chair stated that President Obama issued an Executive Order in 2011 to have the FDA begin tackling the issue of drug shortages.

The committee discussed whether a database could be created so healthcare centers would more easily locate other healthcare centers with a surplus of the specific drug and discussed the legal requirements for licensure if an entity is brokering drugs. The committee discussed the current provisions that allow a pharmacy to sell drugs back to the wholesaler in response to drug shortages.

The committee also heard public comment regarding the possibility of relying more on compounding pharmacies to fill the need during times of drug shortages as well as the need for state and federal government to oversee the safety of compounding manufacturing while also allowing flexibility in allowing compounding manufacturers to fill an important need.

The committee did not take action on this item.

4. FOR INFORMATION: Implementation of Penal Code section 11105 – Board Requirement to Provide Criminal Offender Record Information to an Applicant or Licensee When the Information is Used as the Basis for a Licensing Decision

Background:

As part of its licensing process, the Board is required to conduct a criminal background check to determine whether an applicant has committed acts that would constitute grounds for denial of a license. Applicants must submit their fingerprints to the California Department of Justice (DOJ) who then matches the fingerprints against state and federal criminal history databases. The DOJ provides the results of the background check to the Board who uses the information to help determine the suitability of the applicant for licensure. The Board also receives a notice from the DOJ when a licensee is arrested in California subsequent to initial licensure.

Penal Code section 11105 authorizes the DOJ to release criminal offender record information (CORI) to law enforcement and other authorized agencies such as the Board. The Board cannot share criminal offender record information (CORI), including responses that indicates no criminal history exists, with anyone unless expressly authorized. Individuals have the right to request a copy of their own criminal history record from the DOJ to review for accuracy and completeness, but CORI is not subject to disclosure under the Public Records Act. Release of information to unauthorized individuals can result in civil or criminal penalties pursuant to Penal Code sections 11142 and 11143.

Effective January 1, 2013, however, Penal Code section 11105 (Amended by Stats. 2012, c. 256, A.B. 2343) requires authorized agencies to expeditiously furnish a copy of CORI to the person to whom the information relates if the information is the basis for an adverse employment, licensing or certification decision.

The Board implemented procedures on January 1, 2013, to comply with this new requirement and since that time has provided a copy of the CORI to every applicant who has been denied and every licensee who has received a Letter of Admonishment, Citation or has been referred to the Attorney General's office for disciplinary action based, to some degree, on information contained in the CORI.

Committee Discussion and Action:

Chair Gutierrez provided information on the new law and the board's implementation efforts. There were no questions or comments from the committee or public.

5. FOR DISCUSSION: National Association of Boards of Pharmacy Report on Sales of Fake and Substandard Medications

Attachment 3

Background:

The National Association of Boards of Pharmacy (NABP) issued a report on April 26, 2013 which focused on the global distribution of counterfeit and substandard medications. The report found that the proliferation of these medications was primarily due to illegal distribution by internet pharmacies operating out of compliance with US pharmacy laws.

A copy of the report is provided as an attachment, and can also be found on the NAB website at
https://awarerx.s3.amazonaws.com/system/redactor_assets/documents/179/NABP_Internet_Drug_Outlet_Report_Apr2013.pdf

Committee Discussion:

Ms. Herold stated the Board has a very limited role in regulating internet pharmacies short of disciplining people or businesses for unlicensed activity. Ms. Herold described the video on the Board's website that educates and warns the public about the appropriate way to deal with internet pharmacies. She stated the board rarely gets complaints regarding internet pharmacies because the people using them are happy to get their drugs without a prescription or without having to see a prescriber. The board generally receives complaints only when there's a problem regarding continuing shipping or billing and identity fraud. When the Board receives complaints, they are generally referred to the National Association of Boards of Pharmacy and the FDA.

Dr. Gutierrez mentioned consumers can look for ***VIPPS*** (Verified Internet Pharmacy Practice Sites) symbol on the website which indicates that the internet pharmacy is accredited by the NABP and licensed in the state in which they're located.

Public Comment

There were no questions or comments from the public.

6. **FOR DISCUSSION: NABP Announces Development of Standards for the .pharmacy Generic Top Level Domain for Internet Pharmacy Web Sites**

Attachment 4

Background

According to the NABP, 97 percent of the 10,300 Internet drug outlets it has reviewed are out of compliance with pharmacy laws and practice standards established to protect patients. Correspondingly, NABP has labeled 10,082 Web sites as "Not Recommended"; nearly half of these are offering foreign or non-FDA approved drugs, and many include counterfeits.

Generic top level domains are the suffix part of a Web site address (e.g., .com, .org, .edu). Late last year, the NABP sought the formal approval to be able to approve anyone using the general top level domain (gTLD) of .pharmacy. Earlier this year, an international group of experts were convened by the NABP to develop parameters for anyone that would be able to use the .pharmacy gTLD. The board's executive officer was one of the individuals who participated in this process, and the intent is to have the parameters for the .pharmacy gTLD in place by the end of 2013.

Committee Discussion

Ms. Herold stated the Board was one of two state Boards of Pharmacy invited was to participate in the development of the .pharmacy internet domain.

There were no questions or comments from the public.

A copy of the press release is included in **Attachment 4.**

7. FOR INFORMATION: Fourth Quarterly Report on the Committee's Goals for 2012/13

Attachment 5

The fourth quarterly report on the Enforcement Committee's goals is provided in **Attachment 5.** Regrettably, with one exception, the board is not meeting its strategic planning performance measures in enforcement activities. Board staff is working diligently to address backlogs in both investigations and related activities and will continue to advise the board of progress in these areas.

8. FOR INFORMATION: Enforcement Statistics for July 2012 – June 2013 and Three Year Comparison.

Attachment 6

Attachment 6 includes enforcement statistics for Fiscal Year 2012/13 as well as a three year comparison.

Last year the board initiated 2934 investigations about a 17 percent increase from FY 2010/11. In addition, the board closed 3180 investigations, about a 20% increase from FY 2010/11. As of June 30, 2013, the board has 1934 investigations pending.

Of the investigations closed last fiscal year, 633 (or 20%) resulted in referral to the AG's Office. The board currently has 713 cases pending at the AG's Office, a 27 percent increase from June 30, 2011.

b. Compounding Matters

1. **FOR DISCUSSION: Discussion on Pending California Legislation on Sterile Compounding: Senate Bill 294 (Emmerson) and Assembly Bill 1045 (Quirk-Silva)**

Background **Attachment 7**

Following two large-scale public health emergencies last year in which dangerous products compounded by two out-of-state pharmacies were shipped nationwide, staff suggested modifying existing sterile compounding requirements in California. As a result, Senator Emmerson has authored Senate Bill 294 (SB 294) to carry this Board-sponsored legislation.

Senate Bill 294 strengthens the Board's ability to regulate and monitor pharmacies that compound sterile drug products. This legislation will prohibit a pharmacy from compounding or dispensing, and a nonresident pharmacy from compounding for shipment into this state, sterile drug products for injection, administration into the eye, or inhalation, unless the pharmacy has obtained a sterile compounding pharmacy license from the board.

Additionally, on April 22, 2013, Assembly Member Quirk-Silva amended Assembly Bill 1045 to carry provisions that would amend existing law to allow the Board to suspend or revoke a nonresident pharmacy's license if its license is suspended or revoked in the pharmacy's home state. It would also require resident and nonresident pharmacies that issue a recall notice regarding a sterile compounded drug to contact the recipient pharmacy, prescriber or patient of the recalled drug and the Board within 24 hours of the recall notice if use of or exposure to the recalled drug may cause serious adverse health consequences or death and if the recalled drug was dispensed or is intended for use in this state.

Discussion

There were no committee comments.

Public Comment

The committee heard public comment asking about current licensing requirements. With regard to AB 1045, Ms. Herold clarified that the qualifying method for someone to become licensed as a non-resident pharmacy in California is for the pharmacy to be licensed in the home state. If the license in the home state is revoked, suspended or cancelled for any reason, the California license will correspondingly be revoked, suspended or cancelled by operation of law. Ms. Herold also clarified that the California license could still be disciplined whether or not the license is disciplined in the home state.

Copies of SB 294 and AB 1045 are provided in **Attachment 7**.

2. <u>FOR DISCUSSION: Discussion of Recent Federal Reports and Articles Relating to Compounding Pharmacies</u>

<u>Background</u>: **Attachment 8**

Recently several reports and articles relating to compounding pharmacies have been published. The committee was provided with copies of the following:

a. FDA's oversight of NECC and Ameridose: A history of missed opportunities
b. Office of the Inspector General Memorandum Report: High-Risk Sterile Preparations and Outsourcing by Hospitals That Use Them, OEI-01-013-00150
c. ASHP Guidelines on Outsourcing Sterile Compounding Services, January 14, 2010, *available at:*
http://www.ashp.org/DocLibrary/Bestpractices/MgmtGdlOutsourcingSterileComp.aspx
American Society of Health-System Pharmacists. ASHP guidelines on outsourcing sterile compounding services. *Am J Health-Syst Pharm.* 2010; 67:757-65. Copyright © 2010, American Society of Health-System Pharmacists, Inc. All rights reserved.
d. FDA's Guidance for FDA Staff and Industry – Marketed Unapproved Drugs , Compliance Policy Guide
e. U.S. Senate Health, Education and Pensions Committee Report: The Case for Clarifying FDA Authority: Large-Scale Drug Compounding and the Ongoing Risk to Public Health
f. Miscellaneous Articles

<u>Committee Discussion:</u>

Dr. Gutierrez provided some background and a brief overview of each report and article. There were no questions or comments from the committee or public.

Copies of the articles are included in **Attachment 8**.

3. FOR INFORMATION: <u>Proposed Federal Legislation on Compounding Introduced by the U.S. Senate (S. 959)</u>

Attachment 9

<u>Background:</u>

On May 22, 2013, the United States Senate Committee on Health Education Labor & Pensions passed S. 959, the *Pharmaceutical Compounding Quality and Accountability Act*. A copy of a statement from Senator Harkin made Wednesday, May 22, 2013, and is provided in **Attachment 9.**

Committee Discussion:

Ms. Herold stated the pending Senate legislation is currently linked with the supply chain security provisions which would preempt California's e-pedigree law if enacted. There is competing legislation for the e-pedigree law which just passed the House.

Regarding compounding, the proposal would require non-patient specific drugs moving across state lines to be regulated by the FDA and drugs within a state would be regulated by the respective state board.

Public Comment:

In response to a question about whether out-of-state pharmacies are able to ship high-risk sterile injectable compounded drugs, all in attendance were advised that an out-of-state pharmacy would have to hold a California specialty license or be accredited by one of the accrediting agencies.

4. **FOR DISCUSSION: Discussion Regarding USP's 797 Standards and Regulation Requirements of the Board of Pharmacy**

Attachment 10

Background

For a number of years, California has had its own statutory and regulation requirements for those pharmacies that compound medication or perform parenteral compounding. Since 2001, again through legislation as well as through regulations, the board has several times developed additional requirements to respond to emergent public health or regulatory concerns.

Many states rely upon USP 797 components to regulate compounding activities. California, instead, relies on its own standards for compounders and sterile compounding.

Discussion and Comment:

Dr. Ratcliff and Dr. Smith presented a crosswalk document that compared CA law to USP 797. The Committee reviewed and compared the two sets of requirements. Ms. Herold advised that the Committee make sure all the requirements in USP 797 eventually be included in the Board's regulation and that the regulations be written as clearly and concisely as possible for the benefit of everyone.

The committee and public made several comments regarding the best process for making sure the Board's regulations are inclusive of the requirements in USP 797.

The committee heard several comments from the public on the best path to move for with its analysis of the two requirements and recommended changes that may result from this analysis including creation of a list of suggested regulations then invite comments as opposed to having other associations submit suggestions.

Committee Recommendation: Form subcommittee to work with staff to create a third column on the crosswalk document with proposed regulation changes for public comment.

Attachment 10 includes a copy of the crosswalk document.

5. **FOR DISCUSSION: <u>Discussion Regarding "Batches"</u>**

<u>Background:</u>

Board regulations related to compounding are found in Title 16 of the California Code of Regulations, Article 4.5 (all compounding) and Article 7 (related to sterile injectable compounding). On April 1, 2013, regulation changes went into effect that apply to compounding definitions, expiration dating, recordkeeping requirements, and labeling of cytotoxic agents. During this rulemaking, the board was asked what the board's definition of "batch" is, and what requirements apply to batching – but these topics were not within the scope of the regulation change.

The committee considered the following references as part of its discussion.

Existing Board Regulation
§ 1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.

(c) Batch-produced sterile injectable drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing for sterility and pyrogens and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens.

(d) Batch-produced sterile to sterile transfers shall be subject to periodic testing through process validation for sterility as determined by the pharmacist-in-charge and described in the written policies and procedures.

United States Pharmacopeial Convention (USP)

"Batch" – More than 25 units

[1]**American Society of Health System Pharmacists** (ASHP)

Excerpt:

Risk Level 2.

Risk level 2 sterile products exhibit characteristic 1, 2, *or* 3, stated below. All risk level 2 products should be prepared with sterile equipment, sterile ingredients and solutions, and sterile contact surfaces for the final product and with closed-system transfer methods.
[1] American Society of Health-System Pharmacists. ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products. *Am J Health-Syst Pharm.* 2000; 57:1150-69. Available at http://www.ashp.org

Risk level 2 includes the following:

1. Products stored beyond 7 days under refrigeration, stored beyond 30 days frozen, or administered beyond 28 hours after preparation and storage at room temperature.
2. Batch-prepared products *without preservatives* (e.g., epidural products) that are intended for use by more than one patient. (Note: Batch-prepared products without preservatives that will be administered to multiple patients carry a greater risk to the patients than products prepared for a single patient because of the potential effect of inaccurate ingredients or product contamination on the health and well-being of a larger patient group.)
3. Products compounded by complex or numerous manipulations of sterile ingredients obtained from licensed manufacturers in a sterile container or reservoir obtained from a licensed manufacturer by using closed-system aseptic transfer; for example, TPN solutions prepared with an automated compounder. (Note: So many risks have been associated with automated compounding of TPN solutions that its complexity requires risk level 2 procedures.)

Committee Discussion:

Dr. Ratcliff stated that the term "batch" is defined as 25 more or by USP 797 and as 10 or more by ASHP. Dr. Ratcliff stated he believed the two numbers were arbitrary and there was no scientific evidence to support either. He has advised that, in the interest of public safety, the batch should be defined as affecting more than one patient.

Dr. Gutierrez stated the Board should adopt the definition of a batch from the CGMP (Current Good Manufacturing Practices from the federal register) which doesn't have a number associated with it. She also said she believed the reason USP came up with 25 was because that's the smallest amount you can sample and actually have any useful data.

Public Comment:

The committee heard questions relating to non-patient specific batches vs. something made in multiple units for a single patient as well as encouraging the committee to

consider sampling, processes and process validation as part of its continued discussion on the definition.

6. **FOR DISCUSSION: <u>Discussion on the Board of Pharmacy's Questions and Answers Document on Compounding</u>**

<u>Background:</u>

To provide guidance to pharmacies and others, the board has various "Questions and Answers" on its website in response to questions from practitioners. To reflect recent changes in the board's compounding regulations which took effect April 1, 2013, the Board is in the process of amending some of its "Questions and Answers."

<u>Discussion:</u>

There were no questions or comments from the committee.

7. **FOR INFORMATION: <u>Outcomes of Recent Sterile Compounding Inspections</u>**

Attachment 11

<u>Presentation and Discussion</u>

Dr. Ratcliff provided the committee with a summary of outcomes from recent board inspections of sterile compounding pharmacies. Between January 1, 2013 and mid-May 2013, staff completed 87 inspections. **Attachment 11** includes more specific information.

The committee did not take action on this item.

8. **FOR INFORMATION: <u>Recalls of Compounded Drugs Throughout the United States</u>**

<u>Background</u>

Between April 11, 2013 and May 20, 2013, the Board posted seven subscriber alerts related to compounding drug recalls and two subscriber alerts related to cease and desist orders issued. A summary of the alerts are listed below.

- Green Valley Drugs in Henderson, Nevada, voluntarily recalled all lots of sterile products compounded, repackaged, and distributed by the pharmacy due to lack of sterility assurance and concerns associated with the quality control processes.
- ApotheCure, Inc. recalled all lots of sterile products compounded by the pharmacy that are not expired to the user. The recall was initiated due to lack of sterility assurance and concerns associated with the quality control processes.

- NuVision Pharmacy recalled all unexpired lots of lyophilized compounds of HcG 5000IU-5ml and Sermorelin/GHRH6-5ml to the user. The recall was initiated due to the lack of sterility assurance and concerns associated with the quality control processes identified during a FDA inspection.
- Balances Solutions Compounding Pharmacy, LLC recalled all lots of sterile products compounded by the pharmacy that were not expired. The recall was initiated due to concerns associated with quality control processes, which present a lack of sterility assurance.
- Nora Apothecary & alternative Therapies recalled a multi-state recall of all sterile drug products compounded by the pharmacy that have not reached the expiration date listed on the product. The compounded products that are subject to the recall were products within their expiration date that were compounded and dispensed by the pharmacy on or before Friday, April 19, 2013. The recall was initiated due to concerns associated with quality control processes that present a lack of sterility assurance and were observed during a recent FDA inspection.
- The U.S. Food and Drug Administration alerted health care providers, hospital supply managers, and pharmacists that the FDA's preliminary findings of practices at The Compounding Shop of St. Petersburg, Florida, raised concerns about a lack of sterility assurance for sterile drugs produced at and distributed from this site.
- Pentec Health, Inc. initiated a limited recall of in-date nutritional prescriptions for renal patients due to lack of sterility assurance associated with one of its laminar flow hoods used in compounding.
- Southern California Compounding Pharmacy, LLC was issued a cease and desist order on April 19, 2013, for any and all non-sterile compounding.
- Advance Outcome Management Pharmacy Services was issued a cease and desist order on April 29, 2013, from furnishing sterile injectable compounded products.

Discussion and Comment

Chair Gutierrez presented information on the recalls and Board actions. There were no questions or comments from the committee or public.

FOR INFORMATION: Meeting Summary

Attachment 12

A copy of the June 2013 Enforcement Committee meeting summary is provided in **Attachment 12**.

ATTACHMENT 1

PROPOSAL

Delivery of new and refill prescriptions to Sharp HealthCare employees through an automated delivery device.

Automated delivery device will be used to deliver finished prescriptions to employees. Employees working at the Sharp HealthCare corporate offices do not currently have access to secure and convenient prescription pick up. By providing secure and convenient prescription pick up for employees, they will have better access to their prescriptions without having to leave work.

This proposal outlines the request for one pilot system at Sharp HealthCare. The automated delivery device will be in a secured area and serviced by a California licensed pharmacy. In accordance with regulation 1706.5, the experimental program will be monitored and reported on by an accredited school of pharmacy, UCSD Skaggs School of Pharmacy and Pharmaceutical Sciences. The automated delivery device will be accessible anytime by the board for unannounced board inspection and evaluation.

REGULATION SECTION 1713

Current regulations allow the delivery of prescriptions to employees at their work site.

(b) A licensee may pick up prescriptions at the office or home of the prescriber or pick up or deliver prescriptions or prescription medications at the office of or a residence designated by the patient or at the hospital, institution, medical office or clinic at which the patient receives health care services. In addition, the Board may, in its sole discretion, waive application of subdivision (a) for good cause shown.

The two areas of the regulation that we are requesting to amend.

Current:
(d)(6) The device is located adjacent to the secure pharmacy area.

Proposed Change:
Allow for placement of the device in a secured area located inside a building serviced by a current pharmacy licensee in an alternate location with access readily available for Board of Pharmacy inspection.

Current:
(d) A pharmacy may use an automated delivery device to deliver previously dispensed prescription medications.

Proposed Change:
Allow for new prescriptions to be delivered from the automated kiosk after consultation and proper documentation have taken place.

Sharp HealthCare

Introduction

Sharp HealthCare employs over 14,000 people. More than 3,000 are in the Spectrum Center campus. Today, employees are required to travel 2 miles to pick up prescriptions from our Sharp pharmacy. We hear feedback from our employees that it is difficult for them to use our pharmacy due to heavy traffic, parking difficulties, and our limited hours (the pharmacy is currently open from 8:30a – 5:30p).

Summary of Sharp Rees-Stealy Pharmacy Survey Findings

Sharp Rees-Stealy (SRS) surveyed 500 patients to assess what they value in a pharmacy. The survey was fielded January 30 through February 19, 2009 at 10 locations.

Reasons for Pharmacy Use

By far, the top reason patients choose a pharmacy is because of location convenience (26%). This is followed by convenient hours at 11% and speed of filling prescriptions at 10%.

Reasons for Switching from an SRS Pharmacy

Almost a quarter of patients (22%) who switched from using an SRS pharmacy did so because of location convenience. The next most popular reason for a switch was hours of operation at 18%. These findings correspond with reasons why people choose a pharmacy.

Kiosk location

Spectrum Center corporate office- 8965 Spectrum Center Blvd, San Diego, CA 92123

Security desk at Spectrum Center

Human Resource center at Spectrum Center

Servicing pharmacy

Sharp Rees-Stealy, 2929 Health Center Dr., San Diego, CA (2 mi.). Service the kiosk once daily, Monday – Friday. The pharmacy is open Monday-Friday 8:30am-5:30pm.

Program responsible manager

Kim Allen, RPh
Pharmacy Manager
Sharp Rees Stealy Pharmacy
2001 4th Ave., San Diego, CA 92101
Tel: 619 446 1515
Fax: 619 232 5865
kim.allen@sharp.com

Supervising Pharmacy & Dean's Letter

UC San Diego
SKAGGS SCHOOL OF PHARMACY
AND PHARMACEUTICAL SCIENCES

July 16, 2013

RE: 1706.5 Experimental Programs

Dear Ms. Herold,

Pursuant to 1706.5, UC San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences is requesting the granting of an experimental program to allow:

1) For automated delivery device to be placed away from the pharmacy
2) For new prescriptions to be delivered from the automated delivery device after consultation and proper documentation have taken place.

We would like to study whether the kiosk placed in a location convenient to employees will lead to better access to their prescriptions and subsequently an increase compliance and adherence. In order to pursue the regulation change, in accordance with regulation 1706.5, UC San Diego Skaggs School will monitor and report on the following experimental program:

An automated delivery device placed in a secure area of a corporate building used to deliver finished prescriptions to employees. The program will last 6 months and we will monitor and report on the following:

- Number of prescriptions picked up by patients
- Number of prescriptions not picked up by patients
- Number of telephone calls by patients requesting counseling
- Mechanical issues/downtime
- Complaints or malfunctions

Sincerely,

Charles E. Daniels, R.Ph., Ph.D., FASHP
Associate Dean and Professor of Clinical Pharmacy
Pharmacist-In-Chief
University of California San Diego
Skaggs School of Pharmacy and Pharmaceutical Sciences
9500 Gilman Drive, MC0657
La Jolla, California 92093

Skaggs School of Pharmacy and Pharmaceutical Sciences
9500 Gilman Drive, MC 0657 La Jolla, California 92093-057
Email: cdaniels@ucsd.edu Web: http://pharmacy.ucsd.edu

Time period and reporting

The pilot will last 6 months. Two program assessments will be presented to the board of pharmacy; one at 90 days and the second at the end of the 6 month pilot.

Number of prescriptions picked up by patients

Number of prescriptions not picked up by patients

Number of telephone calls by patients requesting counseling

Mechanical issues/downtime

Complaints or malfunctions

On-screen survey

A survey of questions will be presented to each employee picking up their prescription. The results will be compiled as part of the report for the board.

1) How many times have you used the Sharp Reese Stealy pharmacy in the last year to pick up a prescription for you or a family member?
    a. Today is the first time
    b. 1-2 times
    c. 2-5 times
    d. More than 5 times

2) What has prevented you from using the Sharp Reese Stealy pharmacy more often?
    a. I didn't have prescriptions for me or my family
    b. The pharmacy hours are not convenient
    c. The pharmacy location is not convenient
    d. Other

3) Is the convenience of after-hours prescription pick-up an important reason to use this kiosk?
    a. Yes
    b. No

4) Would you recommend ScriptCenter to a friend or colleague?
    a. Yes
    b. No

How it Works

1) Employee enrolls for the automated delivery device

    a. Employee uses their prescription number and birth date to create their unique ID and PIN *(see reference material page 3 'enrollment')*

    b. Enrollment triggers patient record through the interface that they have opted into the automated delivery device

2) Employee orders their prescription as usual by calling the pharmacy or online in the MySharp employee portal.

3) Pharmacy fills the prescription as usual and conducts all typical filling and quality control procedures put in place by the pharmacy.

4) Prescriptions with the automated delivery device indicator are each put into a ScriptCenter® container. Prescriptions are then linked to the container by scanning the prescription and then scanning the container *(see reference material page 4 'pharmacy').*

5) Linked prescriptions are brought to the automated delivery device by trained pharmacy personnel each afternoon Monday through Friday.

6) Pharmacy personnel logs into automated delivery device with their unique credentials and loads prescriptions.

7) Pharmacy personnel closes the door of the automated delivery device and waits for the system to inventory. Pharmacy personnel then logs back into the system to print off an inventory slip to bring back to pharmacy for confirmation and verification *(see reference material page 4 'pharmacy'.)*

8) Employee receives text message once their item has been loaded (optional) and picks it up at their convenience.

Counseling

Patients are presented with a 24 hour telephone number on the ScriptCenter screen and receipt connecting them with a Sharp HealthCare licensed pharmacist.

New prescriptions will be filled as usual. Those with the ScriptCenter indicator will be automatically placed on hold. The prescriptions will be loaded into the automated delivery device like the others, but new prescriptions will remain on-hold until counseling has taken place. A pharmacist will run an inventory report each day and call all patients whose prescriptions are on hold. Once the patient has been reached and counseled, the pharmacist will release the prescription in AsteresCentral® *(see reference materials page 7)*. This will give the ability for the employee to then pick up their prescription. If a patient comes to the automated delivery device before receiving counseling, they will receive a 'See Pharmacy Staff' message *(see reference materials page 5)* directing them to call the 24 hour number provided.

Security Measures

ScriptCenter will be placed within a 24 hour secured and monitored building. During the hours of 7:00a to 6:00p, the doors are unlocked, but visitors must sign in at the front desk and receive a visitor badge. Between the hours of 6:00p to 7:00am, only employees may access the building and do so by swiping their employee badge.

ScriptCenter is bolted to the floor. It is also equipped with an interior camera that photographs each person completing a transaction and keeps a photographic log on file *(see reference materials page 9).*

Pharmacy personnel train with HIPAA certified Asteres employees. A policy and procedures document along with training materials are provided to the pharmacy. Pharmacy personnel are given a role by the pharmacy administrator with varying levels of access. Pharmacy personnel logging into the automated delivery device are tracked and a complete audit trail of all ScriptCenter activity is recorded *(see reference materials page 8).* After loading prescriptions into ScriptCenter, pharmacy staff is required to return a confirmation slip to the pharmacy for verification and sign off *(see reference materials page 4).*

Conclusion

By providing a secure automated delivery device in our corporate office we will be able to better service our employees' pharmacy needs by offering convenient 24/7 prescription pick up. Sharp HealthCare is dedicated to providing wellness services to our employees and with ScriptCenter we hope to increase employee satisfaction by making it easier for employees to purchase and pick up their prescription medications.

REFERENCE MATERIALS

Regulation Section 1713

1713. Receipt and Delivery of Prescriptions and Prescription Medications Must be to or from Licensed Pharmacy

(a) Except as otherwise provided in this Division, no licensee shall participate in any arrangement or agreement, whereby prescriptions, or prescription medications, may be left at, picked up from, accepted by, or delivered to any place not licensed as a retail pharmacy.
(b) A licensee may pick up prescriptions at the office or home of the prescriber or pick up or deliver prescriptions or prescription medications at the office of or a residence designated by the patient or at the hospital, institution, medical office or clinic at which the patient receives health care services. In addition, the Board may, in its sole discretion, waive application of subdivision (a) for good cause shown.
(c) A patient or the patient's agent may deposit a prescription in a secure container that is at the same address as the licensed pharmacy premises. The pharmacy shall be responsible for the security and confidentiality of the prescriptions deposited in the container.
(d) A pharmacy may use an automated delivery device to deliver previously dispensed prescription medications provided:
(1) Each patient using the device has chosen to use the device and signed a written consent form demonstrating his or her informed consent to do so.
(2) A pharmacist has determined that each patient using the device meets inclusion criteria for use of the device established by the pharmacy prior to delivery of prescription medication to that patient.
(3) The device has a means to identify each patient and only release that patient's prescription medications.
(4) The pharmacy does not use the device to deliver previously dispensed prescription medications to any patient if a pharmacist determines that such patient requires counseling as set forth in section 1707.2(a)(2).
(5) The pharmacy provides an immediate consultation with a pharmacist, either in-person or via telephone, upon the request of a patient.
(6) The device is located adjacent to the secure pharmacy area.
(7) The device is secure from access and removal by unauthorized individuals.
(8) The pharmacy is responsible for the prescription medications stored in the device.
(9) Any incident involving the device where a complaint, delivery error, or omission has occurred shall be reviewed as part of the pharmacy's quality assurance program mandated by Business and Professions Code section 4125.
(10) The pharmacy maintains written policies and procedures pertaining to the device as described in subdivision (e).
(e) Any pharmacy making use of an automated delivery device as permitted by subdivision
(d) shall maintain, and on an annual basis review, written policies and procedures providing for:
(1) Maintaining the security of the automated delivery device and the dangerous drugs within the device.
(2) Determining and applying inclusion criteria regarding which medications are appropriate for placement in the device and for which patients, including when consultation is needed.
(3) Ensuring that patients are aware that consultation with a pharmacist is available for any prescription medication, including for those delivered via the automated delivery device.
(4) Describing the assignment of responsibilities to, and training of, pharmacy personnel regarding the maintenance and filing procedures for the automated delivery device.
(5) Orienting participating patients on use of the automated delivery device, notifying patients when expected prescription medications are not available in the device, and ensuring that patient use of the device does not interfere with delivery of prescription medications.

(6) Ensuring the delivery of medications to patients in the event the device is disabled or· malfunctions.
(f) Written policies and procedures shall be maintained at least three years beyond the last use of an automated delivery device.
(g) For the purposes of this section only, "previously-dispensed prescription medications" are those prescription medications that do not trigger a non-discretionary duty to consult under section 1707 .2(b)(1), because they have been previously dispensed to the patient by the pharmacy in the same dosage form, strength, and with the same written

1706.5 Experimental Programs

In order to enable any accredited school of pharmacy recognized by the Board to experiment with new and innovative methods for drug handling, teaching, research, or to develop new and better methods or concepts involving the ethical practice of pharmacy, the Board enacts the following:

(a) The application of particular provisions of the Pharmacy Rules and Regulations contained in Title 16, California Administrative Code, Chapter 17, may be waived as to an accredited school of pharmacy recognized by the Board if the Dean of said school has filed with the Board an experimental plan or program which specifies the particular provisions to be waived, and which has been approved by the Board.

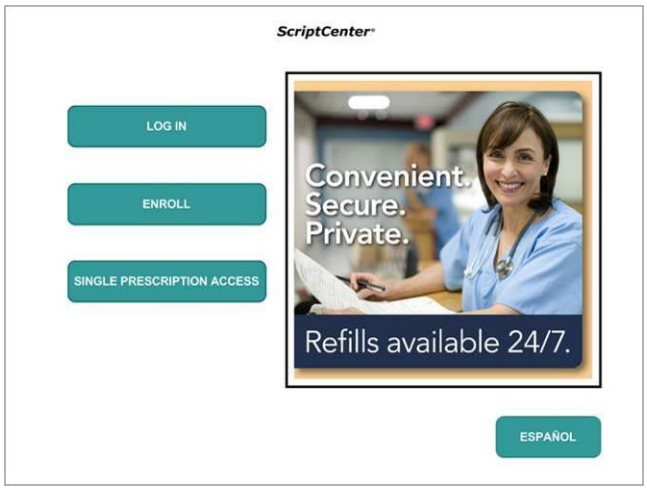
(b) Any plan or program approved by the Board shall have: definite time limitations; progress reports which shall be filed as required by the Board.

(c) The Board may rescind approval and terminate said plan or program at its discretion, at any time it may deem the public interest is not fully protected; nor shall any such plan or program be approved by the Board if such proposal might jeopardize public health or welfare or conflict with provisions of Chapter 9, Div. 2, Business and Professions Code.

Automated Delivery Device Screens

Enrollment:

1.

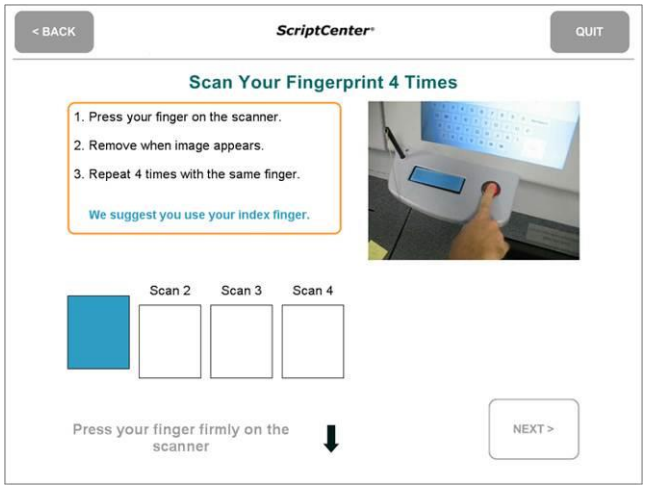


Patient/Employee selects 'Enroll'.

2.

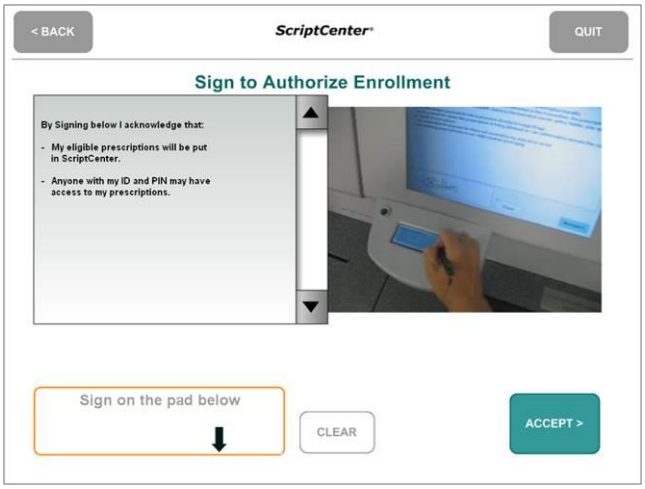
Patient/Employee enters their prescription number (one prescription number needed for enrollment) and creates their ID and PIN.

3.



Patient/Employee adds their fingerprint for quicker login (optional).

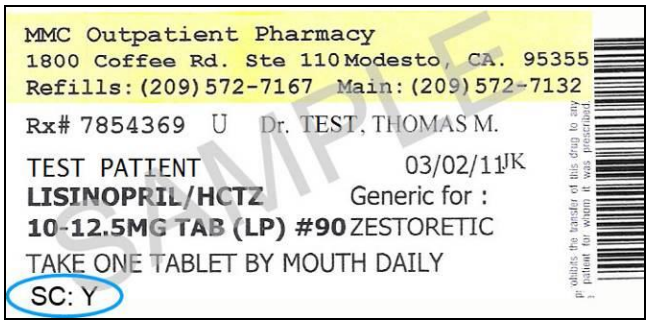
4.



Patient/Emloyee signs.

Pharmacy:

1.



Prescriptions with the ScriptCenter indicator get put in a separate bin for for ScriptLinking.

2.

ScriptCenter prescriptions are put into a ScriptCenter containers.

3.

Prescription is ScriptLinked to ScriptCenter container using a barcode scanner.

4.

Prescriptions are transported to ScriptCenter via authorized pharmacy personnel.

5.

Pharmacy staff logs into ScriptCenter kiosk using unique ID and PIN or fingerprint and loads prescriptions.

6.

ScriptCenter Inventory Status

Total Packages:	171
New Packages Loaded*:	19
Packages Unloaded*:	16
Ready to Unload:	5
Unknown:	5
Incomplete Orders:	0
Trays to Inspect:	0
Missing Trays:	0

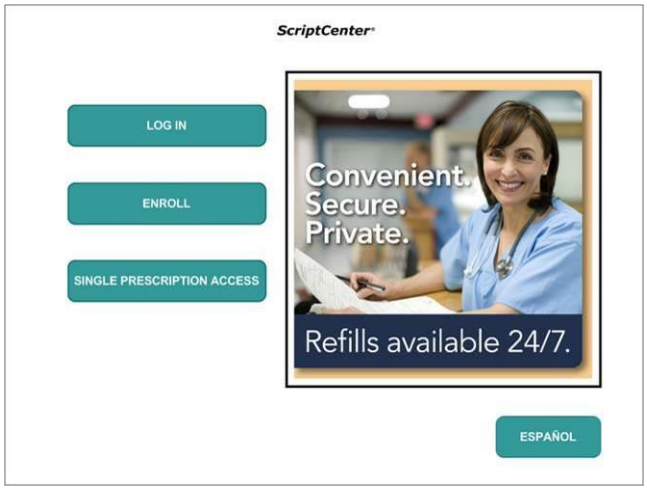
*Since 6/27/2013 12:58 PM.

Run by Sara Lake at 1:02 PM on 6/27/2013.

Pharmacy personnel prints inventory slip and returns to pharmacy to hand in for confirmation.

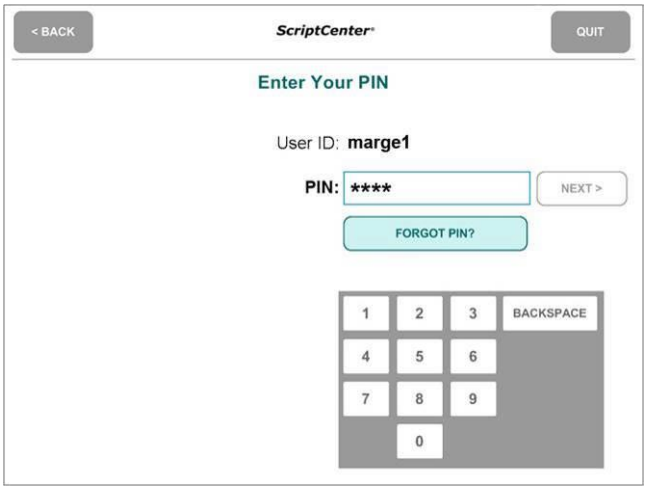
Delivery:

1.



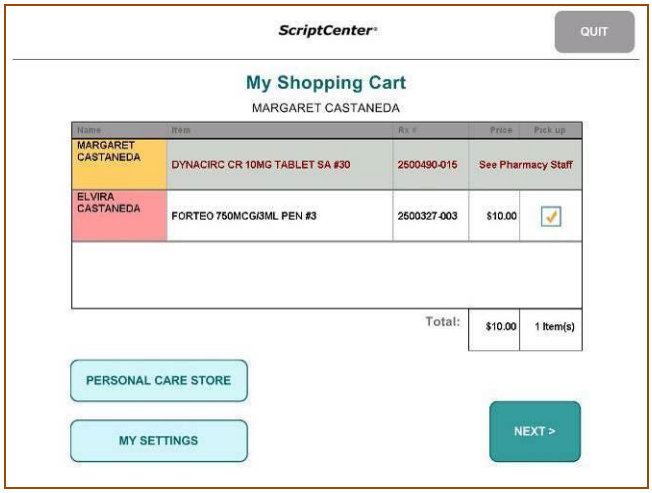
Employee logs in and discharge patient uses unique code for one-time pick up.

2.

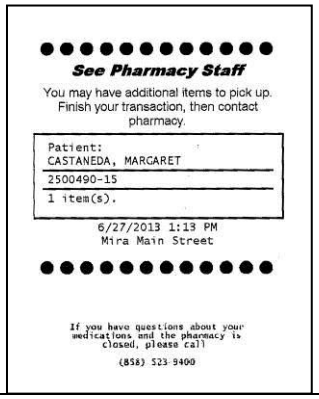


ID and PIN or fingerprint and PIN used for employee login.

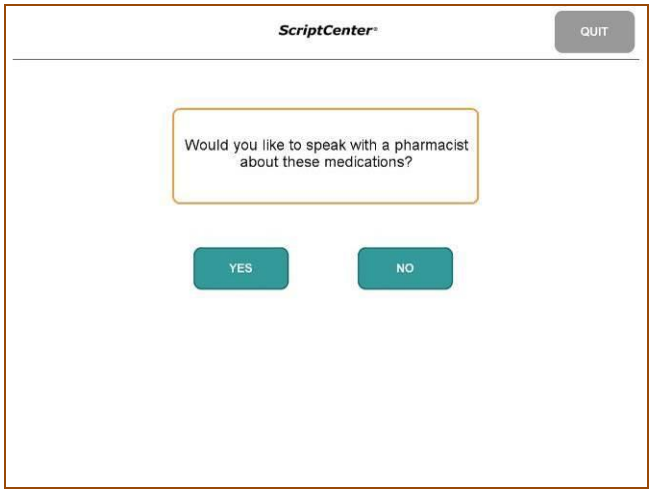
3.



Prescriptions reviewed for pick up. Note that family members can be added to an account for quick and convenient pick up. Prescriptions on-hold requiring consultation are presented as 'See Pharmacy Staff'. A 'See Pharmacy Staff' slip also prints from ScriptCenter.



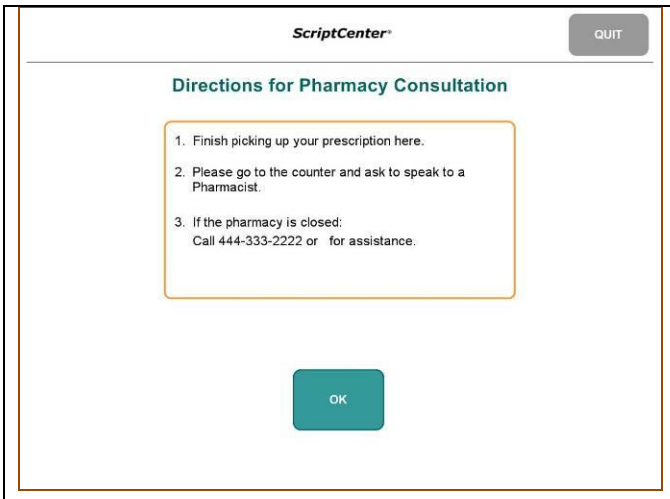
4.



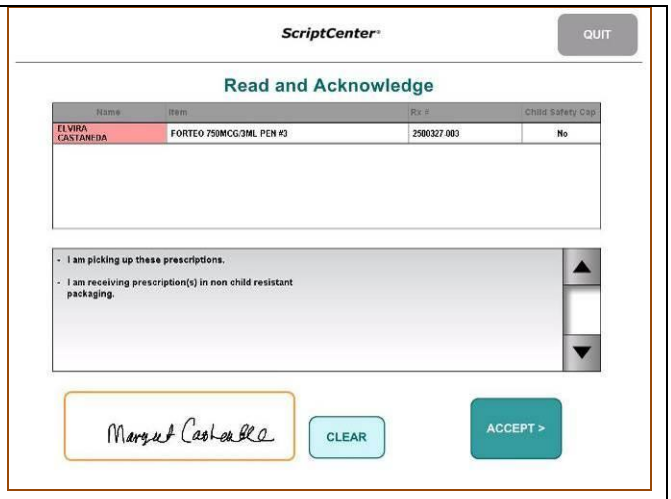
Offer for consultation presented.

5.

6.

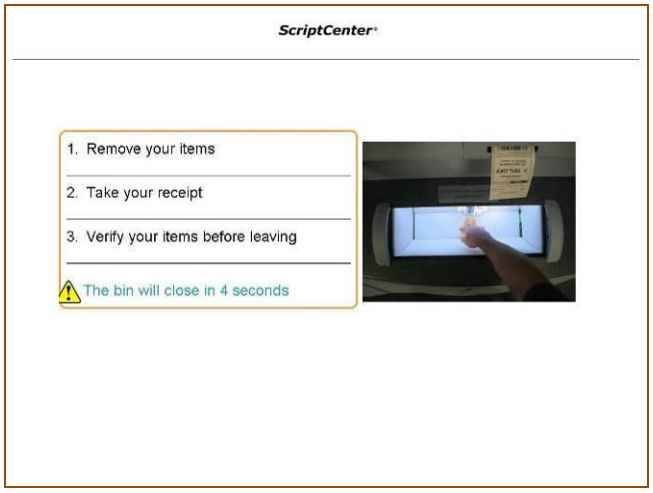


Directions for consultation provided. A log is kept for those who decline consultation.



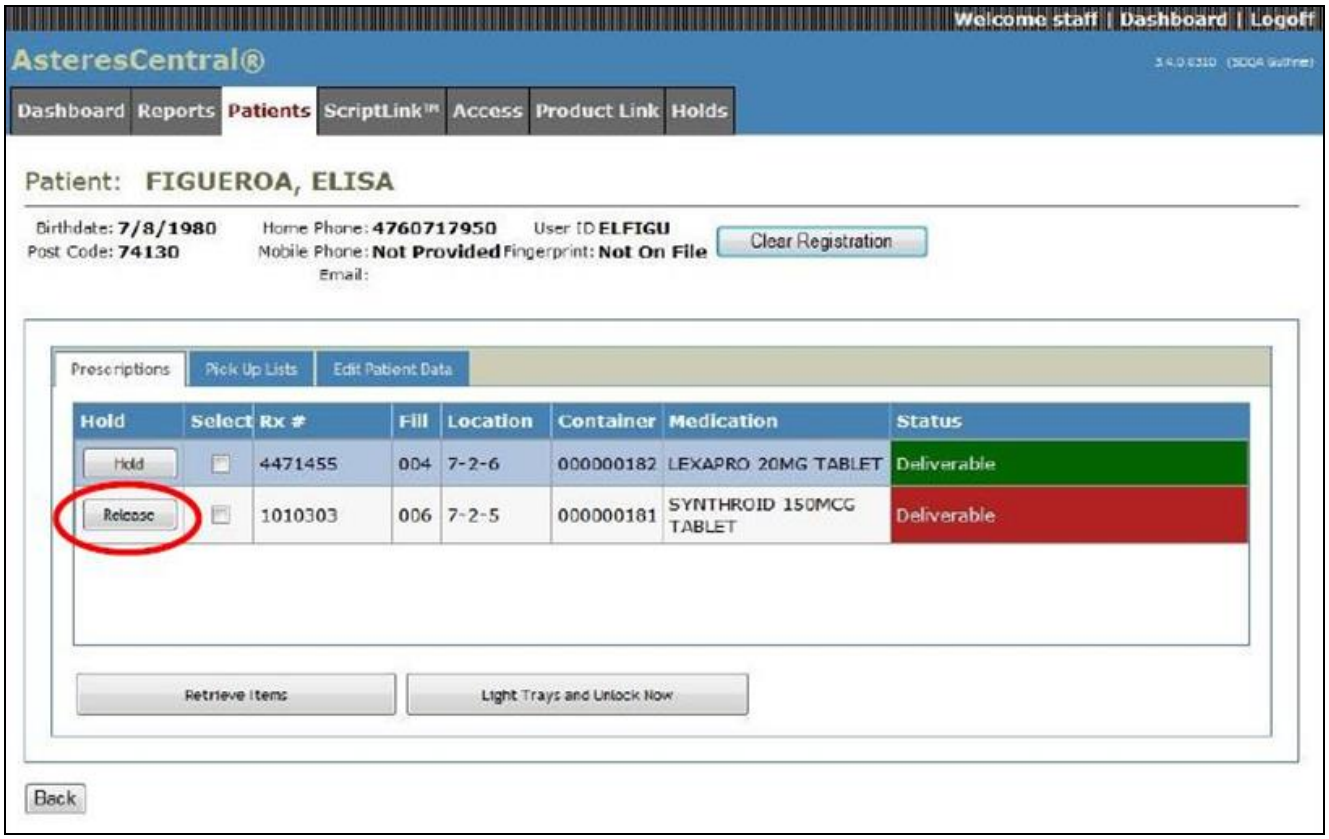
Employee/patient signs for prescription(s).

7.



Employee/patient pays for prescription(s) and picks them up from the delivery bin. Prescriptions left behind are flushed into a secure bin on accessible by pharmacy.

Hold and Release in AsteresCentral®:



AsteresCentral® Reports:

Asteres Activity

48 Transactions

Filter: "Today"

Date and Time	Transaction Type	Container No.	Rx Number	Fill	User / Shopper	Patient / Product
08/10/10 09:57:24	UNLINKED	002001095	3500502	002	LAKE, SARA	VANCE, WARREN
08/10/10 09:56:42	UNLOADED	002001095	3500502	002	LAKE, SARA	VANCE, WARREN
	The package was moved from location 6/4/10 to the holding area.					
08/10/10 09:55:43	SERVICE_REQUEST		*Unknown*		LAKE, SARA	
	[sara] Sara Lake issued a request to unlock the back door by Bio ID.					
08/10/10 09:50:26	DELIVERED	002001028	2500469	002	GODINEZ, LUPE	GODINEZ, LUPE
	The package at location 4/3/5 was delivered.					
08/10/10 09:48:47	UNLOADED	002001053	2500581	001	LAKE, SARA	JOHNSON, GARY C
	The package was moved from location 6/5/6 to the holding area.					
08/10/10 09:48:46	ACCESSED	002001052	2500580	001	LAKE, SARA	LIMON, STACEY
	The package at location 6/5/1 was accessed.					
08/10/10 09:48:45	ACCESSED	002001192	2500673	001	LAKE, SARA	HEUPEL, SANDRA
	The package at location 6/5/5 was accessed.					
08/10/10 09:48:41	LOADED	002001095	3500502	002	LAKE, SARA	VANCE, WARREN
	The package was moved from the holding area to location 6/4/10.					
08/10/10 09:48:23	ACCESSED	002248974	OTC		LAKE, SARA	Schick Quattro
	The package at location 5/2/8 was accessed.					
08/10/10 09:48:23	ACCESSED	002248973	OTC		LAKE, SARA	Schick Quattro
	The package at location 5/2/7 was accessed.					
08/10/10 09:48:23	ACCESSED	002248948	OTC		LAKE, SARA	Gillette MACH3 Turbo
	The package at location 5/2/5 was accessed.					
08/10/10 09:47:53	DOOR_CLOSED		*Unknown*		Unknown	
	Back door was closed.					
08/10/10 09:47:31	DOOR_OPENED		*Unknown*		Unknown	
	Back door was opened.					
08/10/10 09:47:16	SERVICE_REQUEST		*Unknown*		LAKE, SARA	
	[sara] Sara Lake issued a request to unlock the back door by Bio ID.					
08/10/10 09:46:57	LINKED	002001095	3500502	002	LAKE, SARA	VANCE, WARREN
08/10/10 09:44:13	MOVED	002001031	2500475	001	Unknown	AGUILERA, ANA
	The package was moved within ScriptCenter from location 4/5/9 to location 4/4/3.					
08/10/10 09:43:45	MOVED	002001018	2500439	001	Unknown	KELLEY, TIM
	The package was moved within ScriptCenter from location 5/4/2 to location 5/6/7.					
08/10/10 09:41:15	ACCESSED	002010063	2500326	001	DEYSHER, CHERYL	GAXIOLA, HILDA
	The package at location 1/3/6 was accessed.					
08/10/10 09:41:14	ACCESSED	002010069	2500339	001	DEYSHER, CHERYL	NEAL, CHARLES
	The package at location 1/3/5 was accessed.					
08/10/10 09:41:14	ACCESSED	002010075	2500354	001	DEYSHER, CHERYL	JUSTICE, FRANCES

Asteres Activity - Mira Main Street August 10, 2010 9:58 am Page 1 of 3

Photo Capture Log

Filter: Date Signed is between '6/25/2009' and '6/26/2009'

RX #	Fill	Date Signed	Medi-Cal Relationship	Third Party	Co-Pay	Credit/Debit Card	POS ID	Photo
2500302	1	6/25/2009 1:32:52PM		SBHA	$20.00			
2500228	1	6/26/2009 9:27:18AM			$10.00			
2500302	2	6/26/2009 9:46:09AM		SBHA	$10.00			
2500301	1	6/26/2009 9:47:36AM		CRK	$15.00			
2500306	1	6/26/2009 10:04:31AM		PACS	$10.00			

Photo Capture Log - Mira Demo Room June 26, 2009 1:40 pm

ATTACHMENT 2

Ms. Herold:

On behalf of Asteres, we hereby request an appearance before the California Board of Pharmacy at the January 20/21 meeting in Sacramento.

The purpose of our appearance will be to seek approval for the installation of an automated prescription "pick up" system in a hospital environment whereby the unit is not directly attached to the pharmacy.

Upon review of Section 1713, we feel that the Board has regulatory authority to grant this request based upon Paragraph 1713 (b) which states in part:

"In addition, the Board may, in its sole discretion, waive application of subdivision (a) for good cause. Subdivision (a) contains the language prohibiting the picking up of prescriptions from "any place not licensed as a retail pharmacy". We will be prepared to justify this action by the Board demonstrating how that the unit will be in a high-traffic, secure area on the hospital campus and that a telephone installation immediately adjacent to the unit will allow readily available access by the patient to a pharmacist for counseling.

Failing this argument, then we would request a specific waiver from Section 1713 (d) (6) requiring that "the device is located adjacent to the secure pharmacy area". We are prepared to have representatives appear from California hospitals to represent to the Board that by allowing flexibility in the placement of these "pick-up" devices on their campuses, that the net result will be to improve patient compliance and thereby improve patient care. Asteres will present past history to show to the Board that these devices can be installed in an area not adjacent to the pharmacy, yet in a secure manner..as well as in a manner where counseling by a pharmacist to the patient will be equally if not more readily available than in a standard retail environment..

Thank you for your consideration.

Phil

Philip P. Burgess, RPh, MBA
Philip Burgess Consulting, LLC
3800 N. Lake Shore Drive
Chicago, IL 60613
(773) 595-5990
www.philburgessconsulting.com

Title 16, California Code of Regulations

1713. Receipt and Delivery of Prescriptions and Prescription Medications Must be to or from Licensed Pharmacy

(a) Except as otherwise provided in this Division, no licensee shall participate in any arrangement or agreement, whereby prescriptions, or prescription medications, may be left at, picked up from, accepted by, or delivered to any place not licensed as a retail pharmacy.

(b) A licensee may pick up prescriptions at the office or home of the prescriber or pick up or deliver prescriptions or prescription medications at the office of or a residence designated by the patient or at the hospital, institution, medical office or clinic at which the patient receives health care services. In addition, the Board may, in its sole discretion, waive application of subdivision

(a) for good cause shown.

(c) A patient or the patient's agent may deposit a prescription in a secure container that is at the same address as the licensed pharmacy premises. The pharmacy shall be responsible for the security and confidentiality of the prescriptions deposited in the container.

(d) A pharmacy may use an automated delivery device to deliver previously dispensed prescription medications provided:

(1) Each patient using the device has chosen to use the device and signed a written consent form demonstrating his or her informed consent to do so.

(2) A pharmacist has determined that each patient using the device meets inclusion criteria for use of the device established by the pharmacy prior to delivery of prescription medication to that patient.

(3) The device has a means to identify each patient and only release that patient's prescription medications.

(4) The pharmacy does not use the device to deliver previously dispensed prescription medications to any patient if a pharmacist determines that such patient requires counseling as set forth in section 1707.2(a)(2).

(5) The pharmacy provides an immediate consultation with a pharmacist, either in-person or via telephone, upon the request of a patient.

(6) The device is located adjacent to the secure pharmacy area.

(7) The device is secure from access and removal by unauthorized individuals.

(8) The pharmacy is responsible for the prescription medications stored in the device.

(9) Any incident involving the device where a complaint, delivery error, or omission has occurred shall be reviewed as part of the pharmacy's quality assurance program mandated by Business and Professions Code section 4125.

(10) The pharmacy maintains written policies and procedures pertaining to the device as described in subdivision (e).

(e) Any pharmacy making use of an automated delivery device as permitted by subdivision (d) shall maintain, and on an annual basis review, written policies and procedures providing for:

(1) Maintaining the security of the automated delivery device and the dangerous drugs within the device.

(2) Determining and applying inclusion criteria regarding which medications are appropriate for placement in the device and for which patients, including when consultation is needed.

(3) Ensuring that patients are aware that consultation with a pharmacist is available for any prescription medication, including for those delivered via the automated delivery device.

(4) Describing the assignment of responsibilities to, and training of, pharmacy personnel regarding the maintenance and filing procedures for the automated delivery device.

(5) Orienting participating patients on use of the automated delivery device, notifying patients when expected prescription medications are not available in the device, and ensuring that patient use of the device does not interfere with delivery of prescription medications.

(6) Ensuring the delivery of medications to patients in the event the device is disabled or malfunctions.

(f) Written policies and procedures shall be maintained at least three years beyond the last use of an automated delivery device.

(g) For the purposes of this section only, "previously-dispensed prescription medications" are those prescription medications that do not trigger a non-discretionary duty to consult under section 1707.2(b)(1), because they have been previously dispensed to the patient by the pharmacy in the same dosage form, strength, and with the same written directions.

Authority cited: Sections 4005, 4075, and 4114 Business and Professions Code. Reference: Sections 4005, 4052, 4116 and 4117 Business and Professions Code.

Open Session

IX. Licensing Committee Report

a. Report of the Committee Meeting Held December 3, 2009

1. Request to Modify Title 16 California Code of Regulations Section 1713(d) Regarding the Requirement that Automated Dispensing Machines Be Adjacent to the Secure Pharmacy Area

Mr. Weisser provided that in 2005 and 2006, the board discussed and eventually promulgated a regulation to allow automated dispensing machines in pharmacies to dispense refill medications -- if requested by the patient and approved by the pharmacist. He stated that this was a use of emerging technology and several pharmacies had sought the board's authority to install such machines in their pharmacies to provide patients with afterhours access (as well as access during times when the pharmacy was open) to refills. Mr. Weisser explained that a patient could pick up refill medication, if approved by the pharmacy, from a vending-like machine using a credit card for payment and not specifically deal with the pharmacy staff. He advised that the machine was to be located near – specifically adjacent -- to the physical area of the pharmacy.

Mr. Weisser provided that a number of conditions were built into the regulations to provide for assurance patients would not be required to use these machines for refills if they were not supportive.

Mr. Weisser advised that this regulation was promulgated cautiously. He stated that throughout 2006, the board modified and adopted the regulation now in effect as section 1713. Mr. Weisser provided that in January 2007, the regulation actually took effect.

Mr. Weisser provided that during the meeting, the committee heard a presentation from Phil Burgess, representing Asteres, one vendor of these automated delivery devices. He stated that Mr. Burgess is seeking a waiver to the requirements in 1713 (d)(6) which requires that the delivery device be located adjacent to the secure pharmacy area. Mr. Weisser explained that in making the request, Mr. Burgess stated that they would like to place the device in a secure area that is readily accessible to the patient and that a telephone would be placed adjacent to the device for patients that wished to speak with a pharmacist.

Presentation - Phil Burgess and Mike de Bruin, Asteres

Phil Burgess, representing Asteres, provided an overview of ScriptCenter, a 24/7 automated pharmacy prescription pick-up machine including the registration and authorization process. He reviewed patient safety and security benefits and

added that ScriptCenter has successfully delivered over 450,000 prescriptions without one delivery error.

Mr. Burgess requested that the board waive regulation Section 1713(d)(6) regarding the placement of automated medication dispensing machines in hospitals.

Board Discussion

Mr. Brooks sought clarification regarding how a pharmacy obtains a ScriptCenter machine.

Mike de Bruin provided that there are multiple methods of acquisition strategies.

Burgess provided that each machine will have a phone located adjacent to the machine to allow the patient to immediately contact the pharmacist.

Mr. Lippe asked if the patient will be charged a transaction fee.

Mr. Burgess provided that no transaction fee is charged.

Mr. de Bruin provided that the machine will collect the patient's insurance co-pay.

Ms. Herold sought clarification regarding if it is intended for the machine to be made available to both hospital staff and patients.

Mr. Burgess indicated that Asteres would like the machine to be available to both hospital staff and patients. He provided that only refill prescriptions would be filled and the machine would only be located on the hospital campus in a secure environment, not necessarily in a hospital.

Mr. Room asked if any machines have been installed outside of a hospital campus.

Mr. de Bruin provided that machines have been installed in other areas in other states.

Mr. Room provided that this request may not be granted under a Section 1713 waiver.

Discussion continued regarding the ScriptCenter system and its applicability to pharmacy law and Section 1713. Advantages and disadvantages of the system were evaluated. Concern was expressed that this process may depersonalize the pharmacist and prescription service. It was clarified that in the event a waiver is granted, the waiver would be granted to the licensed facility and not to Asteres.

Public Comment

Dr. Allan Schaggs, representing Catholic Healthcare West (CHW), provided that CHW would like to provide ScriptCenter as a service to their employees.

Dr. Castellblanch sought clarification regarding why the waiver is also being requested for patients.

Mr. Burgess provided that the machine can benefit the spouses of employees and children of employees.

Discussion continued regarding the request and the placement of the machine in a secure area on the hospital campus. Concern was expressed that the request does not specify placement of the machine.
Dr. Steve Gray, representing Kaiser Permanente, offered support for the ScriptsCenter concept. He encouraged the board to grant a waiver under Section 1713 (b) for employees and to consider further discussion of a waiver for other patients.

Mr. Weisser sought clarification regarding mail order prescriptions and patient requests for phone consultations with a pharmacist.

Dr. Gray provided that in the rare event that a patient does have a question, they can often get their questioned answered faster by calling a pharmacist than if they were to wait in line at a pharmacy.

Mr. Burgess provided that the ScriptsCenter machine allows for a pharmacist to be available to the patient when the adjacent pharmacy is closed during off hours.

Ms. Herold provided that pharmacies using such a device are required to provide immediate access to a telephone for patients to contact a 24-hour pharmacy in the event their pharmacy is closed.

Ms. Herold indicated that board staff will provide some guidelines to assist Asteres with providing the required clarification regarding their request.

There was no additional board discussion or public comment.

2. Final Review on Parameters for Recalls in Hospitals

Mr. Weisser provided that during the spring of 2008, the board identified 94 hospital pharmacies with recalled heparin still within the facilities, two to three months following the last recall.

California State Board of Pharmacy
1625 N. Market Blvd, Suite N 219, Sacramento, CA 95834
Phone (916) 574-7900
Fax (916) 574-8618
www.pharmacy.ca.gov

STATE AND CONSUMERS SERVICES AGENCY
DEPARTMENT OF CONSUMER AFFAIRS
ARNOLD SCHWARZENEGGER, GOVERNOR

Licensing Committee Report

Members:
Stan Weisser, RPh, Chairperson
Randy Kajioka, PharmD
Ramón Castellblanch, Public Member

IX. LICENSING COMMITTEE REPORT AND ACTION

a. Report of the Committee Meeting Held December 3, 2009

1. FOR DISCUSSION: Request to Modify Title 16 California Code of Regulations Section 1713(d) Regarding Requirement that Automated Dispensing Machines Be Adjacent to the Secure Pharmacy Area

Attachment 1

Background

In 2005 and 2006, the board discussed and eventually promulgated a regulation to allow automated dispensing machines in pharmacies to dispense refill medications -- if requested by the patient and approved by the pharmacist. This was a use of emerging technology and several pharmacies had sought the board's authority to install such machines in their pharmacies to provide patients with afterhours access (as well as access during times when the pharmacy was open) to refills. Basically, a patient could pick up refill medication, if approved by the pharmacy, from a vending-like machine using a credit card for payment and not specifically deal with the pharmacy staff. The machine was to be located near – specifically adjacent -- to the physical area of the pharmacy.

A number of conditions were built into the regulations to provide for assurance patients would not be required to use these machines for refills if they were not supportive. A copy of the final regulation is provided below.

This regulation was promulgated cautiously. Throughout 2006, the board modified and adopted the regulation now in effect as section 1713. In January 2007, the regulation actually took effect.

During the meeting, the committee heard a presentation from Phil Burgess, representing Asteris, one vendor of these automated delivery devices. Mr. Burgess is seeking a waiver to the requirements in 1713 (d)(6) which requires that the delivery device be located adjacent to the secure pharmacy area. In making the request, Mr. Burgess stated that they would like to place the device in a secure area that is readily accessible to the patient and that a telephone would be placed adjacent to the device for patients that wished to speak with a pharmacist.

Mr. Burgess will provide a presentation to the board during the meeting.

A written copy of the waiver request as well as a copy of CCR 1713 is provided in **Attachment 1**. At the request of the committee, staff will be prepared to discuss various options for the board to consider.

2. FOR ACTION: Final Review of Parameters for Recalls in Hospitals

During the spring of 2008, the board identified 94 hospital pharmacies with recalled heparin still within the facilities, two to three months following the last recall. The board cited and fined the hospital pharmacies and pharmacists-in-charge of these pharmacies. However, because many of these hospitals and PICs have appealed the citations and fines, board members cannot discuss the specific parameters of any of these cases without recusing themselves from voting on the specific case in the future should they be appealed to the Office of Administrative Hearings.

Over the last year, the board convened a two-board member task force to work with relevant associations, regulators, hospitals, wholesalers and patient advocates on ways to improve recalls, and other changes needed to provide for improved drug distribution and control within a hospital. Three meetings were held, and at the last meeting in September, a draft Best Practices document was refined. A draft document establishing the parameters for recalls in hospitals was one major outcome of these meetings.

The revised document will be provided during the board meeting. The last step will be a presentation to the board for ratification and future publication in the board's newsletter.

3. FOR INFORMATION: Emergency and Disaster Response Planning: Update on the H1N1 Emergency Response Activities in California

For more than one year, health care providers, policy makers and governments worldwide have been dealing with the H1N1 flu worldwide pandemic.

In California, the board has provided assistance. This has included:

- Sharing our subscriber alert system to advise licensees of directives from the California Department of Public Health
- Ensuring the expedited licensing of storage locations for the H1N1 vaccines
- Establishing a specialized list of compounding pharmacies that the Department of Public Health can access if special, compounded formulations of medications are needed
- Transferring messages from board licensees that need a response or intervention from the Department of Public Health's Emergency Planning and Response Branch, Emergency Preparedness Office

Board staff continues to work closely with the Department of Public Health to assist in ways that will benefit the public.

In order to ensure that the board can act quickly to activate the board's emergency response policy in response to a sudden declared crisis, at the October Board Meeting, the board voted that:

ATTACHMENT 3

nabp
National Association of Boards of Pharmacy
1600 Feehanville Drive • Mount Prospect, IL 60056-6014
Tel: 847/391-4406 • Fax: 847/391-4502
Web Site: www.nabp.net

Internet Drug Outlet Identification Program

Progress Report for State and Federal Regulators: April 2013

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nabp
National Association of Boards of Pharmacy
1600 Feehanville Drive • Mount Prospect, IL 60056-6014
Tel: 847/391-4406 • Fax: 847/391-4502
Web Site: www.nabp.net

INTERNET DRUG OUTLET IDENTIFICATION PROGRAM
PROGRESS REPORT: April 2013

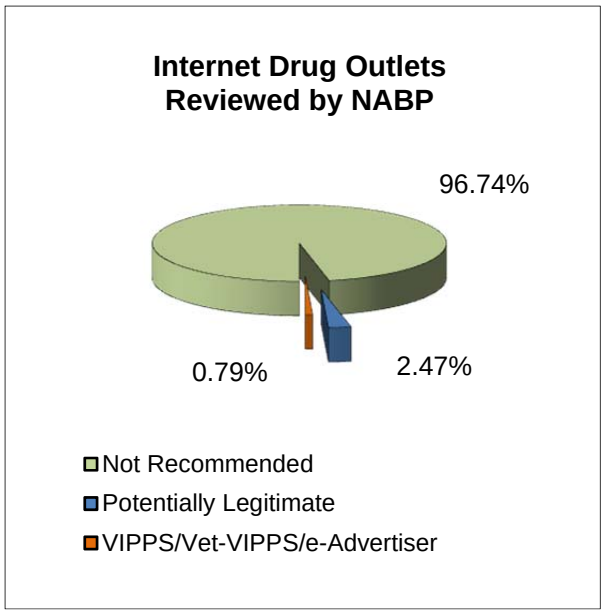
I. INTRODUCTION

Illegal online drug sellers have played a significant role in the global spread of counterfeit and substandard medicine. They pose a public health problem that is indifferent to the jurisdictional boundaries of any one nation, and that must be addressed in cooperation with partners around the world. Recognizing the international scope of this problem, National Association of Boards of Pharmacy® (NABP®) and its member boards are working with regulatory authorities, industry leaders, and stakeholder groups worldwide to protect patient health. These efforts are exemplified in NABP's application to the Internet Corporation for Assigned Names and Numbers (ICANN) to own and operate the .PHARMACY generic Top-Level Domain (gTLD). Domain names in the .PHARMACY gTLD will be available to legitimate online pharmacies and prescription drug-related organizations worldwide. NABP and its partners have made significant progress in recent months to develop best practices for the use of .PHARMACY domain names and to clarify the intent and scope of this initiative.

While the .PHARMACY initiative moves forward on a global scale, NABP's Internet Drug Outlet Identification Program maintains its primary focus on Web sites selling prescription medicine to patients in the United States. NABP continues to find the vast majority of drug sites (97% of those reviewed) to be operating in contravention with US federal and state pharmacy laws. These sites, identified on the NABP Web site as Not Recommended, are characterized in Section II of this report. These findings and the concerns they raise, however, are not unique to the US. The global scope of the problem, and how the .PHARMACY initiative seeks to address this challenge, is discussed in Section III.

II. RESULTS

A. Findings of Site Reviews: In all, as of March 29, 2013, NABP has conducted initial reviews and, via a subsequent review, verified its findings on 10,421 Internet drug outlets selling prescription medications. Of these, 10,082 (96.74%) were found to be operating out of compliance with state and federal laws and/or NABP patient safety and pharmacy practice standards, and are listed as Not Recommended in the "Buying Medicine Online" section, under Consumers, on the NABP Web site, as well as on NABP's consumer protection Web site, *WWW.AWARERX.ORG*. This Web site is part of the AWARxE® Consumer Protection Program, provided by NABP and the state boards of pharmacy to help educate the public about the risks of Internet drug outlets, and includes news, tips, and links to relevant NABP resources. It should be noted that the research findings NABP reports herein and on the Not Recommended list include the total number of Web sites selling prescription drugs to US patients that NABP staff has reviewed and found to be out of compliance with program standards, including those sites that were found to be noncompliant at the time of review but may since have been deactivated. Thanks to the successes of multistakeholder efforts to shut down rogue sites, many of these sites may now be defunct. It should also be noted that the numbers reported here do not represent the entire universe of Web sites selling prescription drugs illegally, but, rather, a representative sampling of the online environment over the last five years. The 10,082 Internet drug outlets currently listed as Not Recommended on the NABP Web site are characterized as follows:

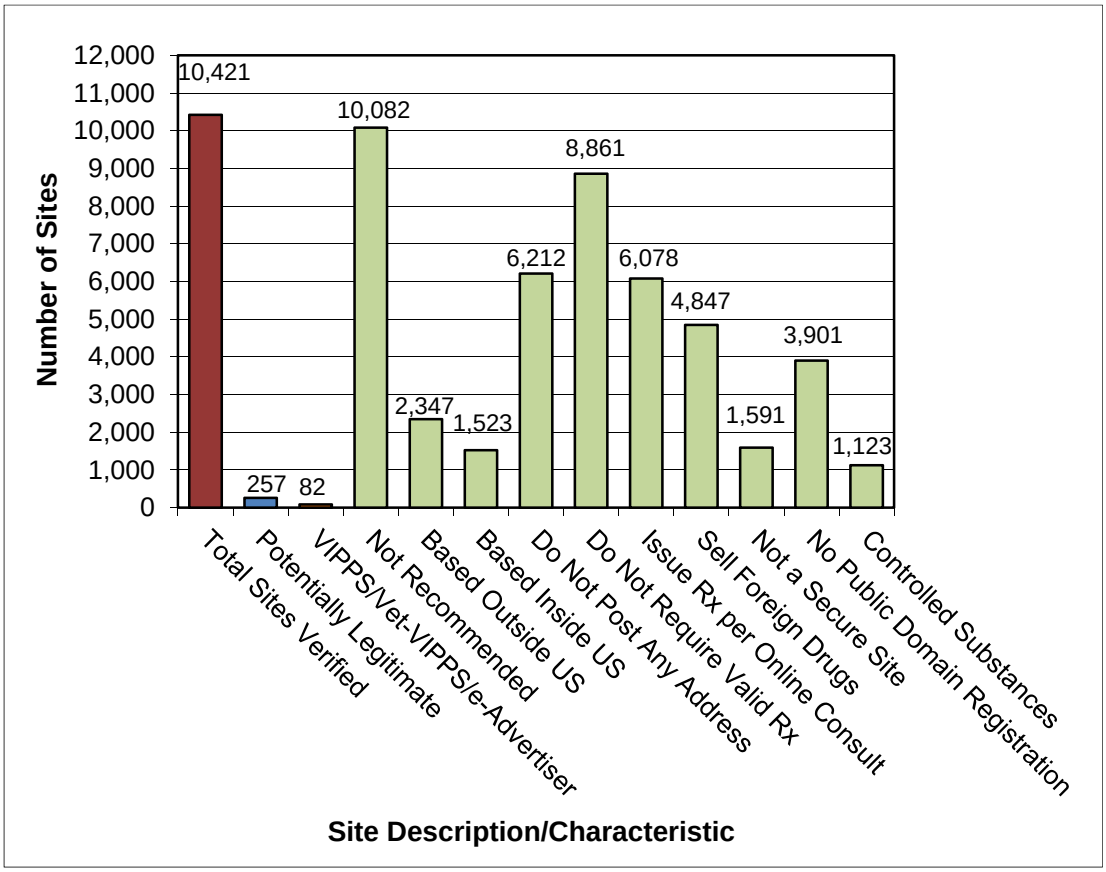


- 2,347 (23.3%) have a physical address located outside of the US
- 1,523 (15.1%) have a physical address located inside of the US
- 6,212 (61.6%) do not post any address
- 8,861 (87.9%) do not require a valid prescription
- 6,078 (60.3%) issue prescriptions per online consultation or questionnaire only
- 4,847 (48.1%) offer foreign or non-Food and Drug Administration (FDA)-approved drugs

- 1,591 (15.8%) do not have secure sites, exposing customers to financial fraud and identity theft
- 4,065 (40.3%) have server locations in foreign countries
- 1,123 (11.1%) dispense controlled substances (of these, 1,094 (97.42%) do not require a valid prescription)
- 3,901 (38.7%) do not have a public domain name registration (WHOIS information is registered using a privacy or proxy service) [1]

Of the total 10,421 sites reviewed, 257 (2.47%) appear to be potentially legitimate, ie, meet program criteria that could be verified solely by looking at the sites and their domain name registration information. Eighty-two (0.79%) of the 10,421 reviewed sites have been accredited through NABP's Verified Internet Pharmacy Practice Sites℠ (VIPPS®) or Veterinary-Verified Internet Pharmacy Practice Sites℠ (Vet-VIPPS®) programs, or approved through the NABP e-Advertiser Approval℠ Program. The standards against which NABP evaluates Internet drug outlets are provided in the appendix of this report.

[1] It is noteworthy that the percentage of sites identified as Not Recommended that are registered privately or by proxy (38.7%) is considerably higher than that of domain names overall. This comparison is based on an ICANN study in 2009 that sampled 2,400 domain names and found 429 (18%) of them to be registered using a WHOIS privacy or proxy service. Domain name registration (ie, WHOIS information) is an issue of contention among Internet policy stakeholders. Some have suggested that privacy/proxy services are being abused to obscure the identity of perpetrators that use the domains for illegal activities. Enforcement authorities have encouraged requirements for accurate registrant and contact information in WHOIS records to enable the identification and prosecution of bad actors. NABP considers accurate domain name registration to be an important indicator of accountability and approval standards require accurately registered domain names. Further studies are ongoing in the Internet community to support or refute this correlation.



Findings of NABP Web site reviews, in total, as of March 29, 2013

B. Recommended Internet Pharmacies: NABP, along with many patient safety advocates, continues to recommend that US patients use Internet pharmacies accredited through the VIPPS and Vet-VIPPS programs when buying medication online. These sites have undergone and successfully completed the thorough NABP accreditation process, which includes a review of all policies and procedures regarding the practice of pharmacy and dispensing of medicine over the Internet, as well as an on-site inspection of facilities used by the site to receive, review, and dispense medicine. Currently, 52 VIPPS and Vet-VIPPS pharmacy sites, representing more than 12,000 pharmacies, are listed as Recommended Internet Pharmacies. Several more applications are in progress.

C. Accreditation and Approval Programs: In addition to identifying rogue sites, the Internet Drug Outlet Identification program staff continues to assist in screening applicant Web sites for the VIPPS, Vet-VIPPS, and

e-Advertiser Approval programs. Sites that have received e-Advertiser Approval status do not fill new prescription drug orders via the Internet, and thus, are ineligible for VIPPS, but accept refill requests from their existing customers, provide drug information or pharmacy information, or offer other prescription drug-related services. Sites that have received e-Advertiser Approval status have been found to be safe, reliable, and lawful. These sites are listed on the NABP Web site as Approved e-Advertisers. The standards that NABP uses to screen e-Advertiser Approval Program applicants are posted in the e-Advertiser Approval Program section, under Accreditation, on the NABP Web site. As of March 29, 2012, there were 30 entities listed on the NABP Web site as Approved e-Advertisers, and several more applications are in progress.

III. INTERNATIONAL SCOPE AND DEVELOPMENT OF .PHARMACY gTLD

A. Internet-Fueled Threat of Counterfeit Medicine Warrants Global Action: While the illegal distribution of prescription drugs over the Internet poses many dangers, the threat that most worries public health agencies is the spread of substandard and counterfeit medicine. In its February 2013 report, *Countering the Problem of Falsified and Substandard Drugs*, the Institute of Medicine (IOM) notes that illegal online drug sellers contribute significantly to the spread of counterfeit and substandard medications worldwide, owing to the poor quality of the products they sell and the lack of official oversight of their operations. "All drugs sold outside the legitimate chains are suspect," the IOM report states. "This includes medicines sold in unregulated markets and most drugs sold on the Internet."

On its Web site, INTERPOL highlights the role of the Internet in perpetuating this problem, stating, "The increasing prevalence of counterfeit and illicit goods has been compounded by the rise in Internet trade, where they can be bought easily, cheaply and without a prescription." INTERPOL announced on March 12, 2013, that, with the support of the pharmaceutical industry, it is expanding the scope of its Medical Product Counterfeiting and Pharmaceutical Crime Unit to combat the global health threat of counterfeit and fake medicines. A representative of INTERPOL participated in a recent meeting of the .PHARMACY gTLD Advisory Committee at NABP Headquarters.

Partnership for Safe Medicines applauds INTERPOL's enhanced law enforcement effort in a March 12, 2013 news release, stating, "Counterfeit medicines threaten the lives of millions of people around the world, and finding ways to address such a complex, far-reaching issue requires ever-increasing global cooperation."

The situation is similar the United Kingdom, where the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) describes on its Web site an "explosion" in recent years of Web sites selling medicine online, most of which do not meet regulatory standards established in the region to protect patient health. In a March 27, 2013 news release announcing the sentencing of perpetrators in a counterfeit medicines case, MHRA stresses its commitment to "pursuing those involved in the illicit supply of medicines and taking action to ensure the public is protected." MHRA warns consumers that buying medicines from unauthorized sources significantly increases the risk of getting substandard or fake medicines.

B. International Coalition of Stakeholders Backs .PHARMACY gTLD Initiative: Mindful of the international spread of unapproved, substandard, and counterfeit medicine, and the contributing role that illegal online drug sellers play, NABP it taking steps to establish an online space exclusively for legitimate Internet pharmacies and other trustworthy prescription drug-related organizations. NABP has applied for the .PHARMACY gTLD as a community-based application on behalf of international pharmacy coalitions and national pharmacy associations, representing legitimate online pharmacies and prescription drug-related organizations worldwide.

ICANN's new gTLD program is expected to vastly alter the Internet landscape with the addition of hundreds of new gTLDs. Not surprisingly, it has led to some confusion and misinformation in relation to new gTLDs, including .PHARMACY. Contrary to misinformation that has appeared recently in some public forums, the .PHARMACY gTLD will *not* be limited to US pharmacies. It will be available to legitimate online pharmacies and prescription drug-related organizations worldwide. It has been suggested that .PHARMACY would give an unfair advantage to US pharmacies, would work against the interests of the public health, and impede online access to safe and affordable medicine. To clarify, NABP confirms that its intent for .PHARMACY is to ensure that only legitimate Internet pharmacies and related entities – those that adhere to pharmacy laws in the countries where they are based, as well as in the countries where they sell medicine – would be permitted to register in .PHARMACY. This includes legitimate online pharmacies and related entities that are located in countries other than the US. It is the position of NABP, and of the global coalition of stakeholders that has encouraged and supported this initiative, that requiring .PHARMACY registrants to comply with international standards does serve the public interest.

In February 2013, NABP convened its first meeting of the .PHARMACY gTLD Advisory Committee, composed of industry experts representing multiple countries and disciplines.

The meeting provided a history and overview of ICANN's new gTLD program, NABP's impetus and objectives in taking on this initiative, as well as input and perspectives from stakeholders including LegitScript, EAASM, and International Pharmaceutical Federation (FIP). Other industry experts working with NABP on the .PHARMACY initiative are the Canadian National Association of Pharmacy Regulatory Authorities, the US Alliance for Safe Online Pharmacies, Eli Lilly and Company, Merck and Company Inc, INTERPOL, and several of NABP's member boards of pharmacy.

Discussion at the February meeting focused on establishing a system of governance for the .PHARMACY gTLD that will ensure that it represents the global pharmacy community in the best interest of patient safety. Committee members are also considering a plan to identify and define a universal, common set of standards that would be consistently required of all domain name registrants in the .PHARMACY gTLD. These common standards would be supplemented by national specifications that would be required of registrants in those jurisdictions and may address variant policies relating to patient privacy, controlled substances, prescription requirements, and practitioner license requirements. The committee also discussed the scope of the .PHARMACY gTLD described in the application; domain names in the .PHARMACY gTLD will be available not only to legitimate pharmacies but also to approved schools and colleges of pharmacy, prescription drug manufacturers, patient advocacy groups, and other entities providing pharmacy or prescription drug-related services or information, in the interest of patient safety and the global pharmacy community.

Advisory committee members will hold follow-up discussions in the coming months to define domain name registration criteria, authorized usage policy, and compliance strategy for the .PHARMACY gTLD, as well as partnership opportunities for public outreach and consumer education to build public awareness of, and confidence in .PHARMACY. The advisory committee will reconvene via teleconference and/or Webinar in third quarter 2013 to further discuss the governance, standards, and outreach of the .PHARMACY gTLD.

IV. DISCUSSION

Rogue Internet drug outlets fuel the spread of counterfeit and substandard medicine, along with the public health problems they cause on a global scale. By working in concert with regulatory authorities, law enforcement, industry experts, and patient safety advocates across national borders, NABP seeks to help establish a safe online space where the health care community and patients alike can be sure the medicine they buy online is authentic and safe. The .PHARMACY gTLD, as proposed, will be available to legitimate pharmacies and other prescription drug-related

organizations worldwide that adhere to all applicable pharmacy laws in the countries where they are based and where they do business. Recognizing that international collaboration is needed to protect patient health, NABP and its partners are committed to upholding the integrity of the practice of pharmacy, curtailing the online trade of illicit and counterfeit medications, and ensuring that patients have access to safe and effective prescription drugs. Ultimately, this initiative will assure the health care community and patients worldwide that all pharmacy sites ending in the .PHARMACY gTLD are safe and legitimate. More information about NABP's application for the .PHARMACY gTLD is available on the NABP Web site at *www.nabp.net/programs/pharmacy/pharmacy-and-nabp.* For further information on this initiative or the Internet Drug Outlet Identification Program, please contact Melissa Madigan, policy and communications director, via e-mail at mmadigan@nabp.net.

V. APPENDIX

Internet Drug Outlet Identification Program Standards

1. **Pharmacy licensure.** The pharmacy must be licensed or registered in good standing to operate a pharmacy or engage in the practice of pharmacy in all required jurisdictions.

2. **DEA registration.** The pharmacy, if dispensing controlled substances, must be registered with the US Drug Enforcement Administration (DEA).

3. **Prior discipline.** The pharmacy and its pharmacist-in-charge must not have been subject to significant recent and/or repeated disciplinary sanctions.

4. **Pharmacy location.** The pharmacy must be domiciled in the United States.

5. **Validity of prescription.** The pharmacy shall dispense or offer to dispense prescription drugs only upon receipt of a valid prescription, as defined below, issued by a person authorized to prescribe under state law and, as applicable, federal law. The pharmacy must not distribute or offer to distribute prescriptions or prescription drugs solely on the basis of an online questionnaire or consultation without a preexisting patient-prescriber relationship that has included a face-to-face physical examination, except as explicitly permitted under state telemedicine laws or regulations.

   Definition. A valid prescription is one issued pursuant to a legitimate patient-prescriber relationship, which requires the following to have been established: a) The patient has a legitimate medical complaint; b) A face-to-face physical examination adequate to establish the legitimacy of the medical complaint has been performed by the prescribing practitioner, or through a telemedicine practice approved by the appropriate practitioner board; and c) A logical connection exists between the medical complaint, the medical history, and the physical examination and the drug prescribed.

6. **Legal compliance.** The pharmacy must comply with all provisions of federal and state law, including but not limited to the Federal Food, Drug, and Cosmetic Act and the Federal Controlled Substances Act (including the provisions of the Ryan Haight Online Pharmacy Consumer Protection Act, upon the effective date). The pharmacy must *not* dispense or offer to dispense medications that have not been approved by the US Food and Drug Administration.

7. **Privacy.** If the pharmacy Web site transmits information that would be considered Protected Health Information (PHI) under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CRF 164), the information must be transmitted in accordance with HIPAA requirements, including the use of Secure-Socket Layer or equivalent technology for the transmission of PHI, and the pharmacy must display its privacy policy that accords with the requirements of the HIPAA Privacy Rule.

8. **Patient services.** The pharmacy must provide on the Web site an accurate US street address of the dispensing pharmacy or corporate headquarters. The pharmacy must provide on the Web site an accurate, readily accessible and responsive phone number or secure mechanism via the Web site, allowing patients to contact or consult with a pharmacist regarding complaints or concerns or in the event of a possible adverse event involving their medication.

9. **Web site transparency.** The pharmacy must not engage in practices or extend offers on its Web site that may deceive or defraud patients as to any material detail regarding the pharmacy, pharmacy staff, prescription drugs, or financial transactions.

10. **Domain name registration.** The domain name registration information of the pharmacy must be accurate, and the domain name registrant must have a logical nexus to the dispensing pharmacy. Absent extenuating circumstances, pharmacy Web sites utilizing anonymous domain name registration services will not be eligible for approval.

11. **Affiliated Web sites.** The pharmacy, Web site, pharmacy staff, domain name registrants, and any person or entity that exercises control over, or participates in, the pharmacy business must not be affiliated with or control any other Web site that violates these standards.

ATTACHMENT 4

IMMEDIATE RELEASE May 21, 2013
For more information contact:
Deborah Zak, Communications Manager
847/391-4405; custserv@nabp.net

NABP's .PHARMACY Proposal Passes Initial ICANN Evaluation *Achieves Critical Milestone in Creating Safe Online Pharmacy Space for Consumers Worldwide*

Reaching a critical milestone in the generic Top-Level Domain (gTLD) approval process, the National Association of Boards of Pharmacy® (NABP®) application to own and operate the .PHARMACY domain suffix has passed the Internet Corporation for Assigned Names and Numbers (ICANN) initial evaluation. NABP intends to launch the .PHARMACY gTLD by the end of 2013, and will make the new domain available to legitimate online pharmacies and related entities that are located in the United States as well as in other countries. Passing ICANN's initial evaluation is a key success in realizing the Association's vision - established in partnership with a global coalition of stakeholders - of creating a secure and trustworthy online space for pharmacy, benefiting consumers around the world.

Having reached this key point, NABP will now work toward operationalizing the .PHARMACY gTLD program, as it awaits the final stages of ICANN's evaluation process. Next steps in the process include execution of the registry agreement with ICANN and performance of pre- delegation testing, which ensures that NABP and its technical partners have the capacity to operate the new .PHARMACY gTLD in a stable and secure manner.

"Passing this hurdle in the .PHARMACY application process is a significant success in NABP's initiative to establish a safe online space that will benefit patients and the health care community around the world. With the online distribution of counterfeit and substandard medications posing a growing threat to consumers, NABP is extremely pleased to move forward with its plans for the .PHARMACY gTLD," states NABP President Karen M. Ryle, MS, RPh. "By distinguishing .PHARMACY as a domain space exclusively for appropriately licensed, legitimate Internet pharmacies operating in compliance with international pharmacy standards, NABP aims to protect the global public health from dangers of substandard drugs distributed by rogue online sellers."

With the support of a global coalition of stakeholders, including international pharmacy organizations, regulators, industry experts, and law enforcement agencies, NABP applied to ICANN in June 2012 to own and operate the .PHARMACY gTLD. This global coalition shares the Association's concern about illegal online drug sellers distributing products that endanger patient health worldwide. Thus, in its application, NABP stated the importance of ensuring that only legitimate Web site operators that adhere to pharmacy laws in the jurisdictions in which they are based and to which they sell medicine will be able to register domain names in .PHARMACY.

NABP continues to monitor Web sites selling prescription drugs to patients in the US and as of April 2013, has reviewed over 10,400 Internet drug outlets and found 97% of them to be out of compliance with pharmacy laws and practice standards established in the US to protect the public health. Of these 10,082 Web sites identified as Not Recommended, nearly half offer foreign or non-Food and Drug Administration-approved drugs to US residents, and many of these distribute dangerous counterfeits to unsuspecting consumers. Further, health and regulatory agencies in the US and abroad have reported cases of patients harmed by counterfeit, substandard, and adulterated medications distributed by illegal Internet sellers.

The .PHARMACY application was submitted as part of ICANN's expansion of available gTLDs, which currently include familiar suffixes such as .EDU, .GOV, and .COM. Stakeholders that support NABP's application include many groups in the global pharmacy community. Among the coalition of stakeholders behind this initiative are the Alliance for Safe Online Pharmacies, Eli Lilly and Company, European Alliance for Access to Safe Medicines, Gilead Sciences, Inc, International Pharmaceutical Federation, INTERPOL,

Janssen Pharmaceuticals, Inc, LegitScript, Merck/MSD, National Association of Pharmacy Regulatory Authorities, and state boards of pharmacy.

For more information about NABP and the .PHARMACY application, visit *www.nabp.net/programs/pharmacy/pharmacy-and-nabp.*

NABP is the independent, international, and impartial Association that assists its member boards and jurisdictions in developing, implementing, and enforcing uniform standards for the purpose of protecting the public health.

ATTACHMENT 5

Strategic Planning: Enforcement

Success Indicators		Related Performance Measures	Acceptance Parameters	Actual Percentage Green Light Status	Explanation
1A	Complete all desk investigations within 120 days.	[CP, CC, EF, QE, RC]	93% 75% 74%	58%	Cases with multiple offenses take longer to investigate. In addition to relying on other agencies to provide documents as well as staff vacancies.
1B	Open all complaints within 10 days.	[CP, CC, EF, QE, RC]	90% 76% 75%	53%	Staff vacancy in complaint unit prevented the board from opening complaints within 10 days.
1C	Review all investigations within 30 days.	[CP, CC, EF, QE, RC]	97% 94% 93%	n/a	Under Development
1D	Complete all field investigations within 120 days.	[CP, CC, EF, QE, RC]	94% 75% 74%	44%	Inspector vacancies and new inspector training prevented inspector staff to complete investigations timely.
1E	Close all Board investigations and mediations within 180 days.	[CP, CC, EF, QE, RC]	97% 94% 93%	38%	Inspector vacancies and new inspector training prevented inspector staff to complete investigations timely.
1F	Issue citations and fines within 30 days.	[CP, CC, EF, QE, RC]	96% 92% 91%	16%	Due to the number of cases to be split and issued there was a delay in issuing citations.

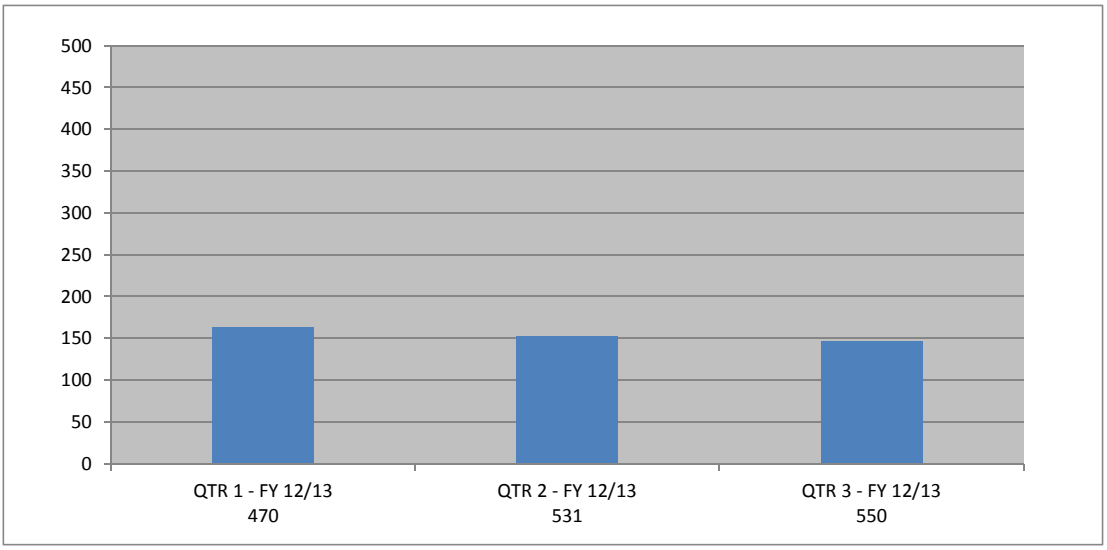
Strategic Planning: Enforcement

1G	Issue letters of admonishment within 30 days.	[CP, CC, EF, QE, RC]	○ 98% ○ 95% ● 94%	55%	Due to the number of cases to be split and issued there was a delay in issuing letters of admonishments.
1H	Complete all field investigations for cases involving drug abuse within 60 days.	[CP, HE, QE, RC]	○ 90% ○ 80% ○ 70%	n/a	Under Development
1I	Refer all cases to the AG's office within 10 days.	[CP, QE, RC]	○ 97% ○ 82% ● 81%	41%	Due to staff absences and the volume of cases to be referred, cases were not sent over within 10 days or less.
1J	Secure pleadings from AG's office within 90 days after referral.	[CP, QE, RC]	○ 96% ○ 82% ● 81%	33%	The board relies on the deputies from the Attorney Generals Office to forward pleadings within 90 days. Staff workload has prevented follow ups with the AGs Office.
1K	Inspect 100 percent of all licensed facilities once every three years by June 30, 2015.	[CP, QE, RC]	○ 90% ○ 80% ○ 70%	n/a	This section is still under development however the board conducted 472 inspections this quarter.
1L	Review draft pleadings within 30 days.	[CP, QE, RC]	○ 90% ○ 88% ● 87%	9%	Due to the high volume of workload this objective is not currently being met.
1M	Perform quarterly status reports for all referral cases pending.	[CP, QE, RC]	○ 90% ○ 80% ● 70%	1%	Workload with mail votes and board packet preparation did not allow analyst to perform this function.

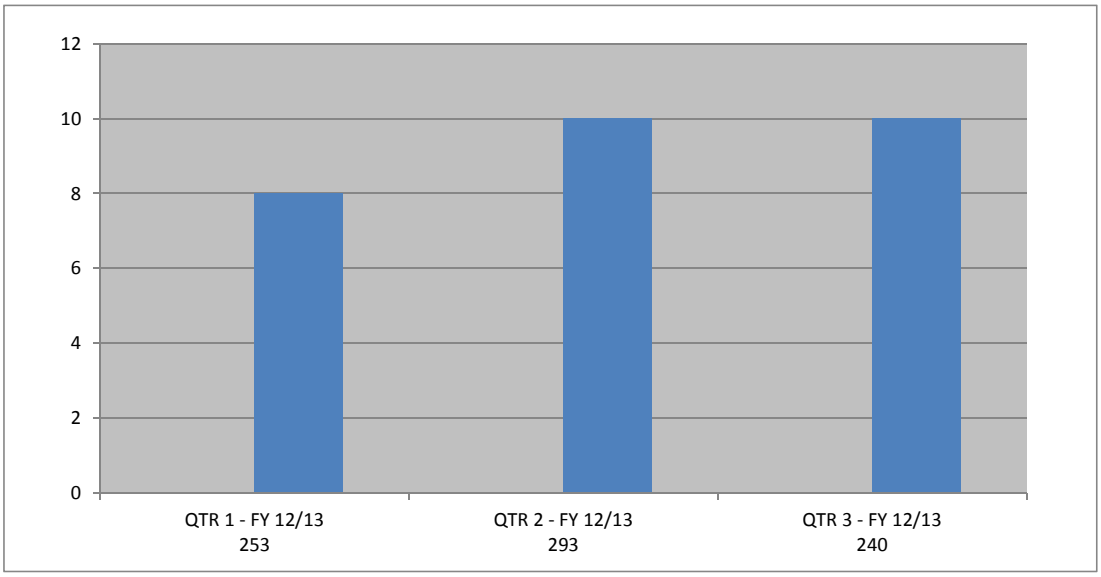
Strategic Planning: Enforcement

1N	Secure mail votes on all decisions within 30 days of receipt.	[CP, QE, RC]	○ 97% ○ 91% ● 90%	36%	Delay in sending and securing votes to and from board members.
1O	Complete petitions to revoke probation cases within 30 days.	[CP, QE, RC]	○ 98% ○ 95% ● 94%	2%	High volume of staff workload has prevented the analyst to complete these cases timely.
1P	Quarterly evaluate 5% of the Pharmacist Recovery Program (PRP) participants to ensure the PRP Contractor is in compliance with the contract.	[CP, QE, RC]	○ 98% ○ 95% ● 94%	0%	Staff manager training in complaint unit did not allow manager to perform this task.
1Q	Pursue disciplinary action, within 10 days, on a licensee closed a public risk from the Pharmacists Recovery Program.	[CP, QE, RC]	● 98% ○ 95% ○ 94%	100%	

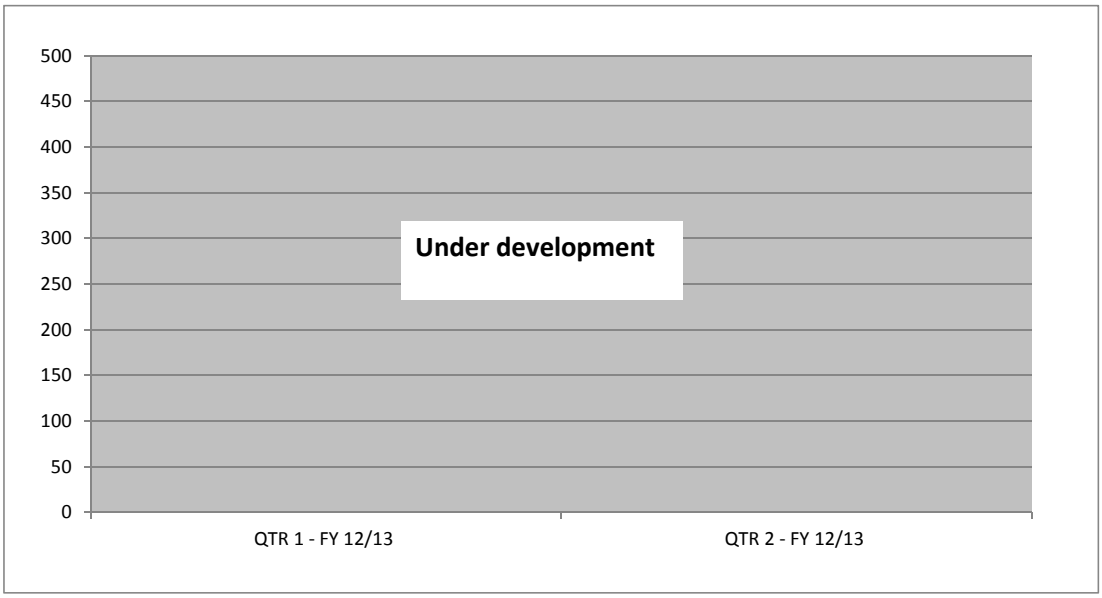
1A. Complete all desk investigations within 120 days.
(Recorded as number of cases submitted)



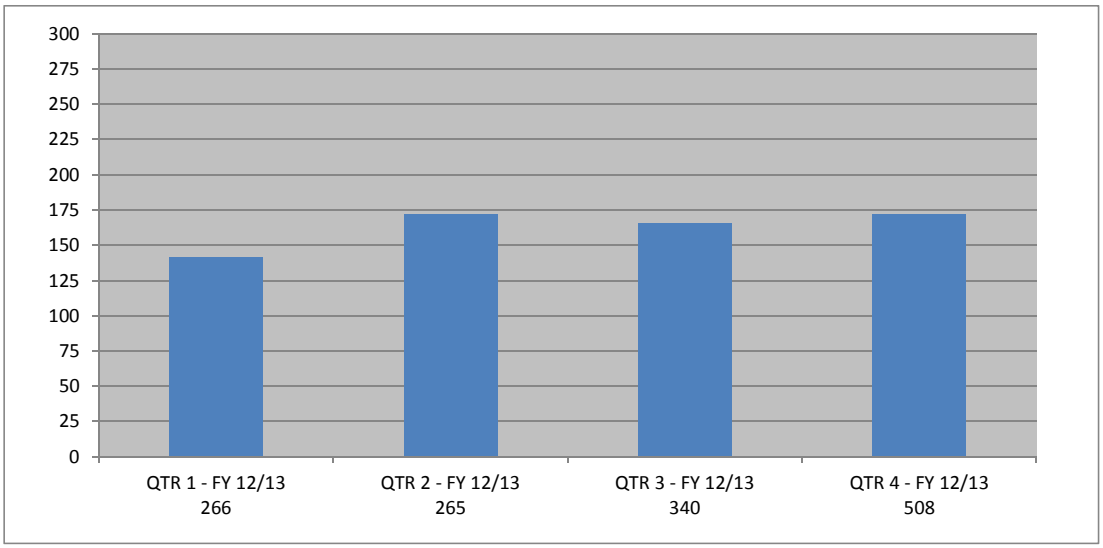
1B. Open all consumer complaints within 10 days.
(Recorded as number of cases opened)



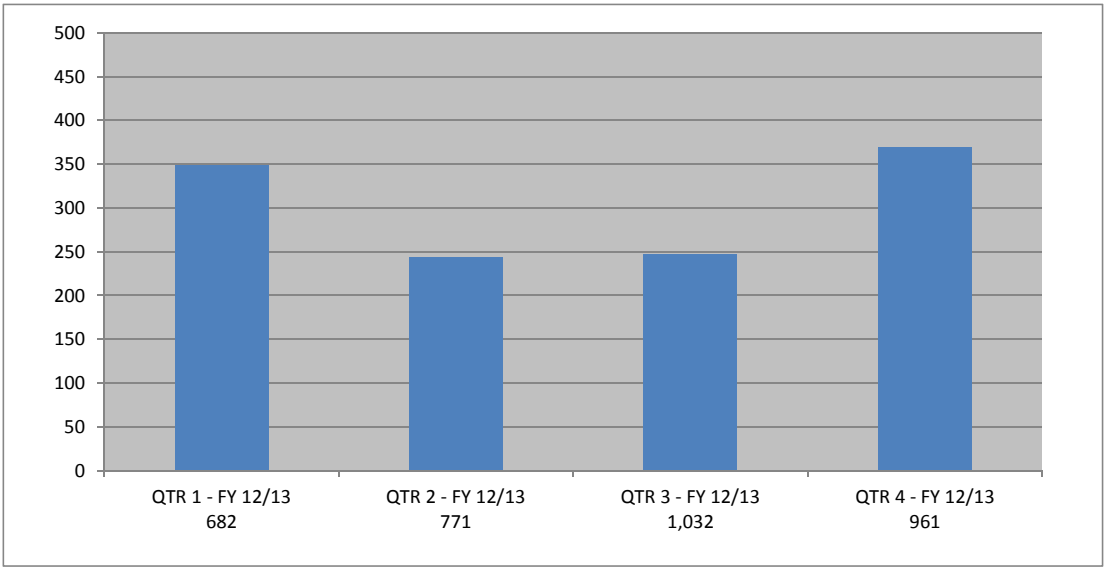
1C. Review all investigations within 30 days.
(Recorded as number of cases reveiwed)



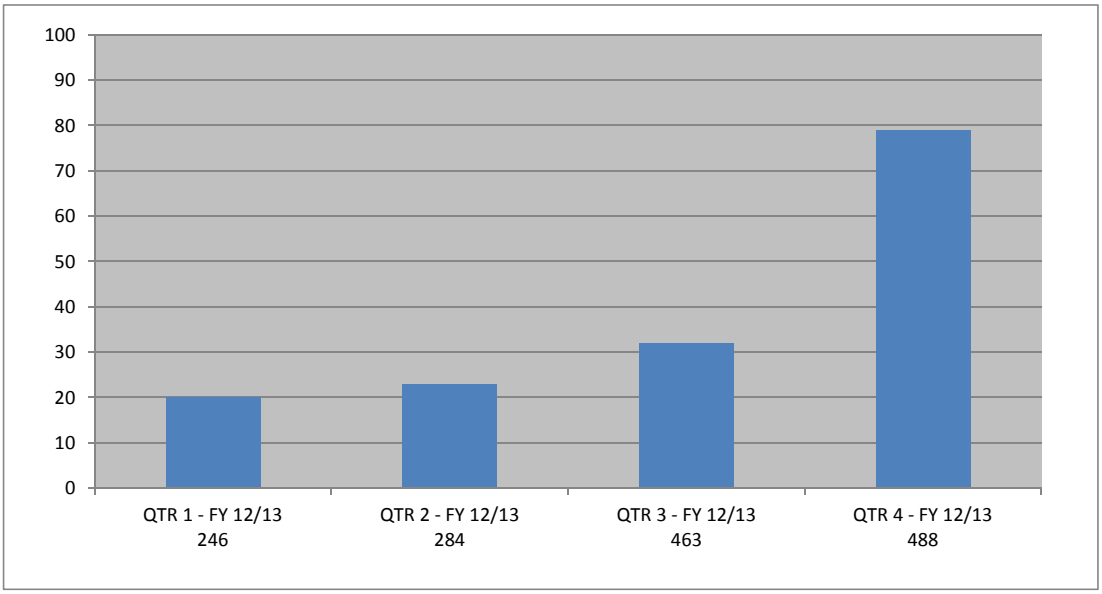
1D. Complete all field investigations within 120 days.
(Recorded as number of cases submitted)



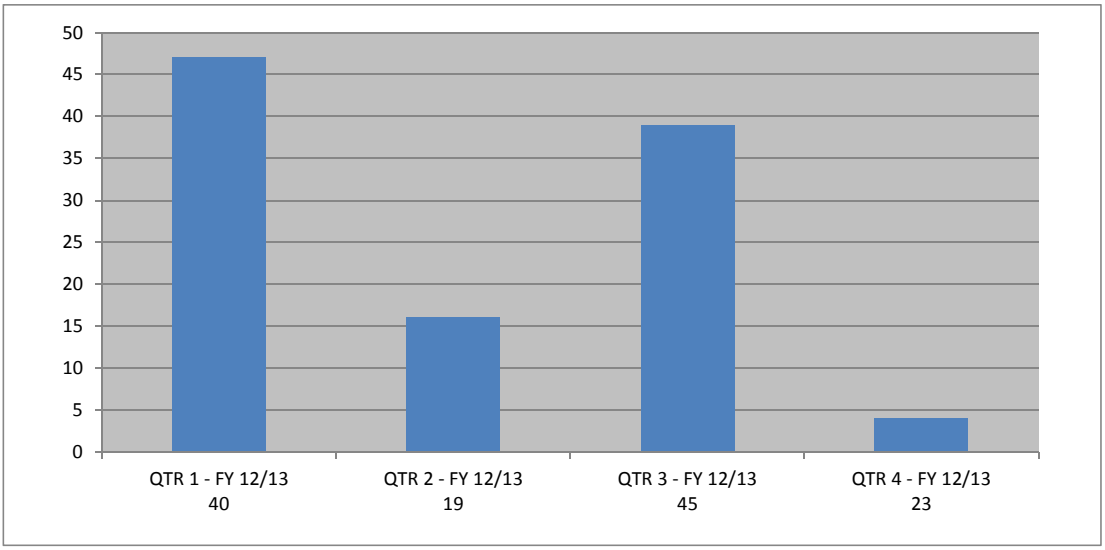
1E. Close all Board investigations and mediations within 180 days.
(Recorded as number of cases closed)



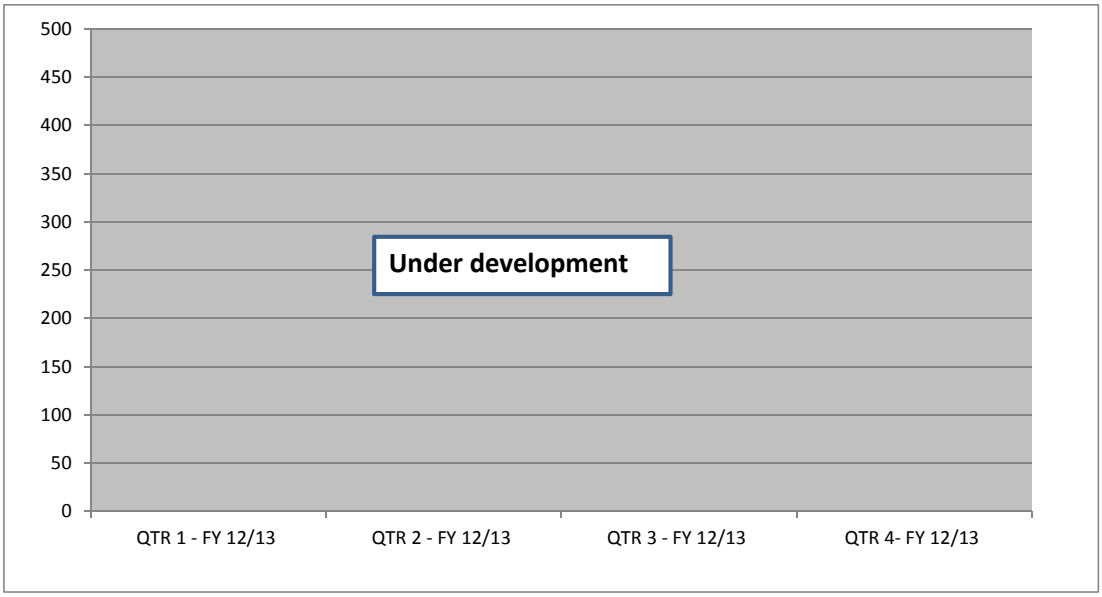
1F. Issue citations and fines within 30 days.
(Recorded as number of citations issued)



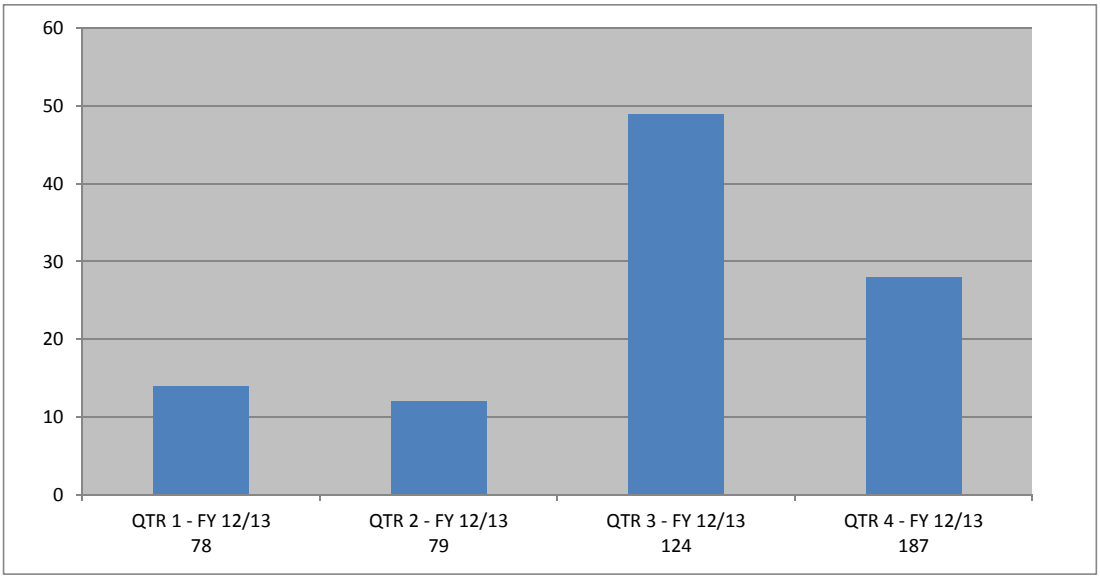
1G. Issue letters of admonishiment within 30 days.
(Recorded as number of letters of admonishment issued)



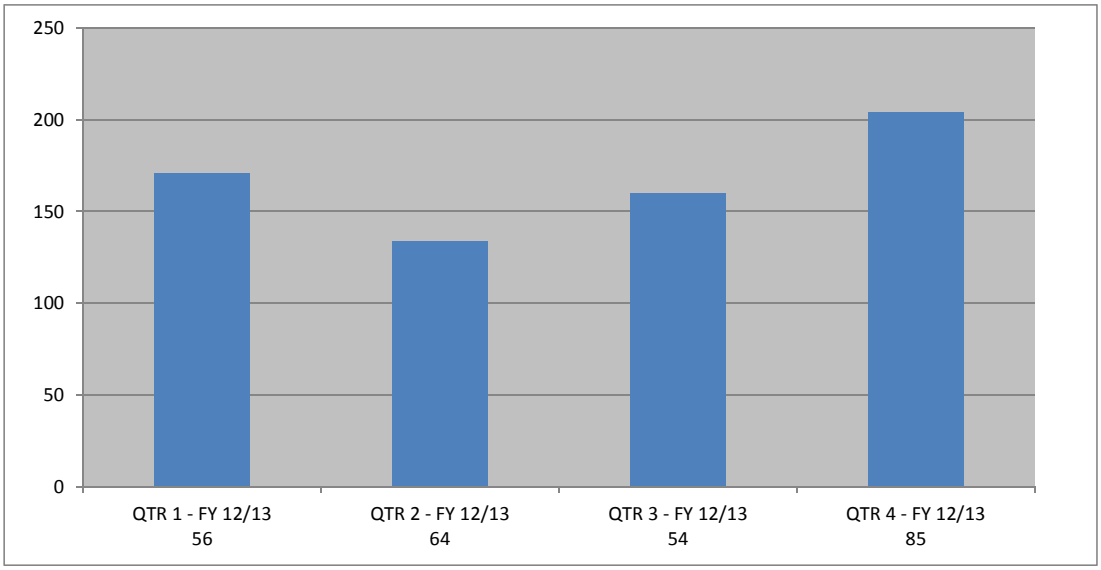
1H. Complete all field investigations for cases involving drug abuse within 60 days.



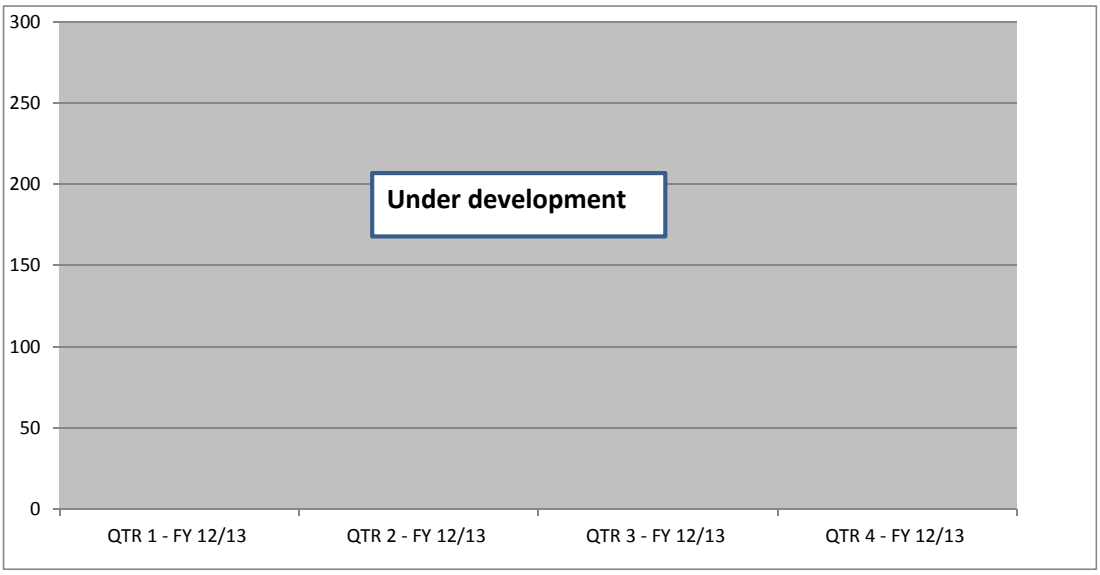
1I. Refer all cases to the AG's Office within 10 days.
(Recorded as number of cases referred)



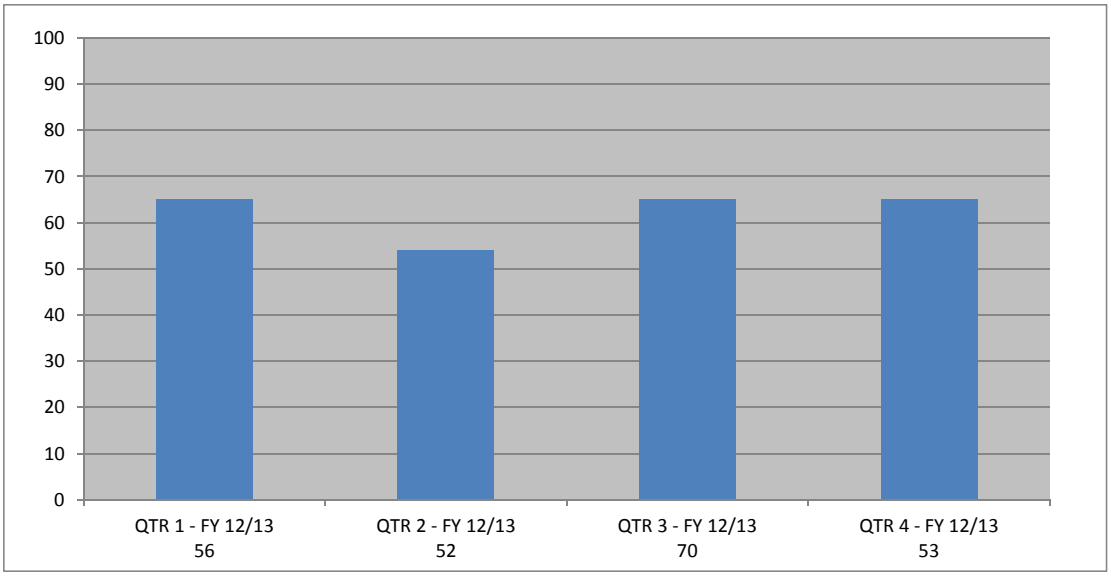
1J. Secure pleadings from AG's Office within 90 days after referral.
(Recorded as number of pleadings received)



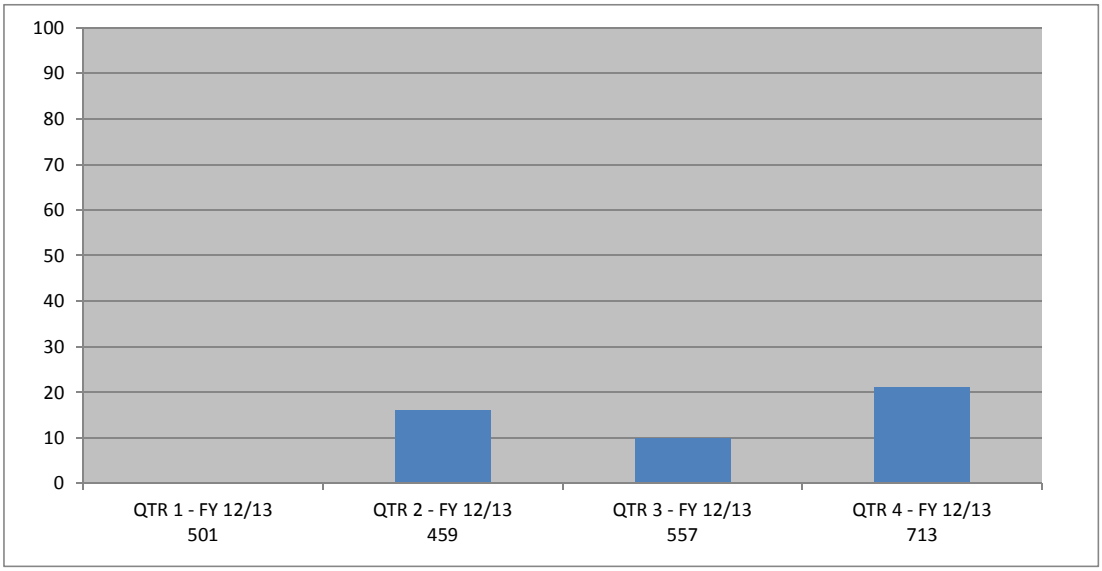
1K. Inspect 100 percent of all licensed facilities once every three years by June 30, 2015.



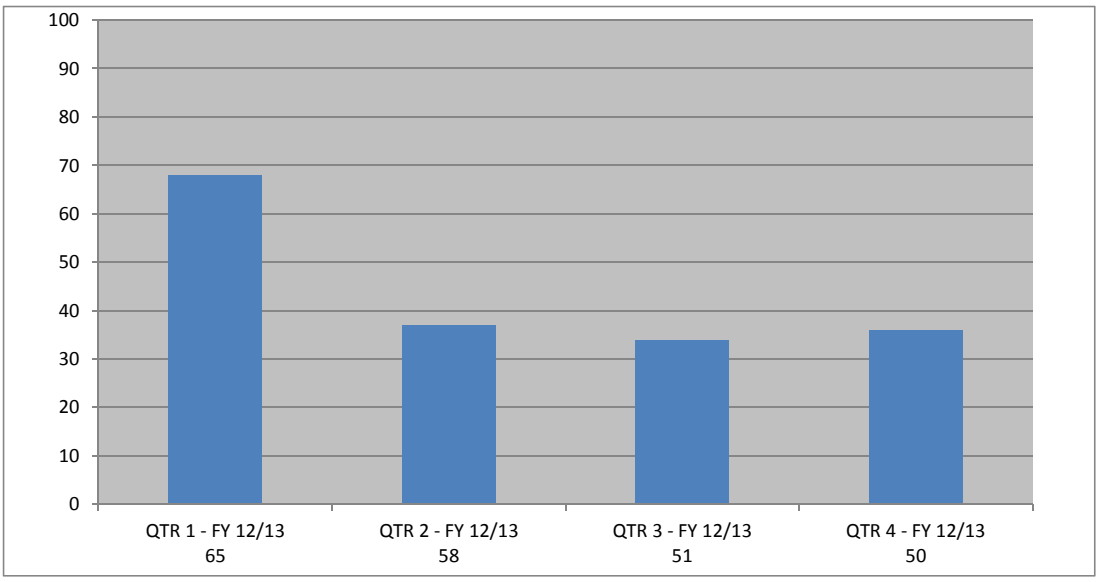
1L. Review draft pleadings within 30 days.
(Recorded as number of pleadings filed)



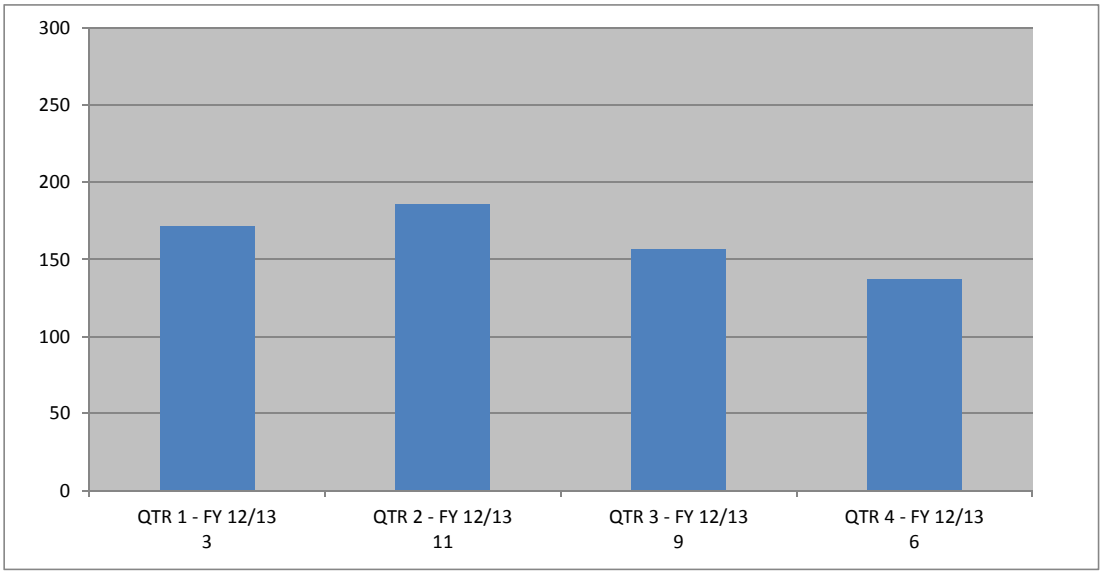
1M. Perform quarterly status reports for all referral cases pending.
(Recorded as number of cases pending over 90 days.



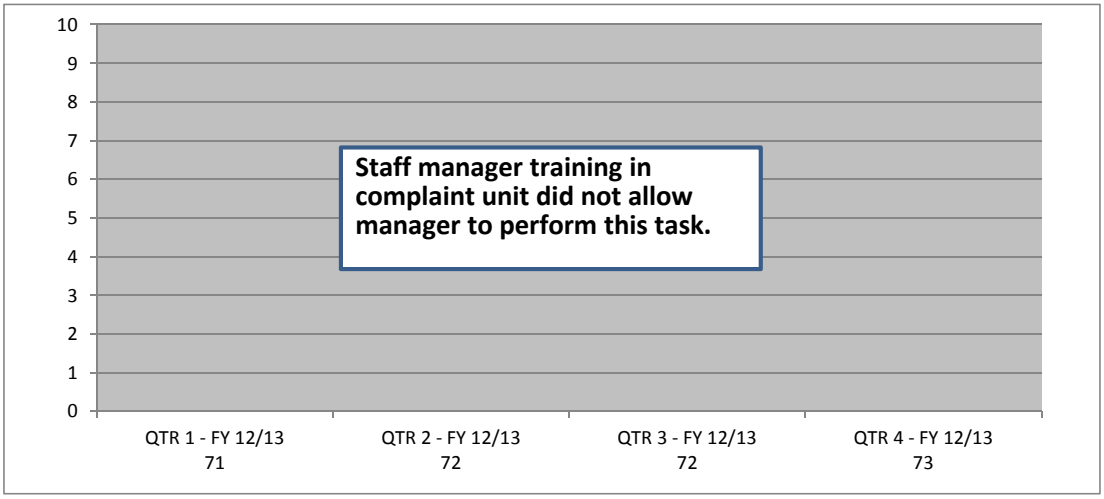
1N. Secure mail votes on all decisions within 30 days of receipt.
(Recorded as number of decisions received for mail vote)



1O. Complete petitions to revoke probation within 30 days.
(Recorded as number of cases submitted)

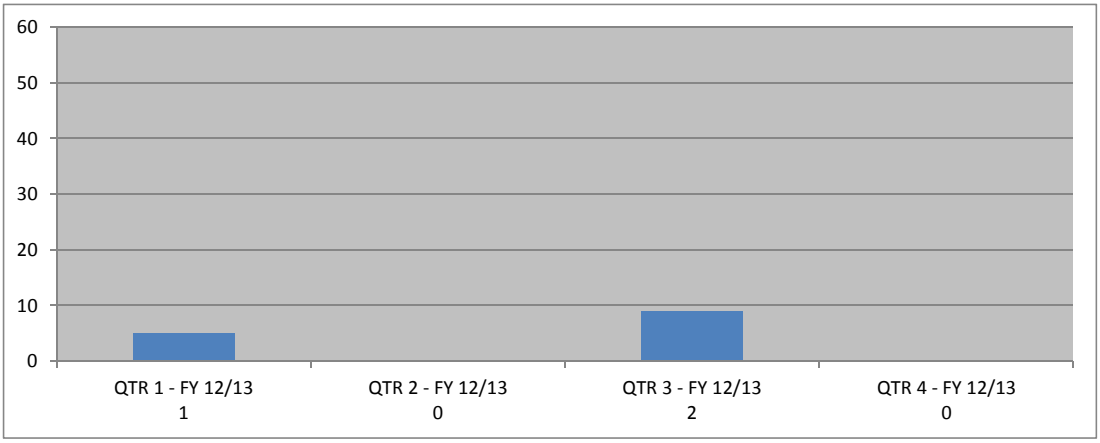


1P. Quarterly evaluate 5% of the Pharmacist Recovery Program (PRP) participants to ensure the PRP Contractor is in compliance with the contract.
(Recorded as number of participants in the PRP.)



1Q. Pursue disciplinary action, within 10 days, on a licensee closed a public risk from the Pharmacists Recovery Program.

(Recorded as number of participants closed a public risk)



ATTACHMENT 6

Board of Pharmacy Enforcement Statistics
Fiscal Year 2012/2013

Workload Statistics	July-Sept	Oct-Dec	Jan-Mar	Apr-June	Total 12/13
Complaints/Investigations					
Received	674	753	651	856	2934
Closed	585	610	926	1059	3180
4301 letters	40	34	47	24	145
Pending (at the end of quarter)	2193	2362	2198	1934	1934
Cases Assigned & Pending (by Team) at end of quarter*					
Compliance / Routine Team	819	981	833	946	946
Drug Diversion/Fraud	380	321	420	231	231
Probation/PRP	107	98	117	93	93
Mediation/Enforcement **	243	337	370	222	222
Criminal Conviction	644	625	458	442	442
Application Investigations					
Received	220	177	164	169	730
Closed					
Approved	162	144	34	91	431
Denied	41	31	39	37	148
Total ***	283	226	224	173	906
Pending (at the end of quarter)	235	191	136	134	134
Letter of Admonishment (LOA) / Citation & Fine					
LOAs Issued	53	19	45	28	145
Citations Issued	249	284	463	487	1483
Total Fines Collected ****	$831,660.29	$450,459.00	$489,622.15	$518,445.86	$2,290,187.30

* This figure includes reports submitted to the supervisor and cases with SI awaiting assignment.

** This figure include reports submitted to the citation and fine unit, AG referral, as well as cases assigned to enf. Staff

*** This figure includes withdrawn applications.

****Fines collected (through 6/30/2013 and reports in previous fiscal year.)

Board of Pharmacy Enforcement Statistics
Fiscal Year 2012/2013

Workload Statistics	July-Sept	Oct-Dec	Jan-Mar	Apr-June	Total 12/13
Administrative Cases (by effective date of decision)					
Referred to AG's Office*	149	125	141	218	633
Accusations Filed	42	38	52	31	163
Statement of Issues Filed	14	16	17	13	60
Petitions to Revoke Filed	5	3	2	5	15
Pending					
Pre-accusation	189	214	267	403	403
Post Accusation	223	203	228	211	211
Total*	501	459	557	713	713
Closed					
Revocation					
Pharmacist	2	1	5	4	12
Intern Pharmacist	0	0	0	0	0
Pharmacy Technician	20	26	13	22	81
Designated Representative	1	0	0	0	1
Wholesaler	1	0	0	0	1
Pharmacy	2	3	0	0	5
Revocation,stayed; suspension/probation					
Pharmacist	2	4	1	3	10
Intern Pharmacist	0	0	0	0	0
Pharmacy Technician	0	0	0	0	0
Designated Representative	0	0	0	0	0
Wholesaler	0	0	0	0	0
Pharmacy	0	0	0	1	1
Revocation,stayed; probation					
Pharmacist	4	3	2	3	12
Intern Pharmacist	0	0	0	0	0
Pharmacy Technician	3	7	5	10	25
Designated Representative	0	0	0	0	0
Wholesaler	0	0	0	0	0
Pharmacy	0	1	0	2	3
Surrender/Voluntary Surrender					
Pharmacist	2	2	0	4	8
Intern Pharmacist	0	1	0	0	1
Pharmacy Technician	5	6	2	10	23
Designated Representative	0	0	0	0	0
Wholesaler	0	0	1	0	1
Pharmacy	0	3	1	2	6

Board of Pharmacy Enforcement Statistics
Fiscal Year 2012/2013

Workload Statistics	July-Sept	Oct-Dec	Jan-Mar	Apr-June	Total 12/13
Public Reproval/Reprimand					
Pharmacist	1	0	0	0	1
Intern Pharmacist	0	0	0	0	0
Pharmacy Technician	0	0	0	0	0
Designated Representative	0	0	0	0	0
Wholesaler	0	0	0	0	0
Pharmacy	0	0	0	0	0
Cost Recovery Requested**	$113,913.52	$257,487.00	$98,451.00	$406,284.25	$876,135.77
Cost Recovery Collected**	$149,899.65	$217,472.09	$141,213.29	$67,555.94	$576,140.97

* This figure includes Citation Appeals

** This figure includes administrative penalties

Immediate Public Protection Sanctions					
Interim Suspension Order	0	0	0	0	0
Automatic Suspension / Based on Conviction	0	0	3	3	6
Penal Code 23 Restriction	0	3	0	0	3
Cease & Desist - Sterile Compounding	1	3	0	3	7

Probation Statistics

Licenses on Probation					
Pharmacist	127	129	123	122	123
Intern Pharmacist	4	4	3	3	3
Pharmacy Technician	49	54	57	54	57
Designated Representative	2	3	2	2	2
Pharmacy	26	25	6	25	6
Wholesaler	4	4	4	4	4
Probation Office Conferences	21	26	35	41	123
Probation Site Inspections	67	53	61	27	208
Successful Completion	7	3	6	6	22
Probationers Referred to AG for non-compliance	4	3	13	7	27

As part of probation monitoring, the board requires licensees to appear before the supervising inspector at probation office conferences. These conferences are used as 1) an orientation to probation and the specific requirements of probation at the onset, 2) to address areas of non-compliance when other efforts such as letters have failed, and 3) when a licensee is scheduled to end probation.

As of June 30, 2013.

Board of Pharmacy Enforcement Statistics
Three Year Comparison

Workload Statistics	Total 10/11	Total 11/12	Total 12/13
Complaints/Investigations			
Received	2425	2492	2934
Closed	2572	2091	3180
Pending (at the end of fiscal year)	1324	1941	1934
Cases Under Investigation (by Team) at end of fiscal year*			
Compliance / Routine Team	450	670	946
Drug Diversion/Fraud	175	276	231
Probation/PRP	78	87	93
Mediation/Enforcement**	75	214	222
Criminal Conviction	524	642	442
Application Investigations			
Received	798	1089	730
Closed			
Approved	538	624	431
Denied	136	112	148
Total***	1021	1033	906
Pending (at the end of quarter)	223	409	134
Letter of Admonishment (LOA) / Citation & Fine			
LOAs Issued	186	147	145
Citations Issued	1043	985	1483
Total Fines Collected ****	$1,173,552.00	$1,259,642.06	$2,290,187.30

* This figure includes reports submitted to the supervisor and cases with SI awaiting assignment.

** This figure include reports submitted to the citation and fine unit, AG referral, as well as cases assigned to Enforcement Staff

*** This figure includes withdrawn applications.

**** Fines collected (through 6/30/2013 and reports in previous fiscal year.)

Board of Pharmacy Enforcement Statistics
Three Year Comparison

Workload Statistics	Total 10/11	Total 11/12	Total 12/13
Administrative Cases (by effective date of decision)			
Referred to AG's Office*	475	304	633
Pleadings Filed	305	231	238
Pending			
Pre Accusation	188	194	403
Post Accusation	257	224	211
Total *	520	461	713
Closed			
Revocation			
Pharmacist	9	11	12
Intern Pharmacist	0	1	0
Pharmacy Technician	127	98	82
Designated Representative	0	2	1
Wholesaler	0	0	1
Pharmacy	0	1	5
Revocation,stayed; suspension/probation			
Pharmacist	23	17	10
Intern Pharmacist	0	0	0
Pharmacy Technician	26	3	0
Designated Representative	0	0	0
Wholesaler	0	0	0
Pharmacy	0	0	1
Revocation,stayed; probation			
Pharmacist	15	18	12
Intern Pharmacist	0	1	0
Pharmacy Technician	16	23	25
Designated Representative	1	1	0
Wholesaler	1	1	0
Pharmacy	9	16	3
Surrender/Voluntary Surrender			
Pharmacist	8	12	8
Intern Pharmacist	0	0	1
Pharmacy Technician	35	32	23
Designated Representative	0	2	0
Wholesaler	0	1	1
Pharmacy	3	2	6

Board of Pharmacy Enforcement Statistics
Three Year Comparison

Workload Statistics	Total 10/11	Total 11/12	Total 12/13
Public Reproval/Reprimand			
Pharmacist	0	1	1
Intern Pharmacist	0	0	0
Pharmacy Technician	0	1	0
Designated Representative	0	0	0
Wholesaler	0	0	0
Pharmacy	0	0	0
Cost Recovery Requested**	$1,011,606.20	$1,258,291.20	$876,135.77
Cost Recovery Collected**	$422,530.21	$469,718.56	$576,140.97

* This figure includes citation appeals

** This figure includes adminstrative penalties

Immediate Public Protection Sanctions			
Interim Suspension Order	2	3	0
Automatic Suspension / Based on Conviction	0	9	6
Penal Code 23 Restriction	4	2	3
Cease & Desist - Sterile Compounding	0	3	7

Probation Statistics

Licenses on Probation			
Pharmacist	110	131	123
Intern Pharmacist	5	4	3
Pharmacy Technician	26	50	57
Designated Representative	2	2	2
Wholesaler	2	5	6
Pharmacy	17	27	4
Probation Office Conferences	141	147	123
Probation Site Inspections**	231	268	208
Successful Completion	19	16	22
Probationers Referred to AG for non-compliance	9	3	27

As part of probation monitoring, the board requires licensees to appear before the lead inspector at probation office conferences. These conferences are used as 1) an orientation to probation and the specific requirements of probation at the onset, 2) to address areas of non-compliance when other efforts such as letters have failed, and 3) when a licensee is scheduled to end probation.

SB 1441 – Program Statistics

Pharmacist Recovery Program (PRP)

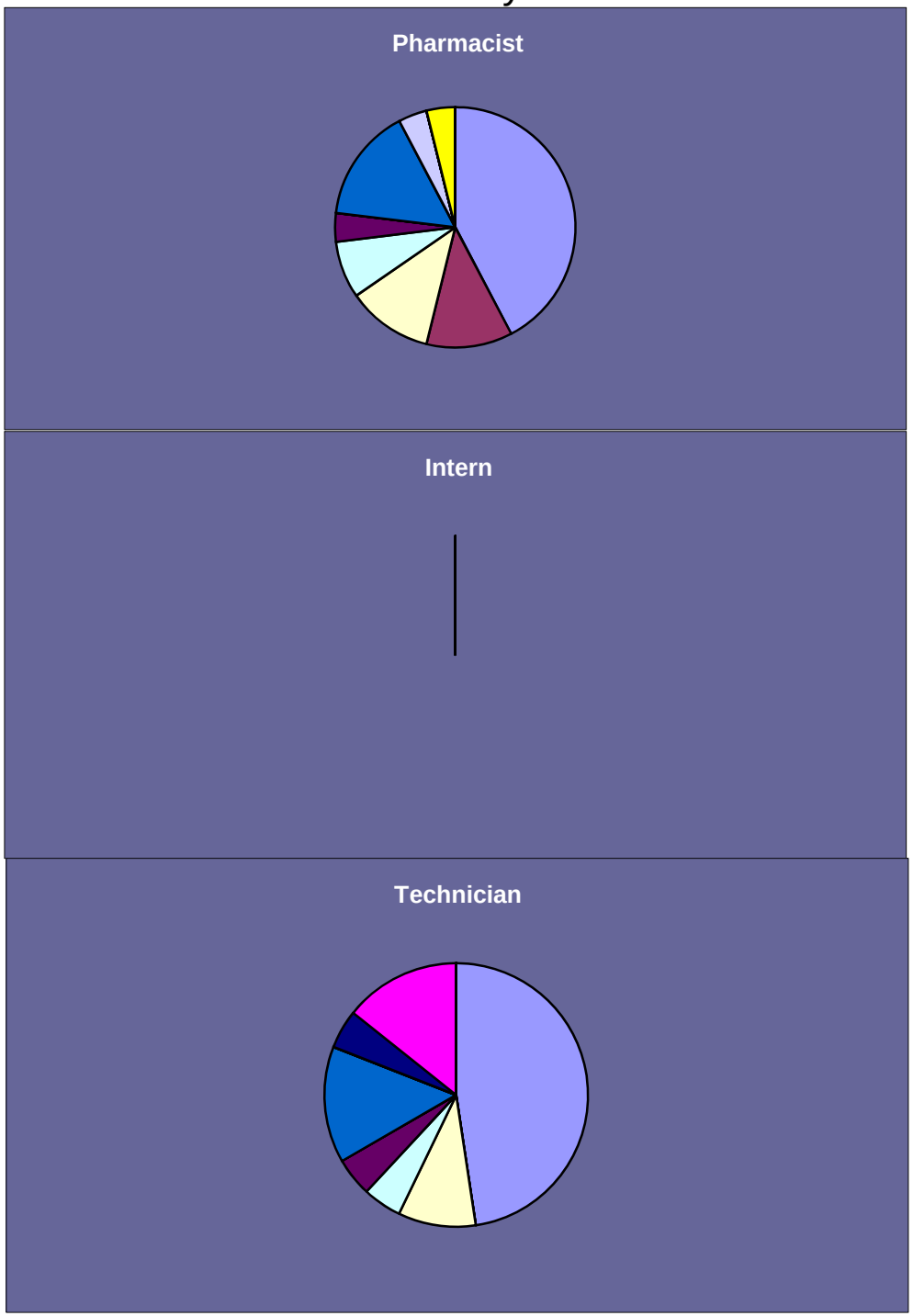
Board of Pharmacy	July Sep	Oct – Dec	Jan-Mar	Apr Jun	Total 12/13
PRP Self-Referrals	1	2			3
PRP Board Referrals	2	4	1	2	9
PRP Under Investigation	2	2	1	1	6
PRP In Lieu Of					
PRP Intakes	5	8	2	3	18
New Probationers					
Pharmacists	3	4	2	1	10
Interns					
Technicians	3	7	2	4	16
Total PRP Participants	71	72	72	73	N/A
Contracts Reviewed	65	73	67	73	278
Total Probationers	125	118	119	112	N/A
Inspections Completed	84	79	61	68	292
Referrals to Treatment					
Referrals to Treatment	3	5			8
Drug Test Ordered	1175	1223	1265	1214	4877
Drug Tests Conducted	986	987	1068	1062	4103
Relapsed					
Relapsed	2	1	1	3	7
Major Violation Actions					
Cease Practice/Suspension	1	2	1	3	7
Termination - PRP	1		2	1	4
Referral for Discipline	4			5	9
Exit from PRP or Probation					
Successful Completion	9	6	7	9	31
Termination - Probation	1	2	1	3	7
Voluntary Surrender	8	5	10	10	33
Surrender as a result of PTR			1	1	1
Public Risk	1		2	1	4
Non-compliance	19	7	6	9	41
Other	1	1		1	3
Number of Patients Harmed					
Drug of Choice at PRP Intake or Probation					
Pharmacists	**July-Sep**	**Oct-Dec**	**Jan-Mar**	**Apr-Jun**	Total 12/13
Alcohol	5	4	1	1	11
Ambien	1	2			3
Opiates		2	1		3
Hydrocodone	1			1	2
Oxycodone		1			1
Morphine	1				1
Benzodiazepines	2			2	4
Barbiturates		1			1
Marijuana					
Heroin					
Cocaine	1				1

SB 1441 – Program Statistics

Pharmacist Recovery Program (PRP)

Board of Pharmacy	July Sep	Oct – Dec	Jan-Mar	Apr Jun	Total 12/13
Methamphetamine					
Pharmaceutical Amphetamine					
Phentermine					
Methadone					
Zolpidem Tartrate					
Hydromorphone					
Promethazine w/Codeine					
Intern Pharmacists	**July-Sep**	**Oct-Dec**	**Jan-Mar**	**Apr-Jun**	Total 12/13
Alcohol					
Opiates					
Hydrocodone					
Oxycodone					
Benzodiazepines					
Barbiturates					
Marijuana					
Heroin					
Cocaine					
Methamphetamine					
Pharmaceutical Amphetamine					
Phentermine					
Methadone					
Zolpidem Tartrate					
Hydromorphone					
Promethazine w/Codeine					
Pharmacy Technicians	**July-Sep**	**Oct-Dec**	**Jan-Mar**	**Apr-Jun**	Total 12/13
Alcohol	1	4	1	4	10
Opiates					
Hydrocodone		1	1		2
Oxycodone		1			1
Benzodiazepines	1				1
Barbiturates					
Marijuana		1		2	3
Heroin					
Cocaine		1			1
Methamphetamine	1	2			3
Pharmaceutical Amphetamine					
Phentermine					
Methadone					
Zolpidem Tartrate					
Hydromorphone					
Promethazine w/Codeine					
Pharmacist Recovery Program	**July-Sep**	**Oct-Dec**	**Jan-Mar**	**Apr-Jun**	Total 12/13
Participant Files Audited					

Drug Of Choice - Data entered from July 2012 to June 2013



1 Alcohol
2 Opiates
3 Hydrocodone
4 Oxycodone
5 Benzodiazepines
6 Barbiturates
7 Marijuana
8 Heroin
9 Cocaine
10 Methamphetamine
11 Pharmaceutical Amphetamine

Printed on 7/15/2013

ATTACHMENT 7

California LEGISLATIVE INFORMATION

SB-294 Sterile drug products. (2013-2014)

CALIFORNIA LEGISLATURE— 2013–2014 REGULAR SESSION

SENATE BILL **No. 294**

Introduced by Senator Emmerson

February 15, 2013

An act to amend Sections 4127.1, 4127.2, and 4400 of, to amend the heading of Article 7.5 (commencing with Section 4127) of Chapter 9 of Division 2 of, and to repeal and add Section 4127 of, the Business and Professions Code, relating to pharmacy.

LEGISLATIVE COUNSEL'S DIGEST

SB 294, as introduced, Emmerson. Sterile drug products.

The Pharmacy Law provides for the licensure and regulation of pharmacists and pharmacy corporations in this state by the California State Board of Pharmacy. Existing law requires the board to adopt regulations establishing standards for compounding injectable sterile drug products in a pharmacy. Existing law requires pharmacies to obtain a license from the board, subject to annual renewal, in order to compound injectable sterile drug products. A similar licensing requirement applies to nonresident pharmacies compounding injectable sterile drug products for shipment into California. A violation of the Pharmacy Law is a crime.

This bill would expand these provisions to prohibit a pharmacy from compounding or dispensing, and a nonresident pharmacy from compounding for shipment into this state, sterile drug products for injection, administration into the eye, or inhalation, unless the pharmacy has obtained a sterile compounding pharmacy license from the board. The bill would specify requirements for the board for issuance or renewal of a license, and requirements for the pharmacy as a licensee. By adding additional requirements to the Pharmacy Law concerning sterile drug products, the violation of which is a crime, the bill would impose a state-mandated local program.

Existing law specifies the fee for issuance or renewal of a nongovernmental license to compound sterile drug products.

This bill would provide that the fee for a nonresident sterile compounding pharmacy license shall also require payment of the travel expenses incurred by the board in inspecting the pharmacy at least once annually.

The California Constitution requires the state to reimburse local agencies and school districts for certain costs mandated by the state. Statutory provisions establish procedures for making that reimbursement.

This bill would provide that no reimbursement is required by this act for a specified reason.

Vote: majority Appropriation: no Fiscal Committee: yes Local Program: yes

THE PEOPLE OF THE STATE OF CALIFORNIA DO ENACT AS FOLLOWS:

SECTION 1. The heading of Article 7.5 (commencing with Section 4127) of Chapter 9 of Division 2 of the Business and Professions Code is amended to read:

Article 7.5. ~~Injectable~~ Sterile Drug Products

SEC. 2. Section 4127 of the Business and Professions Code is repealed.

~~4127.The board shall adopt regulations establishing standards for compounding injectable sterile drug products in a pharmacy.~~

SEC. 3. Section 4127 is added to the Business and Professions Code, to read:

4127. A pharmacy that compounds sterile drug products for injection, administration into the eye, or inhalation shall possess a sterile compounding pharmacy license as provided in this article before dispensing the compounded medication.

SEC. 4. Section 4127.1 of the Business and Professions Code is amended to read:

4127.1. (a) A pharmacy shall not compound ~~injectable~~ sterile drug products ~~in this state~~ unless the pharmacy has obtained a *sterile compounding pharmacy* license from the board pursuant to this section. The license shall be renewed annually and is not transferable.

(b) A license to compound ~~injectable~~ sterile drug products ~~may only~~ *shall* be issued ~~for~~ *only to* a location that is licensed as a pharmacy. Furthermore, the license to compound ~~injectable~~ sterile drug products ~~may only~~ *shall* be issued *only* to the owner of the pharmacy ~~license~~ *licensed* at that location. A license to compound ~~injectable~~ sterile drug products ~~may~~ *shall* not be issued until the location is inspected by the board and found in compliance with this article and regulations adopted by the board.

(c) A license to compound ~~injectable~~ sterile drug products ~~may~~ *shall* not be *issued or* renewed until the ~~location has been inspected by the board and found to be in compliance with this article and regulations adopted by the board.~~ *board does all of the following:*

~~(d)Pharmacies operated by entities that are licensed by either the board or the State Department of Public Health and that have current accreditation from the Joint Commission on Accreditation of Healthcare Organizations, or other private accreditation agencies approved by the board, are exempt from the requirement to obtain a license pursuant to this section.~~

(1) Performs an onsite inspection of the premises, and any deficiencies noted are corrected.

(2) Reviews a current copy of the pharmacy's policies and procedures for sterile compounding.

(3) Reviews the pharmacy's completed self-assessment form required by Section 1735.2 of Title 16 of the California Code of Regulations.

(4) Is provided with copies of all inspection reports conducted of the pharmacy's premises, and any reports from a private accrediting agency, conducted in the prior 12 months documenting the pharmacy's operations.

(5) Receives a list of all sterile medications compounded by the pharmacy since the last license renewal.

(d) A pharmacy licensed pursuant to this section shall do all of the following:

(1) Provide to the board a copy of any disciplinary or other action taken by another state within 10 days of the action.

(2) Notify the board within 10 days of the suspension of any accreditation held by the pharmacy.

(3) Provide to the board, within 24 hours, any recall notice issued by the pharmacy for sterile drug products it has compounded.

(e) Adverse effects reported or potentially attributable to a pharmacy's sterile drug product shall be immediately reported to the board and the MedWatch program of the federal Food and Drug Administration.

~~(e)~~

(f) The reconstitution of a sterile powder shall not require a license pursuant to this section if both of the following are met:

(1) The sterile powder was obtained from a manufacturer.

(2) The drug is reconstituted for administration to patients by a health care professional licensed to administer drugs by injection pursuant to this division.

SEC. 5. Section 4127.2 of the Business and Professions Code is amended to read:

4127.2. (a) A nonresident pharmacy ~~may~~ *shall* not compound ~~injectable~~ sterile drug products for shipment into ~~the State of California~~ *this state* without a *sterile compounding pharmacy* license issued by the board pursuant to this section. The license shall be renewed annually and shall not be transferable.

(b) A license to compound ~~injectable~~ sterile drug products ~~may only~~ *shall* be issued ~~for~~ *only to* a location that is licensed as a nonresident pharmacy. Furthermore, the license to compound ~~injectable~~ sterile drug products ~~may only~~ *shall* be issued *only* to the owner of the nonresident pharmacy ~~license~~ *licensed* at that location. A license to compound ~~injectable~~ sterile drug products ~~may~~ *shall* not be issued ~~or renewed until the board receives the following from the nonresident pharmacy:~~ *until the location is inspected by the board and found in compliance with this article and any regulations adopted by the board.*

~~(1)A copy of an inspection report issued by the pharmacy's licensing agency, or a report from a private accrediting agency approved by the board, in the prior 12 months documenting the pharmacy's compliance with board regulations regarding the compounding of injectable sterile drug products.~~

~~(2)A copy of the nonresident pharmacy's proposed policies and procedures for sterile compounding.~~

~~(c)Nonresident pharmacies operated by entities that are licensed as a hospital, home health agency, or a skilled nursing facility and have current accreditation from the Joint Commission on Accreditation of Healthcare Organizations, or other private accreditation agencies approved by the board, are exempt from the requirement to obtain a license pursuant to this section.~~

~~(d)This section shall become effective on the earlier of July 1, 2003, or the effective date of regulations adopted by the board pursuant to Section 4127.~~

(c) A license to compound sterile drug products shall not be issued or renewed until the board does all of the following:

(1) Performs an onsite inspection of the premises, and any deficiencies noted are corrected. The nonresident pharmacy shall be responsible for payment of reasonable travel expenses incurred by the board in connection with inspecting the pharmacy at least once annually pursuant to subdivision (v) of Section 4400.

(2) Reviews a current copy of the nonresident pharmacy's policies and procedures for sterile compounding.

(3) Reviews the pharmacy's completed self-assessment form required by Section 1735.2 of Title 16 of the California Code of Regulations.

(4) Is provided with copies of all inspection reports conducted of the nonresident pharmacy's premises, and any reports from a private accrediting agency, conducted in the prior 12 months documenting the nonresident pharmacy's operations.

(5) Receives a list of all sterile drug products compounded by the pharmacy within the prior 12 months.

(d) A pharmacy licensed pursuant to this section shall do all of the following:

(1) Provide to the board a copy of any disciplinary or other action taken by its state of residence or another state within 10 days of the action.

(2) Notify the board within 10 days of the suspension of any accreditation held by the pharmacy.

(3) Provide to the board, within 24 hours, any recall notice issued by the pharmacy for sterile drug products it has compounded that have been shipped into, or dispensed in, California.

(4) Advise the board of any complaint it receives from a provider, pharmacy, or patient in California.

(e) Adverse effects reported or potentially attributable to a nonresident pharmacy's sterile compounded drug products shall be immediately reported to the board and the MedWatch program of the federal Food and Drug Administration.

SEC. 6. Section 4400 of the Business and Professions Code is amended to read:

4400. The amount of fees and penalties prescribed by this chapter, except as otherwise provided, is that fixed by the board according to the following schedule:

(a) The fee for a nongovernmental pharmacy license shall be four hundred dollars ($400) and may be increased to five hundred twenty dollars ($520). The fee for the issuance of a temporary nongovernmental pharmacy permit shall be two hundred fifty dollars ($250) and may be increased to three hundred twenty-five dollars ($325).

(b) The fee for a nongovernmental pharmacy license annual renewal shall be two hundred fifty dollars ($250) and may be increased to three hundred twenty-five dollars ($325).

(c) The fee for the pharmacist application and examination shall be two hundred dollars ($200) and may be increased to two hundred sixty dollars ($260).

(d) The fee for regrading an examination shall be ninety dollars ($90) and may be increased to one hundred fifteen dollars ($115). If an error in grading is found and the applicant passes the examination, the regrading fee shall be refunded.

(e) The fee for a pharmacist license and biennial renewal shall be one hundred fifty dollars ($150) and may be increased to one hundred ninety-five dollars ($195).

(f) The fee for a nongovernmental wholesaler license and annual renewal shall be six hundred dollars ($600), and may be increased to seven hundred eighty dollars ($780). The application fee for any additional location after licensure of the first 20 locations shall be two hundred twenty-five dollars ($225) and may be increased to three hundred dollars ($300). A temporary license fee shall be five hundred fifty dollars ($550) and may be increased to seven hundred fifteen dollars ($715).

(g) The fee for a hypodermic license and renewal shall be one hundred twenty-five dollars ($125) and may be increased to one hundred sixty-five dollars ($165).

(h) (1) The fee for application, investigation, and issuance of license as a designated representative pursuant to Section 4053 shall be two hundred fifty-five dollars ($255) and may be increased to three hundred thirty dollars ($330).

(2) The fee for the annual renewal of a license as a designated representative shall be one hundred fifty dollars ($150) and may be increased to one hundred ninety-five dollars ($195).

(i) (1) The fee for the application, investigation, and issuance of a license as a designated representative for a veterinary food-animal drug retailer pursuant to Section 4053 shall be two hundred fifty-five dollars ($255) and may be increased to three hundred thirty dollars ($330).

(2) The fee for the annual renewal of a license as a designated representative for a veterinary food-animal drug retailer shall be one hundred fifty dollars ($150) and may be increased to one hundred ninety-five dollars ($195).

(j) (1) The application fee for a nonresident wholesaler's license issued pursuant to Section 4161 shall be six hundred dollars ($600) and may be increased to seven hundred eighty dollars ($780).

(2) For nonresident wholesalers who have 21 or more facilities operating nationwide the application fees for the first 20 locations shall be six hundred dollars ($600) and may be increased to seven hundred eighty dollars ($780). The application fee for any additional location after licensure of the first 20 locations shall be two hundred twenty-five dollars ($225) and may be increased to three hundred dollars ($300). A temporary license fee shall be five hundred fifty dollars ($550) and may be increased to seven hundred fifteen dollars ($715).

(3) The annual renewal fee for a nonresident wholesaler's license issued pursuant to Section 4161 shall be six hundred dollars ($600) and may be increased to seven hundred eighty dollars ($780).

(k) The fee for evaluation of continuing education courses for accreditation shall be set by the board at an amount not to exceed forty dollars ($40) per course hour.

(l) The fee for an intern pharmacist license shall be ninety dollars ($90) and may be increased to one hundred fifteen dollars ($115). The fee for transfer of intern hours or verification of licensure to another state shall be twenty-five dollars ($25) and may be increased to thirty dollars ($30).

(m) The board may waive or refund the additional fee for the issuance of a license where the license is issued less than 45 days before the next regular renewal date.

(n) The fee for the reissuance of any license, or renewal thereof, that has been lost or destroyed or reissued due to a name change shall be thirty-five dollars ($35) and may be increased to forty-five dollars ($45).

(o) The fee for the reissuance of any license, or renewal thereof, that must be reissued because of a change in the information, shall be one hundred dollars ($100) and may be increased to one hundred thirty dollars ($130).

(p) It is the intent of the Legislature that, in setting fees pursuant to this section, the board shall seek to maintain a reserve in the Pharmacy Board Contingent Fund equal to approximately one year's operating expenditures.

(q) The fee for any applicant for a nongovernmental clinic license shall be four hundred dollars ($400) and may be increased to five hundred twenty dollars ($520) for each license. The annual fee for renewal of the license shall be two hundred fifty dollars ($250) and may be increased to three hundred twenty-five dollars ($325) for each license.

(r) The fee for the issuance of a pharmacy technician license shall be eighty dollars ($80) and may be increased to one hundred five dollars ($105). The fee for renewal of a pharmacy technician license shall be one hundred dollars ($100) and may be increased to one hundred thirty dollars ($130).

(s) The fee for a veterinary food-animal drug retailer license shall be four hundred five dollars ($405) and may be increased to four hundred twenty-five dollars ($425). The annual renewal fee for a veterinary food-animal drug retailer license shall be two hundred fifty dollars ($250) and may be increased to three hundred twenty-five dollars ($325).

(t) The fee for issuance of a retired license pursuant to Section 4200.5 shall be thirty-five dollars ($35) and may be increased to forty-five dollars ($45).

(u) The fee for issuance or renewal of a nongovernmental *sterile compounding pharmacy* license ~~to compound sterile drug products~~ shall be six hundred dollars ($600) and may be increased to seven hundred eighty dollars ($780). The fee for a temporary license shall be five hundred fifty dollars ($550) and may be increased to seven hundred fifteen dollars ($715).

(v) The fee for a nonresident sterile compounding pharmacy license shall also require payment of the travel expenses incurred by the board in inspecting the pharmacy at least once annually. Failure to pay this fee within 30 days shall result in the suspension of the nonresident sterile compounding pharmacy license.

SEC. 7. No reimbursement is required by this act pursuant to Section 6 of Article XIIIB of the California Constitution because the only costs that may be incurred by a local agency or school district will be incurred because this act creates a new crime or infraction, eliminates a crime or infraction, or changes the penalty for a crime or infraction, within the meaning of Section 17556 of the Government Code, or changes the definition of a crime within the meaning of Section 6 of Article XIIIB of the California Constitution.

California LEGISLATIVE INFORMATION

AB-1045 Sterile compounding pharmacies. (2013-2014)

AMENDED IN ASSEMBLY APRIL 22, 2013

CALIFORNIA LEGISLATURE— 2013–2014 REGULAR SESSION

ASSEMBLY BILL **No. 1045**

Introduced by ***Assembly Member Quirk-Silva***

February 22, 2013

~~**An act to amend Section 4827 of the Business and Professions Code, to amend Sections 1834.6, 1834.7, 1846, and 1847 of the Civil Code, to amend Sections 17003, 31607, 31621, 31622, 32001, and 32003 of the Food and Agricultural Code, to amend Sections 121916 and 122322 of the Health and Safety Code, and to amend Sections 597, 597.1, 597.2, 597c, 597f, 597u, 597v, and 599c of the Penal Code, relating to animal shelters.**~~ ***An act to amend Sections 4112 and 4127.2 of, and to add Section 4127.9 to, the Business and Professions Code, relating to pharmacy.***

LEGISLATIVE COUNSEL'S DIGEST

AB 1045, as amended, Quirk-Silva. ~~Animal shelters.~~ *Sterile compounding pharmacies.*

Existing law, the Pharmacy Law, provides for the licensure and regulation of pharmacies in this state by the California State Board of Pharmacy. A violation of these provisions is a crime.

Existing law provides that a pharmacy located outside this state that ships, mails, or delivers, in any manner, controlled substances, dangerous drugs, or dangerous devices into this state shall be considered a nonresident pharmacy. Existing law prohibits a person from acting as a nonresident pharmacy unless he or she has obtained a license from the board, and authorizes the board to register a nonresident pharmacy that is organized as a limited liability company in the state in which it is licensed. The law also prohibits a resident or nonresident pharmacy from compounding injectable sterile drug products for shipment into this state without a license issued by the board, and authorizes a license to compound injectable sterile drug products to be issued only for a location that is licensed as a nonresident pharmacy.

This bill would provide that if the home state pharmacy license of a nonresident pharmacy is revoked or suspended for any reason, any license issued pursuant to provisions governing the licensing and registration of nonresident pharmacies and authorizing a nonresident pharmacy to compound injectable sterile drug products shall be immediately revoked or suspended by operation of law.

The bill would also require a resident or a nonresident pharmacy that issues a recall notice regarding a sterile compounded drug to contact the recipient pharmacy, prescriber, or patient of the recalled drug and the board

within 24 hours of the recall notice if use of or exposure to the recalled drug may cause serious adverse health consequences or death and if the recalled drug was dispensed or is intended for use in this state. Because a violation of these requirements would be a crime, the bill would impose a state-mandated local program.

The California Constitution requires the state to reimburse local agencies and school districts for certain costs mandated by the state. Statutory provisions establish procedures for making that reimbursement.

This bill would provide that no reimbursement is required by this act for a specified reason.

~~Existing law governs the seizure, rescue, adoption, and euthanasia of abandoned and surrendered animals by animal shelters and rescue organizations.~~

~~This bill would make technical, nonsubstantive changes to those provisions by replacing references to a "pound" with references to an "animal shelter" and by replacing references to destroying an animal with references to humanely euthanizing the animal.~~

Vote: majority Appropriation: no Fiscal Committee: ~~no~~*yes* Local Program: ~~no~~*yes*

THE PEOPLE OF THE STATE OF CALIFORNIA DO ENACT AS FOLLOWS:

SECTION 1. *Section 4112 of the Business and Professions Code is amended to read:*

4112. (a) Any pharmacy located outside this state that ships, mails, or delivers, in any manner, controlled substances, dangerous drugs, or dangerous devices into this state shall be considered a nonresident pharmacy.

(b) A person may not act as a nonresident pharmacy unless he or she has obtained a license from the board. The board may register a nonresident pharmacy that is organized as a limited liability company in the state in which it is licensed.

(c) A nonresident pharmacy shall disclose to the board the location, names, and titles of (1) its agent for service of process in this state, (2) all principal corporate officers, if any, (3) all general partners, if any, and (4) all pharmacists who are dispensing controlled substances, dangerous drugs, or dangerous devices to residents of this state. A report containing this information shall be made on an annual basis and within 30 days after any change of office, corporate officer, partner, or pharmacist.

(d) All nonresident pharmacies shall comply with all lawful directions and requests for information from the regulatory or licensing agency of the state in which it is licensed as well as with all requests for information made by the board pursuant to this section. The nonresident pharmacy shall maintain, at all times, a valid unexpired license, permit, or registration to conduct the pharmacy in compliance with the laws of the state in which it is a resident. As a prerequisite to registering with the board, the nonresident pharmacy shall submit a copy of the most recent inspection report resulting from an inspection conducted by the regulatory or licensing agency of the state in which it is located. *If the home state pharmacy license of a nonresident pharmacy is revoked or suspended for any reason, any license issued pursuant to this section shall be immediately revoked or suspended by operation of law.*

(e) All nonresident pharmacies shall maintain records of controlled substances, dangerous drugs, or dangerous devices dispensed to patients in this state so that the records are readily retrievable from the records of other drugs dispensed.

(f) Any pharmacy subject to this section shall, during its regular hours of operation, but not less than six days per week, and for a minimum of 40 hours per week, provide a toll-free telephone service to facilitate communication between patients in this state and a pharmacist at the pharmacy who has access to the patient's records. This toll-free telephone number shall be disclosed on a label affixed to each container of drugs dispensed to patients in this state.

(g) A nonresident pharmacy shall not permit a pharmacist whose license has been revoked by the board to manufacture, compound, furnish, sell, dispense, or initiate the prescription of a dangerous drug or dangerous device, or to provide any pharmacy-related service, to a person residing in California.

(h) The board shall adopt regulations that apply the same requirements or standards for oral consultation to a nonresident pharmacy that operates pursuant to this section and ships, mails, or delivers any controlled substances, dangerous drugs, or dangerous devices to residents of this state, as are applied to an in-state pharmacy that operates pursuant to Section 4037 when the pharmacy ships, mails, or delivers any controlled substances, dangerous drugs, or dangerous devices to residents of this state. The board shall not adopt any

regulations that require face-to-face consultation for a prescription that is shipped, mailed, or delivered to the patient. The regulations adopted pursuant to this subdivision shall not result in any unnecessary delay in patients receiving their medication.

(i) The registration fee shall be the fee specified in subdivision (a) of Section 4400.

(j) The registration requirements of this section shall apply only to a nonresident pharmacy that ships, mails, or delivers controlled substances, dangerous drugs, and dangerous devices into this state pursuant to a prescription.

(k) Nothing in this section shall be construed to authorize the dispensing of contact lenses by nonresident pharmacists except as provided by Section 4124.

SEC. 2. *Section 4127.2 of the Business and Professions Code is amended to read:*

4127.2. (a) A nonresident pharmacy may not compound injectable sterile drug products for shipment into the State of California without a license issued by the board pursuant to this section. The license shall be renewed annually and shall not be transferable.

(b) A license to compound injectable sterile drug products may only be issued for a location that is licensed as a nonresident pharmacy. Furthermore, the license to compound injectable sterile drug products may only be issued to the owner of the nonresident pharmacy license at that location. *If the home state pharmacy license of a nonresident pharmacy is revoked or suspended for any reason, any license issued pursuant to Section 4112 or this section shall be immediately revoked or suspended by operation of law.* A license to compound injectable sterile drug products may not be issued or renewed until the board receives the following from the nonresident pharmacy:

(1) A copy of an inspection report issued by the pharmacy's licensing agency, or a report from a private accrediting agency approved by the board, in the prior 12 months documenting the pharmacy's compliance with board regulations regarding the compounding of injectable sterile drug products.

(2) A copy of the nonresident pharmacy's proposed policies and procedures for sterile compounding.

(c) Nonresident pharmacies operated by entities that are licensed as a hospital, home health agency, or a skilled nursing facility and have current accreditation from the Joint Commission on Accreditation of Healthcare Organizations, or other private accreditation agencies approved by the board, are exempt from the requirement to obtain a license pursuant to this section.

(d) This section shall become effective on the earlier of July 1, 2003, or the effective date of regulations adopted by the board pursuant to Section 4127.

SEC. 3. *Section 4127.9 is added to the Business and Professions Code, to read:*

4127.9. *(a) A pharmacy licensed pursuant to Section 4127.1 or 4127.2, including a pharmacy that is exempt from licensure pursuant to subdivision (d) of Section 4127.1 and subdivision (c) of Section 4127.2, that issues a recall notice regarding a sterile compounded drug shall, in addition to any other duties, contact the recipient pharmacy, prescriber, or patient of the recalled drug and the board within 24 hours of the recall notice if both of the following apply:*

(1) Use of or exposure to the recalled drug may cause serious adverse health consequences or death.

(2) The recalled drug was dispensed, or is intended for use, in this state.

(b) A recall notice issued pursuant to subdivision (a) shall be made as follows:

(1) If the recalled drug was dispensed directly to the patient, the notice shall be made to the patient.

(2) If the recalled drug was dispensed directly to the prescriber, the notice shall be made to the prescriber, who shall ensure the patient is notified.

(3) If the recalled drug was dispensed directly to a pharmacy, the notice shall be made to the pharmacy, who shall notify the prescriber or patient, as appropriate. If the pharmacy notifies the prescriber, the prescriber shall ensure the patient is notified.

SEC. 4. *No reimbursement is required by this act pursuant to Section 6 of Article XIIIB of the California Constitution because the only costs that may be incurred by a local agency or school district will be incurred because this act creates a new crime or infraction, eliminates a crime or infraction, or changes the penalty for a crime or infraction, within the meaning of Section 17556 of the Government Code, or changes the definition of a crime within the meaning of Section 6 of Article XIIIB of the California Constitution.*

~~SECTION 1.Section 4827 of the Business and Professions Code is amended to read:4827.~~
~~Nothing in this chapter prohibits any person from:~~

~~(a)Practicing veterinary medicine as a bona fide owner of one's own animals. This exemption applies to the following:~~

~~(1)The owner's bona fide employees.~~

~~(2)Any person assisting the owner, provided that the practice is performed gratuitously.~~

~~(b)Lay testing of poultry by the whole blood agglutination test. For purposes of this section, "poultry" means flocks of avian species maintained for food production, including, but not limited to, chickens, turkeys, and exotic fowl.~~

~~(c)Making any determination as to the status of pregnancy, sterility, or infertility upon livestock, equine, or food animals at the time an animal is being inseminated, providing no charge is made for this determination.~~

~~(d)Administering sodium pentobarbital for euthanasia of sick, injured, homeless, or surrendered domestic pets or animals without the presence of a veterinarian when the person is an employee of an animal control shelter and its agencies or humane society and has received proper training in the administration of sodium pentobarbital for these purposes.~~

~~SEC. 2.Section 1834.6 of the Civil Code is amended to read:1834.6.~~
~~An abandoned animal, as described in Section 1834.5, shall not be used for scientific or any other type of experimentation, nor shall such an abandoned animal be turned over to an animal shelter or animal regulation department of a public agency.~~

~~SEC. 3.Section 1834.7 of the Civil Code is amended to read:1834.7.~~
~~(a)In any animal shelter or animal regulation department of a public or private agency where animals are turned over dead or alive to a biological supply facility or a research facility, a sign (measuring a minimum of 28x21 cm — 11x8 1/2 inches — with lettering of a minimum of 3.2 cm high and 1.2 cm wide — 1 1/4x1/2 inch — (91 point)) stating:~~

~~"Animals Turned In To This Shelter May Be Used For Research Purposes or to Supply Blood, Tissue, or Other Biological Products"~~

~~shall be posted in a place where it will be clearly visible to a majority of persons when turning animals over to the shelter. This statement shall also be included on owner surrender forms. The owner surrender forms shall also include the definition of "biological supply facility" contained in subdivision (c).~~

~~(b)For purposes of this section, "animal research facility" includes any laboratory, firm, association, corporation, copartnership, and educational institution.~~

~~(c)For purposes of this section, "biological supply facility" includes any blood bank, laboratory, firm, association, corporation, copartnership, or educational institution that sells biological materials such as blood or animals, either alive or dead, to research facilities, educational institutions, or veterinarians.~~

~~SEC. 4.Section 1846 of the Civil Code is amended to read:1846.~~
~~(a)A gratuitous depositary must use, at least, slight care for the preservation of the thing deposited.~~

~~(b)A gratuitous depositary of a living animal shall provide the animal with necessary and prompt veterinary care, adequate nutrition and water, and shelter, and shall treat it humanely and, if the animal has any identification, make reasonable attempts to notify the owner of the animal's location. Any gratuitous depositary that does not have sufficient resources or desire to provide that care shall promptly turn the animal over to an appropriate care facility.~~

~~(c)If the gratuitous depositary of a living animal is a public animal shelter, shelter operated by a society for the prevention of cruelty to animals, or humane shelter, the depositary shall comply with all other requirements of the Food and Agricultural Code regarding the impounding of live animals.~~

~~SEC. 5.Section 1847 of the Civil Code is amended to read:1847.~~
~~The duties of a gratuitous depositary cease:~~

~~(a)Upon restoration by the depositary of the thing deposited to its owner.~~

~~(b)Upon reasonable notice given by the depositary to the owner to remove it, and the owner failing to do so within a reasonable time. But an involuntary depositary, under subdivision (b) of Section 1815, may not give notice until the emergency that gave rise to the deposit is past. This subdivision shall not apply to a public animal shelter, a shelter operated by a society for the prevention of cruelty to animals, or a humane shelter. The duty to provide care, as required by Section 1846, continues until the public or private animal shelter is lawfully relieved of responsibility for the animal.~~

~~SEC. 6.Section 17003 of the Food and Agricultural Code is amended to read:17003.~~
~~(a)Except as provided in this section, this chapter does not affect any law, ordinance, or regulation regarding estrays, the shelter director, or other animal control officer, or a public animal control agency or shelter within the limits of any city or county where those laws, ordinances, or regulations are in force.~~

~~(b)Upon the impounding of any bovine animal, horse, mule, or burro, the shelter director, other animal control officer, or public animal control agency or shelter shall immediately notify the secretary. Upon receipt of that notice, the secretary shall take possession of any bovine animal and shall dispose of it pursuant to this chapter.~~

~~(c)Any city, county, or city and county that establishes or has established laws, ordinances, or regulations regarding estrays, may opt to follow those laws, ordinances, or regulations instead of this chapter in the handling of estrays that are not bovine animals in accordance with the applicable laws, ordinances, or regulations of the city, county, or city and county.~~

~~(d)This section does not authorize any act that violates Section 597 of the Penal Code.~~

~~SEC. 7.Section 31607 of the Food and Agricultural Code is amended to read:31607.~~
~~"Impounded" means taken into the custody of the public animal shelter or animal control department or provider of animal control services to the city or county where the potentially dangerous or vicious dog is found.~~

~~SEC. 8.Section 31621 of the Food and Agricultural Code is amended to read:31621.~~
~~If an animal control officer or a law enforcement officer has investigated and determined that there exists probable cause to believe that a dog is potentially dangerous or vicious, the chief officer of the public animal shelter or animal control department or his or her immediate supervisor or the head of the local law enforcement agency, or his or her designee, shall petition the superior court of the county wherein the dog is owned or kept for a hearing for the purpose of determining whether or not the dog in question should be declared potentially dangerous or vicious. A proceeding under this section is a limited civil case. A city or county may establish an administrative hearing procedure to hear and dispose of petitions filed pursuant to this chapter. Whenever possible, any complaint received from a member of the public which serves as the evidentiary basis for the animal control officer or law enforcement officer to find probable cause shall be sworn to and verified by the complainant and shall be attached to the petition. The chief officer of the public animal shelter or animal control department or head of the local law enforcement agency shall notify the owner or keeper of the dog that a hearing will be held by the superior court or the hearing entity, as the case may be, at which time he or she may present evidence as to why the dog should not be declared potentially dangerous or vicious. The owner or keeper of the dog shall be served with notice of the hearing and a copy of the petition, either personally or by first-class mail with return receipt requested. The hearing shall be held promptly within no less than five working days nor more than 10 working days after service of notice upon the owner or keeper of the dog. The hearing shall be open to the public. The court may admit into evidence all relevant evidence, including incident reports and the affidavits of witnesses, limit the scope of discovery, and may shorten the time to produce records or witnesses. A jury shall not be available. The court may find, upon a preponderance of the evidence, that the dog is potentially dangerous or vicious and make other orders authorized by this chapter.~~

~~SEC. 9.Section 31622 of the Food and Agricultural Code is amended to read:31622.~~
~~(a)After the hearing conducted pursuant to Section 31621, the owner or keeper of the dog shall be notified in writing of the determination and orders issued, either personally or by first-class mail postage prepaid by the court or hearing entity. If a determination is made that the dog is potentially dangerous or vicious, the owner or~~

~~keeper shall comply with Article 3 (commencing with Section 31641) in accordance with a time schedule established by the chief officer of the public animal shelter or animal control department or the head of the local law enforcement agency, but in no case more than 30 days after the date of the determination or 35 days if notice of the determination is mailed to the owner or keeper of the dog. If the petitioner or the owner or keeper of the dog contests the determination, he or she may, within five days of the receipt of the notice of determination, appeal the decision of the court or hearing entity of original jurisdiction. The fee for filing an appeal, payable to the clerk of the court, is as provided in subdivision (b) of Section 70626 of the Government Code. If the original hearing held pursuant to Section 31621 was before a hearing entity other than a court of the jurisdiction, appeal shall be to the superior court. If the original hearing was held in the superior court, appeal shall be to the superior court before a judge other than the judge who originally heard the petition. The petitioner or the owner or keeper of the dog shall serve personally or by first-class mail, postage prepaid, notice of the appeal upon the other party.~~

~~(b)The court hearing the appeal shall conduct a hearing de novo, without a jury, and make its own determination as to potential danger and viciousness and make other orders authorized by this chapter, based upon the evidence presented. The hearing shall be conducted in the same manner and within the time periods set forth in Section 31621 and subdivision (a). The court may admit all relevant evidence, including incident reports and the affidavits of witnesses, limit the scope of discovery, and may shorten the time to produce records or witnesses. The issue shall be decided upon the preponderance of the evidence. If the court rules the dog to be potentially dangerous or vicious, the court may establish a time schedule to ensure compliance with this chapter, but in no case more than 30 days subsequent to the date of the court's determination or 35 days if the service of the judgment is by first-class mail.~~

~~SEC. 10.Section 32001 of the Food and Agricultural Code is amended to read:32001.~~
~~All public animal shelters, shelters operated by societies for the prevention of cruelty to animals, and humane shelters, that contract to perform public animal control services, shall provide the owners of lost animals and those who find lost animals with all of the following:~~

~~(a)Ability to list the animals they have lost or found on "Lost and Found" lists maintained by the animal shelter.~~

~~(b)Referrals to animals listed that may be the animals the owners or finders have lost or found.~~

~~(c)The telephone numbers and addresses of other animal shelters in the same vicinity.~~

~~(d)Advice as to means of publishing and disseminating information regarding lost animals.~~

~~(e)The telephone numbers and addresses of volunteer groups that may be of assistance in locating lost animals.~~

~~The duties imposed by this section are mandatory duties for public entities for all purposes of the Government Code and for all private entities with which a public entity has contracted to perform those duties.~~

~~SEC. 11.Section 32003 of the Food and Agricultural Code is amended to read:32003.~~
~~All public and private animal shelters shall keep accurate records on each animal taken up, medically treated, or impounded. The records shall include all of the following information and any other information required by the California Veterinary Medical Board:~~

~~(a)The date the animal was taken up, medically treated, euthanized, or impounded.~~

~~(b)The circumstances under which the animal was taken up, medically treated, euthanized, or impounded.~~

~~(c)The names of the personnel who took up, medically treated, euthanized, or impounded the animal.~~

~~(d)A description of any medical treatment provided to the animal and the name of the veterinarian of record.~~

~~(e)The final disposition of the animal, including the name of the person who euthanized the animal or the name and address of the adopting party. These records shall be maintained for three years after the date the animal's impoundment ends.~~

~~SEC. 12.Section 121916 of the Health and Safety Code is amended to read:121916.~~
~~(a) Any person or owner of an attack, guard, or sentry dog that operates or maintains a business to sell, rent, or train an attack, guard, or sentry dog shall obtain a permit from the local public agency or private society or animal shelter contracting with the local public agency for animal care or protection services.~~

~~(b) Each local agency shall adopt and implement a permit program for the administration of subdivision (a) by the local agency or private society or animal shelter contracting with the local public agency for animal care or protection services. A local agency may charge a fee for the issuance or renewal of a permit required under this section. The fee shall not exceed the actual costs for the implementation of the permit program.~~

~~(c) For purposes of this section, "local public agency" means a city, county, or city and county.~~

~~SEC. 13.Section 122322 of the Health and Safety Code is amended to read:122322.~~
~~(a) Any person violating any provision of this chapter shall be subject to a civil penalty of up to one thousand dollars ($1,000) per violation. The action may be prosecuted in the name of the people of the State of California by the district attorney for the county where the violation occurred in the appropriate court or by the city attorney in the city where the violation occurred.~~

~~(b) Nothing in this chapter limits or authorizes any act or omission that violates Section 597 of the Penal Code.~~

~~(c) Nothing in this chapter shall authorize the seizure of an unweaned bird by a peace officer, officer of a humane society, or officer of an animal shelter or animal regulation department of a public agency.~~

~~SEC. 14.Section 597 of the Penal Code is amended to read:597.~~
~~(a)Except as provided in subdivision (c) of this section or Section 599c, every person who maliciously and intentionally maims, mutilates, tortures, or wounds a living animal, or maliciously and intentionally kills an animal, is guilty of a crime punishable pursuant to subdivision (d).~~

~~(b)Except as otherwise provided in subdivision (a) or (c), every person who overdrives, overloads, drives when overloaded, overworks, tortures, torments, deprives of necessary sustenance, drink, or shelter, cruelly beats, mutilates, or cruelly kills any animal, or causes or procures any animal to be so overdriven, overloaded, driven when overloaded, overworked, tortured, tormented, deprived of necessary sustenance, drink, shelter, or to be cruelly beaten, mutilated, or cruelly killed; and whoever, having the charge or custody of any animal, either as owner or otherwise, subjects any animal to needless suffering, or inflicts unnecessary cruelty upon the animal, or in any manner abuses any animal, or fails to provide the animal with proper food, drink, or shelter or protection from the weather, or who drives, rides, or otherwise uses the animal when unfit for labor, is, for each offense, guilty of a crime punishable pursuant to subdivision (d).~~

~~(c)Every person who maliciously and intentionally maims, mutilates, or tortures any mammal, bird, reptile, amphibian, or fish, as described in subdivision (e), is guilty of a crime punishable pursuant to subdivision (d).~~

~~(d) A violation of subdivision (a), (b), or (c) is punishable as a felony by imprisonment pursuant to subdivision (h) of Section 1170, or by a fine of not more than twenty thousand dollars ($20,000), or by both that fine and imprisonment, or alternatively, as a misdemeanor by imprisonment in a county jail for not more than one year, or by a fine of not more than twenty thousand dollars ($20,000), or by both that fine and imprisonment.~~

~~(e)Subdivision (c) applies to any mammal, bird, reptile, amphibian, or fish which is a creature described as follows:~~

~~(1)Endangered species or threatened species as described in Chapter 1.5 (commencing with Section 2050) of Division 3 of the Fish and Game Code.~~

~~(2)Fully protected birds described in Section 3511 of the Fish and Game Code.~~

~~(3)Fully protected mammals described in Chapter 8 (commencing with Section 4700) of Part 3 of Division 4 of the Fish and Game Code.~~

~~(4)Fully protected reptiles and amphibians described in Chapter 2 (commencing with Section 5050) of Division 5 of the Fish and Game Code.~~

~~(5)Fully protected fish as described in Section 5515 of the Fish and Game Code.~~

~~This subdivision does not supersede or affect any provisions of law relating to taking of the described species, including, but not limited to, Section 12008 of the Fish and Game Code.~~

~~(f)For the purposes of subdivision (c), each act of malicious and intentional maiming, mutilating, or torturing a separate specimen of a creature described in subdivision (e) is a separate offense. If any person is charged with a violation of subdivision (c), the proceedings shall be subject to Section 12157 of the Fish and Game Code.~~

~~(g)(1)Upon the conviction of a person charged with a violation of this section by causing or permitting an act of cruelty, as defined in Section 599b, all animals lawfully seized and impounded with respect to the violation by a peace officer, officer of a humane society, or officer of an animal shelter or animal regulation department of a public agency shall be adjudged by the court to be forfeited and shall thereupon be awarded to the impounding officer for proper disposition. A person convicted of a violation of this section by causing or permitting an act of cruelty, as defined in Section 599b, shall be liable to the impounding officer for all costs of impoundment from the time of seizure to the time of proper disposition.~~

~~(2)Mandatory seizure or impoundment shall not apply to animals in properly conducted scientific experiments or investigations performed under the authority of the faculty of a regularly incorporated medical college or university of this state.~~

~~(h)Notwithstanding any other law, if a defendant is granted probation for a conviction under this section, the court shall order the defendant to pay for, and successfully complete, counseling, as determined by the court, designed to evaluate and treat behavior or conduct disorders. If the court finds that the defendant is financially unable to pay for that counseling, the court may develop a sliding fee schedule based upon the defendant's ability to pay. An indigent defendant may negotiate a deferred payment schedule, but shall pay a nominal fee if the defendant has the ability to pay the nominal fee. County mental health departments or Medi-Cal shall be responsible for the costs of counseling required by this section only for those persons who meet the medical necessity criteria for mental health managed care pursuant to Section 1830.205 of Title 9 of the California Code of Regulations or the targeted population criteria specified in Section 5600.3 of the Welfare and Institutions Code. The counseling specified in this subdivision shall be in addition to any other terms and conditions of probation, including any term of imprisonment and any fine. This provision specifies a mandatory additional term of probation and is not to be utilized as an alternative in lieu of imprisonment pursuant to subdivision (h) of Section 1170 or county jail when that sentence is otherwise appropriate. If the court does not order custody as a condition of probation for a conviction under this section, the court shall specify on the court record the reason or reasons for not ordering custody. This subdivision shall not apply to cases involving police dogs or horses as described in Section 600.~~

~~SEC. 15.Section 597.1 of the Penal Code is amended to read:597.1.~~
~~(a)(1)Every owner, driver, or keeper of any animal who permits the animal to be in any building, enclosure, lane, street, square, or lot of any city, county, city and county, or judicial district without proper care and attention is guilty of a misdemeanor. Any peace officer, humane society officer, or animal control officer shall take possession of the stray or abandoned animal and shall provide care and treatment for the animal until the animal is deemed to be in suitable condition to be returned to the owner. When the officer has reasonable grounds to believe that very prompt action is required to protect the health or safety of the animal or the health or safety of others, the officer shall immediately seize the animal and comply with subdivision (f). In all other cases, the officer shall comply with the provisions of subdivision (g). The full cost of caring for and treating any animal properly seized under this subdivision or pursuant to a search warrant shall constitute a lien on the animal and the animal shall not be returned to its owner until the charges are paid, if the seizure is upheld pursuant to this section.~~

~~(2)Notwithstanding any other law, if an animal control officer or humane officer, when necessary to protect the health and safety of a wild, stray, or abandoned animal or the health and safety of others, seeks to administer a tranquilizer that contains a controlled substance, as defined in Division 10 (commencing with Section 11000) of the Health and Safety Code, to gain control of that animal, he or she may possess and administer that tranquilizer with direct or indirect supervision as determined by a licensed veterinarian, provided that the officer has met each of the following requirements:~~

~~(A)Has received training in the administration of tranquilizers from a licensed veterinarian. The training shall be approved by the California Veterinary Medical Board.~~

~~(B)Has successfully completed the firearms component of a course relating to the exercise of police powers, as set forth in Section 832.~~

~~(C)Is authorized by his or her agency or organization to possess and administer the tranquilizer in accordance with a policy established by the agency or organization and approved by the veterinarian who obtained the controlled substance.~~

~~(D)Has successfully completed the euthanasia training set forth in Section 2039 of Title 16 of the California Code of Regulations.~~

~~(E)Has completed a state and federal fingerprinting background check and does not have any drug- or alcohol-related convictions.~~

~~(b)Every sick, disabled, infirm, or crippled animal, except a dog or cat, that is abandoned in any city, county, city and county, or judicial district may be humanely euthanized by the officer if, after a reasonable search, no owner of the animal can be found. It shall be the duty of all peace officers, humane society officers, and animal control officers to cause the animal to be humanely euthanized or rehabilitated and placed in a suitable home on information that the animal is stray or abandoned. The officer may likewise take charge of any animal, including a dog or cat, that by reason of lameness, sickness, feebleness, or neglect, is unfit for the labor it is performing, or that in any other manner is being cruelly treated, and provide care and treatment for the animal until it is deemed to be in a suitable condition to be returned to the owner. When the officer has reasonable grounds to believe that very prompt action is required to protect the health or safety of an animal or the health or safety of others, the officer shall immediately seize the animal and comply with subdivision (f). In all other cases, the officer shall comply with subdivision (g). The full cost of caring for and treating any animal properly seized under this subdivision or pursuant to a search warrant shall constitute a lien on the animal and the animal shall not be returned to its owner until the charges are paid.~~

~~(c)(1)Any peace officer, humane society officer, or animal control officer shall convey all injured cats and dogs found without their owners in a public place directly to a veterinarian known by the officer to be a veterinarian who ordinarily treats dogs and cats for a determination of whether the animal shall be immediately and humanely euthanized or shall be hospitalized under proper care and given emergency treatment.~~

~~(2)If the owner does not redeem the animal within the locally prescribed waiting period, the veterinarian may personally perform euthanasia on the animal. If the animal is treated and recovers from its injuries, the veterinarian may keep the animal for purposes of adoption, provided the responsible animal control agency has first been contacted and has refused to take possession of the animal.~~

~~(3)Whenever any animal is transferred to a veterinarian in a clinic, such as an emergency clinic that is not in continuous operation, the veterinarian may, in turn, transfer the animal to an appropriate facility.~~

~~(4)If the veterinarian determines that the animal shall be hospitalized under proper care and given emergency treatment, the costs of any services that are provided pending the owner's inquiry to the responsible agency, department, or society shall be paid from the dog license fees, fines, and fees for impounding dogs in the city, county, or city and county in which the animal was licensed or, if the animal is unlicensed, shall be paid by the jurisdiction in which the animal was found, subject to the provision that this cost be repaid by the animal's owner. The full cost of caring for and treating any animal seized under this subdivision shall constitute a lien on the animal and the animal shall not be returned to the owner until the charges are paid. No veterinarian shall be criminally or civilly liable for any decision that he or she makes or for services that he or she provides pursuant to this subdivision.~~

~~(d)An animal control agency that takes possession of an animal pursuant to subdivision (c) shall keep records of the whereabouts of the animal from the time of possession to the end of the animal's impoundment, and those records shall be available for inspection by the public upon request for three years after the date the animal's impoundment ended.~~

~~(e)Notwithstanding any other provision of this section, any peace officer, humane society officer, or any animal control officer may, with the approval of his or her immediate superior, humanely euthanize any stray or abandoned animal in the field in any case where the animal is too severely injured to move or where a veterinarian is not available and it would be more humane to euthanize the animal.~~

~~(f)Whenever an officer authorized under this section seizes or impounds an animal based on a reasonable belief that prompt action is required to protect the health or safety of the animal or the health or safety of others, the officer shall, prior to the commencement of any criminal proceedings authorized by this section, provide the owner or keeper of the animal, if known or ascertainable after reasonable investigation, with the opportunity for a postseizure hearing to determine the validity of the seizure or impoundment, or both.~~

~~(1)The agency shall cause a notice to be affixed to a conspicuous place where the animal was situated or personally deliver a notice of the seizure or impoundment, or both, to the owner or keeper within 48 hours, excluding weekends and holidays. The notice shall include all of the following:~~

~~(A)The name, business address, and telephone number of the officer providing the notice.~~

~~(B)A description of the animal seized, including any identification upon the animal.~~

~~(C)The authority and purpose for the seizure or impoundment, including the time, place, and circumstances under which the animal was seized.~~

~~(D)A statement that, in order to receive a postseizure hearing, the owner or person authorized to keep the animal, or his or her agent, shall request the hearing by signing and returning an enclosed declaration of ownership or right to keep the animal to the agency providing the notice within 10 days, including weekends and holidays, of the date of the notice. The declaration may be returned by personal delivery or mail.~~

~~(E)A statement that the full cost of caring for and treating any animal properly seized under this section is a lien on the animal and that the animal shall not be returned to the owner until the charges are paid, and that failure to request or to attend a scheduled hearing shall result in liability for this cost.~~

~~(2)The postseizure hearing shall be conducted within 48 hours of the request, excluding weekends and holidays. The seizing agency may authorize its own officer or employee to conduct the hearing if the hearing officer is not the same person who directed the seizure or impoundment of the animal and is not junior in rank to that person. The agency may utilize the services of a hearing officer from outside the agency for the purposes of complying with this section.~~

~~(3)Failure of the owner or keeper, or of his or her agent, to request or to attend a scheduled hearing shall result in a forfeiture of any right to a postseizure hearing or right to challenge his or her liability for costs incurred.~~

~~(4)The agency, department, or society employing the person who directed the seizure shall be responsible for the costs incurred for caring and treating the animal, if it is determined in the postseizure hearing that the seizing officer did not have reasonable grounds to believe very prompt action, including seizure of the animal, was required to protect the health or safety of the animal or the health or safety of others. If it is determined the seizure was justified, the owner or keeper shall be personally liable to the seizing agency for the full cost of the seizure and care of the animal. The charges for the seizure and care of the animal shall be a lien on the animal. The animal shall not be returned to its owner until the charges are paid and the owner demonstrates to the satisfaction of the seizing agency or the hearing officer that the owner can and will provide the necessary care for the animal.~~

~~(g)Where the need for immediate seizure is not present and prior to the commencement of any criminal proceedings authorized by this section, the agency shall provide the owner or keeper of the animal, if known or ascertainable after reasonable investigation, with the opportunity for a hearing prior to any seizure or impoundment of the animal. The owner shall produce the animal at the time of the hearing unless, prior to the hearing, the owner has made arrangements with the agency to view the animal upon request of the agency, or unless the owner can provide verification that the animal was humanely euthanized. Any person who willfully fails to produce the animal or provide the verification is guilty of an infraction, punishable by a fine of not less than two hundred fifty dollars ($250) nor more than one thousand dollars ($1,000).~~

~~(1)The agency shall cause a notice to be affixed to a conspicuous place where the animal was situated or personally deliver a notice stating the grounds for believing the animal should be seized under subdivision (a) or (b). The notice shall include all of the following:~~

~~(A)The name, business address, and telephone number of the officer providing the notice.~~

~~(B)A description of the animal to be seized, including any identification upon the animal.~~

~~(C)The authority and purpose for the possible seizure or impoundment.~~

~~(D)A statement that, in order to receive a hearing prior to any seizure, the owner or person authorized to keep the animal, or his or her agent, shall request the hearing by signing and returning the enclosed declaration of ownership or right to keep the animal to the officer providing the notice within two days, excluding weekends and holidays, of the date of the notice.~~

~~(E)A statement that the cost of caring for and treating any animal properly seized under this section is a lien on the animal, that any animal seized shall not be returned to the owner until the charges are paid, and that failure to request or to attend a scheduled hearing shall result in a conclusive determination that the animal may properly be seized and that the owner shall be liable for the charges.~~

~~(2)The preseizure hearing shall be conducted within 48 hours, excluding weekends and holidays, after receipt of the request. The seizing agency may authorize its own officer or employee to conduct the hearing if the hearing officer is not the same person who requests the seizure or impoundment of the animal and is not junior in rank to that person. The agency may utilize the services of a hearing officer from outside the agency for the purposes of complying with this section.~~

~~(3)Failure of the owner or keeper, or his or her agent, to request or to attend a scheduled hearing shall result in a forfeiture of any right to a preseizure hearing or right to challenge his or her liability for costs incurred pursuant to this section.~~

~~(4)The hearing officer, after the hearing, may affirm or deny the owner's or keeper's right to custody of the animal and, if reasonable grounds are established, may order the seizure or impoundment of the animal for care and treatment.~~

~~(h)If any animal is properly seized under this section or pursuant to a search warrant, the owner or keeper shall be personally liable to the seizing agency for the cost of the seizure and care of the animal. Further, if the charges for the seizure or impoundment and any other charges permitted under this section are not paid within 14 days of the seizure, or if the owner, within 14 days of notice of availability of the animal to be returned, fails to pay charges permitted under this section and take possession of the animal, the animal shall be deemed to have been abandoned and may be humanely euthanized by the seizing agency.~~

~~(i)If the animal requires veterinary care and the humane society or public agency is not assured, within 14 days of the seizure of the animal, that the owner will provide the necessary care, the animal shall not be returned to its owner and shall be deemed to have been abandoned and may be disposed of by the seizing agency. A veterinarian may humanely euthanize an impounded animal without regard to the prescribed holding period when it has been determined that the animal has incurred severe injuries or is incurably crippled. A veterinarian also may immediately humanely euthanize an impounded animal afflicted with a serious contagious disease unless the owner or his or her agent immediately authorizes treatment of the animal by a veterinarian at the expense of the owner or agent.~~

~~(j)No animal properly seized under this section or pursuant to a search warrant shall be returned to its owner until the owner can demonstrate to the satisfaction of the seizing agency or hearing officer that the owner can and will provide the necessary care for the animal.~~

~~(k)(1)In the case of cats and dogs, prior to the final disposition of any criminal charges, the seizing agency or prosecuting attorney may file a petition in a criminal action requesting that, prior to that final disposition, the court issue an order forfeiting the animal to the city, county, or seizing agency. The petitioner shall serve a true copy of the petition upon the defendant and the prosecuting attorney.~~

~~(2)Upon receipt of the petition, the court shall set a hearing on the petition. The hearing shall be conducted within 14 days after the filing of the petition, or as soon as practicable.~~

~~(3)The petitioner shall have the burden of establishing beyond a reasonable doubt that, even in the event of an acquittal of the criminal charges, the owner will not legally be permitted to retain the animal in question. If the court finds that the petitioner has met its burden, the court shall order the immediate forfeiture of the animal as sought by the petition.~~

~~(4)Nothing in this subdivision is intended to authorize a seizing agency or prosecuting attorney to file a petition to determine an owner's ability to legally retain an animal pursuant to paragraph (3) of subdivision (l) if a petition has previously been filed pursuant to this subdivision.~~

~~(l)(1)Upon the conviction of a person charged with a violation of this section, or Section 597 or 597a, all animals lawfully seized and impounded with respect to the violation shall be adjudged by the court to be forfeited and shall thereupon be transferred to the impounding officer or appropriate public entity for proper adoption or other disposition. A person convicted of a violation of this section shall be personally liable to the seizing agency for all costs of impoundment from the time of seizure to the time of proper disposition. Upon conviction, the court shall order the convicted person to make payment to the appropriate public entity for the costs incurred in the housing, care, feeding, and treatment of the seized or impounded animals. Each person convicted in connection with a particular animal may be held jointly and severally liable for restitution for that particular animal. The payment shall be in addition to any other fine or sentence ordered by the court.~~

~~(2)The court may also order, as a condition of probation, that the convicted person be prohibited from owning, possessing, caring for, or residing with, animals of any kind, and require the convicted person to immediately deliver all animals in his or her possession to a designated public entity for adoption or other lawful disposition or provide proof to the court that the person no longer has possession, care, or control of any animals. In the event of the acquittal or final discharge without conviction of the person charged, if the animal is still impounded, the animal has not been previously deemed abandoned pursuant to subdivision (h), the court has not ordered that the animal be forfeited pursuant to subdivision (k), the court shall, on demand, direct the release of seized or impounded animals to the defendant upon a showing of proof of ownership.~~

~~(3)Any questions regarding ownership shall be determined in a separate hearing by the court where the criminal case was finally adjudicated and the court shall hear testimony from any persons who may assist the court in determining ownership of the animal. If the owner is determined to be unknown or the owner is prohibited or unable to retain possession of the animals for any reason, the court shall order the animals to be released to the appropriate public entity for adoption or other lawful disposition. This section is not intended to cause the release of any animal, bird, reptile, amphibian, or fish seized or impounded pursuant to any other statute, ordinance, or municipal regulation. This section shall not prohibit the seizure or impoundment of animals as evidence as provided for under any other provision of law.~~

~~(m)It shall be the duty of all peace officers, humane society officers, and animal control officers to use all currently acceptable methods of identification, both electronic and otherwise, to determine the lawful owner or caretaker of any seized or impounded animal. It shall also be their duty to make reasonable efforts to notify the owner or caretaker of the whereabouts of the animal and any procedures available for the lawful recovery of the animal and, upon the owner's and caretaker's initiation of recovery procedures, retain custody of the animal for a reasonable period of time to allow for completion of the recovery process. Efforts to locate or contact the owner or caretaker and communications with persons claiming to be the owner or caretaker shall be recorded and maintained and be made available for public inspection.~~

~~SEC. 16.Section 597.2 of the Penal Code is amended to read:597.2.~~
~~(a)It shall be the duty of an officer of an animal shelter, a humane society, or an animal regulation department of a public agency to assist in a case involving the abandonment or voluntary relinquishment of an equine by the equine's owner. This section does not require an animal shelter, a humane society, or an animal regulation department of a public agency to take actual possession of the equine.~~

~~(b)If an animal shelter, a humane society, or an animal regulation department of a public agency sells an equine at a private or public auction or sale, it shall set the minimum bid for the sale of the equine at a price above the current slaughter price of the equine.~~

~~(c)(1)This section does not prohibit an animal shelter, a humane society, or an animal regulation department of a public agency from placing an equine through an adoption program at an adoption fee that may be set below current slaughter price.~~

~~(2)A person adopting an equine under paragraph (1) shall submit a written statement declaring that the person is adopting the equine for personal use and not for purposes of resale, resale for slaughter, or holding or transporting the equine for slaughter.~~

~~SEC. 17.Section 597e of the Penal Code is amended to read:597e.~~
~~Any person who impounds, or causes to be impounded in any animal shelter, any domestic animal, shall supply it during confinement with a sufficient quantity of good and wholesome food and water, and in default thereof, is guilty of a misdemeanor. In case any domestic animal is at any time so impounded and continues to be without necessary food and water for more than 12 consecutive hours, it is lawful for any person, from time to time, as may be deemed necessary, to enter into and upon any animal shelter in which the animal is confined, and supply it with necessary food and water so long as it remains so confined. That person is not liable for the entry and may collect the reasonable cost of the food and water from the owner of the animal, and the owner of the animal is subject to enforcement of a money judgment for the reasonable cost of food and water.~~

~~SEC. 18.Section 597f of the Penal Code is amended to read:597f.~~
~~(a)Every owner, driver, or possessor of any animal, who permits the animal to be in any building, enclosure, lane, street, square, or lot, of any city, city and county, or judicial district, without proper care and attention, shall, on conviction, be deemed guilty of a misdemeanor. And it shall be the duty of any peace officer, officer of the humane society, or officer of an animal shelter or animal regulation department of a public agency, to take possession of the animal so abandoned or neglected and care for the animal until it is redeemed by the owner or claimant, and the cost of caring for the animal shall be a lien on the animal until the charges are paid. Every sick, disabled, infirm, or crippled animal, except a dog or cat, which shall be abandoned in any city, city and county, or judicial district, may, if after due search no owner can be found therefor, be humanely euthanized by the officer; and it shall be the duty of all peace officers, an officer of that society, or officer of an animal shelter or animal regulation department of a public agency to cause the animal to be humanely euthanized on information of that abandonment. The officer may likewise take charge of any animal, including a dog or cat, that by reason of lameness, sickness, feebleness, or neglect, is unfit for the labor it is performing, or that in any other manner is being cruelly treated; and, if the animal is not then in the custody of its owner, the officer shall give notice thereof to the owner, if known, and may provide suitable care for the animal until it is deemed to be in a suitable condition to be delivered to the owner, and any necessary expenses which may be incurred for~~

~~taking care of and keeping the animal shall be a lien thereon, to be paid before the animal can be lawfully recovered.~~

~~(b)(1)It shall be the duty of all officers of animal shelters or humane societies, and animal regulation departments of public agencies to convey, and for police and sheriff departments, to cause to be conveyed all injured cats and dogs found without their owners in a public place directly to a veterinarian known by the officer or agency to be a veterinarian that ordinarily treats dogs and cats for a determination of whether the animal shall be immediately and humanely euthanized or shall be hospitalized under proper care and given emergency treatment.~~

~~(2)If the owner does not redeem the animal within the locally prescribed waiting period, the veterinarian may personally perform euthanasia on the animal; or, if the animal is treated and recovers from its injuries, the veterinarian may keep the animal for purposes of adoption, provided the responsible animal control agency has first been contacted and has refused to take possession of the animal.~~

~~(3)Whenever any animal is transferred pursuant to this subdivision to a veterinarian in a clinic, such as an emergency clinic which is not in continuous operation, the veterinarian may, in turn, transfer the animal to an appropriate facility.~~

~~(4)If the veterinarian determines that the animal shall be hospitalized under proper care and given emergency treatment, the costs of any services which are provided pending the owner's inquiry to the agency, department, or society shall be paid from the dog license fees, fines, and fees for impounding dogs in the city, county, or city and county in which the animal was licensed or if the animal is unlicensed the jurisdiction in which the animal was found, subject to the provision that this cost be repaid by the animal's owner. No veterinarian shall be criminally or civilly liable for any decision which he or she makes or services which he or she provides pursuant to this section.~~

~~(c)An animal control agency which takes possession of an animal pursuant to subdivision (b), shall keep records of the whereabouts of the animal for a 72-hour period from the time of possession and those records shall be available to inspection by the public upon request.~~

~~(d)Notwithstanding any other provisions of this section, any officer of an animal shelter or animal regulation department or humane society, or any officer of a police or sheriff's department may, with the approval of his or her immediate superior, humanely euthanize any abandoned animal in the field in any case where the animal is too severely injured to move or where a veterinarian is not available and it would be more humane to euthanize the animal.~~

~~SEC. 19.Section 597u of the Penal Code is amended to read:597u.~~
~~(a)No person, peace officer, officer of a humane society, or officer of an animal shelter or animal regulation department of a public agency shall kill any animal by using any of the following methods:~~

~~(1)Carbon monoxide gas.~~

~~(2)Intracardiac injection of a euthanasia agent on a conscious animal, unless the animal is heavily sedated or anesthetized in a humane manner, or comatose, or unless, in light of all the relevant circumstances, the procedure is justifiable.~~

~~(b)With respect to the killing of any dog or cat, no person, peace officer, officer of a humane society, or officer of an animal shelter or animal regulation department of a public agency shall use any of the methods specified in subdivision (a) or any of the following methods:~~

~~(1)High-altitude decompression chamber.~~

~~(2)Nitrogen gas.~~

~~SEC. 20.Section 597v of the Penal Code is amended to read:597v.~~
~~No person, peace officer, officer of a humane society, or officer of an animal shelter or animal regulation department of a public agency shall kill any newborn dog or cat whose eyes have not yet opened by any other method than by the use of chloroform vapor or by inoculation of barbiturates.~~

~~SEC. 21.Section 599c of the Penal Code is amended to read:599c.~~
~~Every animal which is unfit, by reason of its physical condition, for the purpose for which those animals are usually employed, and when there is no reasonable probability of that animal ever becoming fit for the purpose for which it is usually employed, shall be by the owner or lawful possessor of the same, deprived of life within~~

~~12 hours after being notified by any peace officer, officer of said society, or employee of an animal shelter or animal regulation department of a public agency who is a veterinarian, to kill the same, and the owner, possessor, or person omitting or refusing to comply with the provisions of this section shall, upon conviction, be deemed guilty of a misdemeanor, and after that conviction the court or magistrate having jurisdiction of that offense shall order any peace officer, officer of said society, or officer of an animal shelter or animal regulation department of a public agency, to immediately kill that animal; provided, that this shall not apply to an owner keeping any old or diseased animal belonging to him or her on his or her own premises with proper care.~~

ATTACHMENT 8

FDA'S OVERSIGHT OF NECC AND AMERIDOSE: A HISTORY OF MISSED OPPORTUNITIES?

PRELIMINARY MAJORITY STAFF REPORT

COMMITTEE ON ENERGY AND COMMERCE

U.S. HOUSE OF REPRESENTATIVES
113TH CONGRESS

APRIL 16, 2013

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Table of Names and Abbreviations

Table of FDA Officials

Margaret Hamburg	*Commissioner, FDA*
Joshua Sharfstein	*Acting Commissioner, FDA; Deputy Commissioner, FDA*
Steven Silverman	*Director, Division of New Drugs and Labeling Compliance (DNDLC), Center for Drug Evaluation and Research (CDER); Assistant Director, Office of Compliance, CDER*
Michael Levy	*Director, DNDLC, Office of Compliance, CDER*
Kathleen Anderson	*Deputy Director, DNDLC, Office of Compliance, CDER*
Samia Nasr	*Team Leader, Compounding Team, Office of Compliance, CDER*
Tamara Ely	*Team Leader, Compounding Team, Office of Compliance, CDER*
Pamela Lee	*Team Leader, Compounding Team, Office of Compliance, CDER*
Deborah Autor	*Director, Office of Compliance, CDER*
Rick Friedman	*Director, Division of Manufacturing and Product Quality, CDER*
Michael Rogers	*Director, Division of Field Investigations, Office of Regulatory Affairs (ORA)*
Michael Chappell	*Acting Associate Commissioner, ORA*
Alyson Saben	*Deputy Director, Office of Enforcement, ORA*
Douglas Stearn	*Director, Division of Compliance Policy, Office of Enforcement, ORA*
Mutahar Shamsi	*Director, Compliance Branch, FDA NWE-DO; Director, FDA NWE-DO*
Amber Wardwell	*Director, Compliance Branch, FDA NWE-DO* David Elder *Director, Compliance Branch, FDA New England District Office (NWE-DO)*

FDA Office Abbreviations

Center for Drug Evaluation and Research (CDER)
Division of New Drugs and Labeling Compliance (DNDLC)
Office of Regulatory Affairs (ORA)
New England District Office (NWE-DO)
Office of the Chief Counsel (OCC)
Office of Criminal Investigations (OCI)

State of Massachusetts Office Abbreviations

Massachusetts Department of Public Health (MDPH)
Massachusetts Board of Registration in Pharmacy (MBP)

PRELIMINARY STAFF REPORT
FDA'S OVERSIGHT OF NECC AND AMERIDOSE: A HISTORY OF MISSED OPPORTUNITIES?

PART I: INTRODUCTION

In the summer and fall of 2012, a Massachusetts company, the New England Compounding Center (NECC), shipped over 17,000 vials of an injectable steroid solution from three contaminated lots to healthcare facilities in 23 states. The sterility of this drug product is critical. To relieve chronic pain, it is often injected into patients' spinal columns. After receiving injections of NECC's contaminated steroid, over 50 people have died from complications associated with fungal meningitis and almost 700 others have been stricken with meningitis or other persistent fungal infections. This outbreak ranks as one of the worst public health crises associated with contaminated drugs in the history of the United States, and exposed a fundamental failure in drug safety oversight.

In early October 2012, the Energy and Commerce Committee Majority and Minority staff received briefings from the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the Massachusetts Department of Public Health (MDPH). On November 14, 2012, the Subcommittee on Oversight and Investigations held a hearing to examine the meningitis outbreak and determine whether it could have been prevented. The Subcommittee subpoenaed the President and co-owner of NECC, Barry Cadden, to appear at the hearing. Mr. Cadden asserted his right against self-incrimination under the Fifth Amendment to the United States Constitution and refused to testify. The Subcommittee also invited FDA Commissioner Margaret Hamburg, M.D., and then-Interim Director of the MDPH Lauren Smith, M.D., MPH, to testify about their agencies' oversight of NECC. Further, the Subcommittee heard testimony from Ms. Joyce Lovelace, the wife of the first known victim. This hearing did not resolve the fundamental question posed: could the meningitis outbreak have been prevented?

Prior to the hearing, the MDPH produced thousands of pages of documents relating to NECC and Ameridose, another Massachusetts company owned and operated by the same family as NECC, which was also involved in large-scale production and distribution of drug products nationwide. [1] The documents detailed the MDPH's history with these firms. FDA, however, produced only a limited number of documents requested by the Committee prior to the November 2012 hearing, consisting of inspection reports and the agency's formal correspondence with NECC and Ameridose. No internal FDA communications were included. NECC has produced some documents, but has largely been unable to respond to the Committee's

[1] NECC and Ameridose share common ownership and corporate structures. Barry Cadden, his wife, Lisa Conigliaro-Cadden, her brother, Gregory Conigliaro, and his wife, Carla Conigliaro, serve as directors of both companies. NECC is located in Framingham, MA, adjacent to one of the two Ameridose facilities. Ameridose's other facility is located in Westborough, MA.

requests as its files and computers were seized pursuant to a search warrant executed by FDA's Office of Criminal Investigations (OCI) and the Criminal Division of the U.S. Attorney's Office, beginning on October 16, 2012. As a result of this ongoing criminal investigation, the Committee's investigative efforts to date have primarily focused on obtaining and reviewing FDA documents.

Since the hearing, the Committee has pressed FDA to produce all of its documents relating to NECC and Ameridose in order to obtain a full picture of FDA's inspectional history, oversight, and decision-making with respect to these firms. Only after being threatened with the possibility of a subpoena in a February 1, 2013, letter to Commissioner Hamburg, did FDA finally complete its production on March 21, 2013. FDA's production included internal emails between officials and staff at FDA headquarters and staff in FDA District Offices relating to NECC and Ameridose. It also included memoranda and emails exchanged within FDA's Office of the Chief Counsel (OCC) relating to the agency's assessment of its authority over pharmacy compounding. FDA has asserted that all documents and communications responsive to the Committee's requests have been produced.

After reviewing these documents, Majority Committee staff believes there is a strong basis for Members to pursue answers from FDA on whether this tragedy was preventable had the agency taken action under its existing authorities to address the steady stream of complaints it had received about NECC and its sister company, Ameridose, since issuing a Warning Letter to NECC in December 2006. The answer to this question is critical to solving any underlying problems. Operational and/or systemic flaws must be addressed in order to ensure that if any additional laws are passed or administrative actions are taken, they will actually lessen the chances of history repeating itself.

The documents that FDA produced to the Committee are troubling. Contrary to a statement made by Massachusetts Governor Deval Patrick, NECC was not "operat[ing] in the shadows."[2] NECC and Ameridose had long been the topic of significant discussion within FDA; the link between the two companies was well known. Since late 2004, when FDA last inspected NECC prior to the outbreak, the agency received numerous complaints from a range of healthcare providers—and at least one informant at Ameridose—about the companies' products and practices, including many that called into question the safety of the drugs the companies produced.

During the Commissioner's testimony before the Subcommittee in November, and in numerous statements made by her and other FDA officials since, FDA has maintained that uncertainty over its authority prevented the agency from pursuing enforcement actions against companies involved in compounding. For example, in her written statement for the Subcommittee's hearing on November 14, the Commissioner asserted that "FDA's ability to take action against compounding that exceeds the bounds of traditional pharmacy compounding and

[2] Press Release, Mass. Dep't of Health & Human Services, Governor Patrick Announces Legislation to Reform Board of Pharmacy and Fill Gaps in Compounding Industry Oversight (Jan. 4, 2013), *available at* http://www.mass.gov/eohhs/gov/newsroom/press-releases/eohhs/legislation-to-reform-board-of-pharmacy-announced.html.

poses risks to patients has been hampered by gaps and ambiguities in the law."[3] She repeatedly mentioned that FDA's authority over compounding pharmacies—even when such entities were engaged in activities that closely resembled those of a drug manufacturer—was questionable. The Commissioner stated that the "legal framework for FDA activities is very, very unclear, untested, and limited"[4] and that FDA has "ambiguous, fragmented, unclear, and contested authorities in this particular realm of pharmacy and drug manufacturing practice. . . ."[5] Citing these issues as impediments to FDA's ability to act in the face of mounting patient safety and public health concerns associated with NECC and Ameridose, the Commissioner proposed a new framework for regulating drug compounding operations and asked Congress for additional "authorities to support this new regulatory paradigm."[6]

FDA has long been steadfast in its assertions of authority over drug manufacturing being conducted under the guise of pharmacy compounding—and that the agency would enforce such authority when entities like NECC and Ameridose were engaged in significant violations of the Food, Drug, and Cosmetic Act and jeopardizing public health in the process.[7] That being said, internal FDA documents do show that the agency has been grappling with its authority over compounding for decades and that this debate came to a head in early 2009, after two different Circuit Courts of Appeals had issued conflicting opinions on the matter. What is troubling, though, is that FDA allowed this uncertainty to essentially paralyze the agency's oversight efforts from 2009 through 2012, even with respect to companies operating well outside the bounds of traditional pharmacy compounding, including NECC and Ameridose.

In the six years following the 2006 Warning Letter, FDA failed to take any enforcement action against NECC or Ameridose despite receiving complaint after complaint, often relating to the safety of the companies' drugs. Though several inspections and related enforcement actions were considered during this time period, they were repeatedly delayed and ultimately cancelled. In fact, in 2011, FDA made an affirmative decision to suspend inspections and enforcement actions relating to compounding operations, including NECC and Ameridose, until the agency finalized new guidance to industry detailing where it would draw the line between pharmacy compounding and drug manufacturing. Regardless of where this line would ultimately have been drawn, based on a review of the documents, it appears evident that NECC and Ameridose had already crossed it.

FDA's recent decisions not to even re-inspect NECC or Ameridose pursuant to any of the complaints the agency received are perplexing, particularly in light of FDA's flurry of

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[3] *The Fungal Meningitis Outbreak: Could It Have Been Prevented? Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 112th Cong. (2012) (prepared statement of Margaret Hamburg, Comm. of U.S. Food & Drug Admin. (FDA)) [hereinafter, "Hamburg Statement"], *available at* http://www.fda.gov/NewsEvents/Testimony/ucm327664.htm.

[4] *The Fungal Meningitis Outbreak: Could It Have Been Prevented? Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 112th Cong. 61-62 (2012) (testimony of Margaret Hamburg, Comm. of FDA) [hereinafter, "Hamburg Testimony"], *available at* http://energycommerce.house.gov/hearing/fungal-meningitis-outbreak-could-it-have-been-prevented.

[5] *Id.* at 74.

[6] *Id.* at 53.

[7] *See* Jane Axelrad, then-Associate Dir. for Policy, & David Horowitz, then-Dir., Off. of Compliance, Center for Drug Evaluation & Research (CDER), FDA, *FDA Update on Pharmacy Compounding*, Presentation to Int'l Acad. of Compounding Pharmacists (June 9, 2003).

enforcement activity since the meningitis outbreak involving a number of companies engaged in similar practices. According to FDA, since October 1, 2012, the agency has inspected 50 compounding facilities—issuing Form 483s[8] to approximately 30 firms, resulting in five firms recalling their products, and one firm receiving a Warning Letter. FDA staff informed Committee staff that other regulatory actions are under consideration. Like NECC and Ameridose, several of these companies have long histories with FDA. Prior to these inspections taking place, no new laws were passed and no new regulations or guidance documents were issued.

Part II of this memorandum provides a summary of FDA's authority over pharmacy compounding and the agency's related enforcement policies. Parts III and IV will show that, while broader policy discussions about the scope of FDA's authority were ongoing within the agency, a number of FDA employees and officials grew increasingly concerned about the safety of the products and practices at NECC and Ameridose, based on complaints the agency received. Despite its concerns that these companies were jeopardizing patient safety, FDA took no meaningful action against either company since issuing the 2006 Warning Letter to NECC. While the agency has pointed to confusion over its authority, the documents obtained by the Committee reveal that inefficiency, indecisiveness, skewed priorities, and a lack of leadership are what primarily hampered FDA's ability to prevent NECC's products from killing over 50 Americans.

PART II: FDA AUTHORITY OVER PHARMACY COMPOUNDING

FDA has long defined traditional pharmacy compounding as the combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication for an individual patient.[9] In 1992, due to FDA's concerns that certain compounding pharmacies were producing and distributing unapproved new drugs in a manner that was clearly outside the bounds of traditional pharmacy compounding, the agency issued Compliance Policy Guide 7132.16 (1992 CPG). FDA asserted that compounded drugs were not exempt from the requirements of the Food, Drug, and Cosmetic Act (FDCA or the Act), and while the agency did not intend to initiate enforcement actions against entities involved in traditional pharmacy compounding, it did plan to do so in situations where a company's activities resembled those of a drug manufacturer. A list of non-exhaustive factors the agency would consider in making these determinations was included.

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[8] FDA issues a Form 483 at the end of an inspection when the investigators believe that the observed conditions or practices, in their judgment, may indicate violations of the FDCA or any related regulations. FDA has stated that its goal in issuing a 483 is to have the company act quickly to correct potential violations. The FDA considers the 483 along with an Establishment Inspection Report (EIR), prepared by FDA investigators, and any other information, including any responses received from the company, to determine whether further action is appropriate.

[9] *See Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients: Hearing Before the S. Comm. on Health, Educ., Lab., and Pensions,* 108th Cong. (2003) (prepared statement of Steven Galson, Acting Dir., CDER, FDA), *available at* http://www.fda.gov/NewsEvents/Testimony/ucm115010.htm.

In 1997, based on concerns from compounding pharmacists that, according to the 1992 CPG, they were operating in per se violation of the FDCA, Congress added section 503A to the Act as part of the Food and Drug Administration Modernization Act of 1997 (FDAMA). Congress's intent in doing so was to "bring the legal status of compounding in line with FDA's longstanding enforcement policy of regulating only drug manufacturing, not ordinary pharmacy compounding."[10] Section 503A exempts compounded drugs from the new drug requirements and certain adulteration and misbranding provisions of the FDCA so long as certain conditions are met. The conditions listed in the statute parallel the factors included in the 1992 CPG and are intended to limit the exemptions from the FDCA's requirements to traditional pharmacy compounding. These conditions include that the compounding be performed by a licensed pharmacist or physician, that it is done in response to a patient-specific prescription, and that the compounded product is necessary for an identified patient. Section 503A also required that the physician's prescription must be unsolicited and the pharmacy must not advertise or promote the compounding of any particular drug.[11]

The provisions related to solicitation and advertising were challenged in court by a group of pharmacists as impermissible regulation of commercial speech. In February 2001, the U.S. Court of Appeals for the Ninth Circuit agreed and declared that the speech-related provisions were non-severable from the remainder of section 503A and, therefore, the entire section was invalid.[12] In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), the U.S. Supreme Court affirmed the Ninth Circuit's decision with respect to the First Amendment restrictions, but did not rule on the issue of severability.

Because of the uncertainty caused by the Supreme Court's decision in *Western States*, FDA re-issued an updated version of its 1992 CPG in May 2002. Compliance Policy Guide, Section 460.200 (2002 CPG) was very similar to the 1992 CPG; it reaffirmed FDA's authority over compounding under the FDCA and listed nine non-exhaustive "factors the Agency will consider in exercising its enforcement discretion regarding pharmacy compounding," including compounding copies of drugs that are commercially available and compounding drugs for third parties who resell to individual patients.[13] According to the document: "FDA believes that an increasing number of establishments with retail pharmacy licenses are engaged in manufacturing and distributing unapproved new drugs in a manner that is clearly outside the bounds of traditional pharmacy practice and that violates the Act. Such establishments and their activities are the focus of this guidance. . . . Pharmacies engaged in activities analogous to manufacturing and distributing drugs for human use may be held to the same provisions of the Act as manufacturers."[14]

In early 2005, another group of pharmacies brought suit—this time in Texas—contesting FDA's authority to regulate compounded drugs under the FDCA. On appeal, the case reached the Fifth Circuit. In *Medical Center Pharmacy v. Mukasey*, 536 F. 3d 383 (5th Cir. 2008), the

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[10] 143 Cong. Rec. S9839 (daily ed. Sept. 24, 1997) (statement of Sen. Kennedy).
[11] *See* 21 U.S.C. § 353.
[12] Western States Medical Center v. Shalala, 238 F. 3rd 1090 (9th Cir. 2001).
[13] *See* Compliance Policy Guide, Sec. 460.200 Pharmacy Compounding, FDA (May 2002) [hereinafter, "2002 CPG"], *available at* http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074398.htm
[14] *Id.* at 3.

U.S. Court of Appeals for the Fifth Circuit refused to be bound by the Ninth Circuit's decision in *Western States*, and held in July 2008 that the unconstitutional restrictions on commercial speech were in fact severable from the rest of section 503A, which should remain in effect. Therefore, in the Fifth Circuit, compounded drugs are exempt from the new drug, manufacturing, labeling, and other requirements of the FDCA, but only to the extent that the pharmacy complies with the restrictions set out in section 503A. Until the *Medical Center Pharmacy* decision, FDA had been operating under the assumption that section 503A was invalid in its entirety; therefore, as the agency stated in litigation and various correspondence over the previous six years, compounded drugs were subject to the FDCA requirements but FDA would continue to exercise enforcement discretion nationwide, as articulated in the 2002 CPG. After the decision, FDA publicly took the position that it would apply the non-commercial speech related provisions of section 503A in the Fifth Circuit and continue to exercise enforcement discretion with respect to entities located outside the Fifth Circuit. Within FDA, however, debate about the soundness of this approach would continue. These discussions and how they impacted potential enforcement actions against NECC and Ameridose will be addressed throughout this memorandum.

Publicly, FDA has consistently asserted authority over compounding pharmacies engaged in activities more analogous to those of a drug manufacturer. In fact, on June 29, 2012—only days after NECC made and distributed two contaminated batches of methylprednisolone acetate to facilities across the country—FDA released a statement to that effect: "FDA may take enforcement action against compounding pharmacies if warranted. The FDA makes its enforcement decisions about compounded products on a case-by-case basis after considering the particular facts at issue."[15] In a related letter sent to one large-scale compounding pharmacy on the same day, FDA stated that the agency is "applying its normal enforcement policies for compounded drugs" and that the compounding of large volumes of drugs that are essentially copies of FDA-approved products is one factor "the Agency considers in deciding whether to initiate enforcement action with respect to compounding."[16] The letter highlighted that these factors are addressed "in both section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. § 353a) and the Agency's compliance policy guide (CPG) on pharmacy compounding (CPG Sec. 460.200)."[17] The letter then included a footnote discussing the fact that "the Fifth and Ninth Circuit Courts of Appeals have reached different conclusions regarding whether section 503A is invalid or remains in effect."[18]

In her written statement for the November 14, 2012, Oversight Subcommittee hearing, Commissioner Hamburg cited this Circuit Court split as having "amplified the perceived gaps and ambiguity associated with FDA's authority over compounding pharmacies."[19] While there were challenges to FDA's authority, at no point in time did the agency lack sufficient authority

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[15] Press Announcement, FDA, Questions and Answers on Updated FDA Statement on Compounded Versions of hydroxyprogesterone caproate (the active ingredient in Makena) (June 29, 2012), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310215.htm.

[16] Letter from Dir. (acting), Off. of Unapproved Drugs and Labeling Compliance, Off. of Compliance, CDER, FDA, to Pres. & CEO, Wedgewood Pharmacy (June 29, 2012), *available at* http://www.fda.gov/downloads/NewsEvents/Newsroom/PressAnnouncements/UCM314387.pdf.

[17] *Id.* at 2.

[18] *Id.*

[19] Hamburg Statement, *supra* note 3.

under the FDCA to take enforcement action against companies that were clearly manufacturing under the guise of compounding and jeopardizing patient safety in the process. Regardless of whether FDA applied and cited to the factors listed in section 503A or the CPG, NECC and Ameridose were operating well outside the scope of traditional compounding pharmacies and squarely within FDA's authority to take action in response to violations of the FDCA.

PART III: FDA'S OVERSIGHT OF NECC: 2003-2006

NECC first appeared on FDA's radar in March 2002, when two adverse events were reported to the agency through its MedWatch system. Both adverse events involved patients experiencing meningitis-like symptoms after receiving betamethasone injections from the same lot produced and distributed by NECC. Based on the ensuing inspection, which was conducted with the MDPH, FDA issued NECC a Form 483 on April 16, 2002. FDA focused primarily on two violations: the sterility of the betamethasone product and NECC's failure to account for records related to the suspect lot of betamethasone, which subsequently tested positive for contamination.[20]

In October 2002, FDA and State inspectors returned to NECC in response to three MedWatch reports associated with the use of methylprednisolone acetate made by NECC in May 2002. Like betamethasone, methylprednisolone acetate is a steroid solution often injected into the spine to treat pain and swelling. According to FDA's investigative report, the three MedWatch reports involved patients having to be hospitalized with meningitis-like symptoms. Hospital staff informed FDA that vials from the same lot distributed by NECC were tested at the hospital and confirmed positive for contamination.[21] In February 2003, prior to FDA's issuance of another Form 483 to NECC, a meeting was convened with officials from FDA and the MDPH, at which time it was decided that NECC should be treated as a compounding pharmacy and that the State should take the lead on any further regulatory actions.[22]

Part III(A) of this memorandum will show that, not long after the February meeting, FDA began to receive additional information about the nature and scope of NECC's operations that would raise questions about whether the company was in fact operating as a manufacturer, as opposed to a traditional compounding pharmacy. This information would form the basis for an additional inspection beginning in September 2004. As described in Part III(B), FDA's extraordinary delay in issuing a Warning Letter to NECC pursuant to that inspection interfered with FDA's efforts to address new complaints that were submitted between the time of the 2004 inspection and a Warning Letter ultimately being issued in December 2006. Moreover, FDA's failure to address NECC's January 2007 response to the Warning Letter until almost another two years had passed further complicated FDA's enforcement efforts. Part III(C) details the

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[20] *See* FDA, NEW ENGLAND COMPOUNDING PHARMACY, INC. FORM FDA 483 (Apr. 16, 2002).

[21] FDA, INSPECTION REPORT OF NEW ENGLAND COMPOUNDING CENTER, at 4 (Feb. 10, 2003) [hereinafter, "FDA FEB. 10, 2003 INSPECTION REPORT"].

[22] *See* Memorandum from Kristina Joyce, Consumer Safety Officer, New England Dist. Off., FDA & Mark Lookabaugh, Compliance Officer, New England Dist. Off., FDA, to Central File, *February 5, 2003 Meeting with Massachusetts Board of Pharmacy/Division of Professional Licensure (239 Causeway Street, Boston, MA 02114)*, at 1 (Feb. 24, 2003) [hereinafter, "Feb. 24, 2003, FDA Memorandum"].

complaints that FDA continued to receive about NECC after the agency replied, on October 31, 2008, to NECC's response to the Warning Letter. Despite considering several additional inspections of NECC, FDA did not return to the company until the fungal meningitis outbreak.

A. FDA is on Notice that NECC is Operating Outside the Scope of a Traditional Compounding Pharmacy.

FDA has long recognized the importance of traditional pharmacy compounding and acknowledged that the State is primarily responsible for overseeing pharmacies engaged in this often critical practice. However, according to FDA's policy guidance, "when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the [FDCA], FDA has determined that it should seriously consider enforcement action."[23] Documents produced to the Committee show that prior to FDA's issuance of the Warning Letter to NECC the agency understood that the company was substantially engaged in activities resembling those of a drug manufacturer.

As was previously mentioned and discussed at the November 2012 hearing with Commissioner Hamburg, a meeting was convened in February 2003 between FDA and the MDPH, which included representatives from the Massachusetts Board of Registration in Pharmacy (MBP or Massachusetts Board). The purpose of the meeting was to "review the inspectional history of the New England Compounding Center and develop a joint strategy for achieving safe compounding practices at the firm."[24] At this point in time, FDA and State inspectors had already been to NECC on two separate occasions—in April and October 2002—in response to MedWatch reports associated with patients experiencing meningitis-like symptoms after having been administered NECC-produced betamethasone and methylprednisolone acetate injections.

During the February 2003 meeting, "[a] discussion was held to decide if NECC should be considered a manufacturer or a compounder."[25] It was decided that "current findings supported a compounding role" and that "the state would be in a better position to gain compliance or take regulatory action against NECC as necessary."[26] While FDA determined that the Massachusetts Board would take the lead, FDA concluded the meeting by "emphasizing the potential for serious public health consequences if NECC's compounding practices, in particular those relating to sterile products, are not improved."[27] Prior to this meeting taking place, David Elder, FDA's then-Director of Compliance in the New England District Office (NWE-DO) had emailed individuals in the Division of New Drugs and Labeling Compliance (DNDLC) at FDA's Center for Drug Evaluation and Research (CDER), acknowledging the need for FDA to continue to monitor the situation at NECC and the State's oversight of the firm. He stated, "We will have further discussions with the state about any future actions with this company – if the state can't

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[23] 2002 CPG, *supra* note 13, at 3.
[24] Feb. 24, 2003, FDA Memorandum, *supra* note 22.
[25] *Id.* at 2.
[26] *Id.*
[27] *Id.*

or won't take appropriate action, we will work with your office to devise an appropriate enforcement strategy as we remain concerned with this firm's operations."[28]

When asked about FDA's role at the hearing in November 2012, Commissioner Hamburg stated, "[FDA] tried to provide help and assistance. But the responsibility for assuring compliance with sterility issues was, in fact not our direct responsibility."[29] When questioned about whether she thought the State "could have stopped [the meningitis outbreak]," Commissioner Hamburg responded, "They were unsuccessful, and it is, you know, was tragic."[30] What Commissioner Hamburg failed to mention was that the snapshot FDA had of the company in February 2003 was very different from the deep understanding the agency had gained about the nature and scope of NECC's operations from 2003 up until the outbreak in 2012.

In fact, not long after the February 2003 meeting, a different picture of NECC began to emerge. On May 26, 2004, the Massachusetts Board received an email from a hospital pharmacist in Iowa suggesting that NECC was engaged in manufacturing, not traditional compounding. The pharmacist informed the MBP that "I have been receiving a lot of literature from [NECC] promoting compounded products for cataract surgery. . . . I was told I could easily get 15 patients out of every 3ml dropper of solution, so it would be very economical."[31] The pharmacist then stated, "Though I strongly believe in the right of pharmacists to compound prescriptions for their patients, the distribution of products under these circumstances looks much more like manufacturing than dispensing."[32] Based on other documents produced to the Committee, it appears as though the product being referenced was known as trypan blue, reportedly being used for capsular staining during cataract surgery. The lead attorney for the MBP, Susan Manning, asked the Board's Executive Director, Charles Young, in response, "Could you clarify what we may not have known about their operation previously that this email tells us? As in what the FDA might not know in their prior assessment that NECC was not a 'manufacturer'?"[33]

The MBP forwarded this correspondence to FDA along with a copy of a complaint it had received from a pharmacist in Wisconsin about NECC promoting a potent topical anesthetic cream.[34] At this point in time, FDA had in fact already received a complaint from a law firm representing a drug company related to NECC's promotion of trypan blue. On February 27, 2004, the firm informed FDA that its client had a similar, FDA-approved ophthalmic dye and that, while trypan blue had been approved in certain countries, it was not approved in the U.S.[35] Like the complaints that were forwarded to FDA by the MBP, this complaint raised further

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[28] E-mail from David Elder, Dir. of Compliance, New England Dist. Off., FDA, to Fred Richman, Dep. Dir., Div. of New Drugs & Labeling Compliance (DNDLC), Off. of Compliance, CDER, FDA, et al. (Jan. 23, 2003, 10:48 AM).
[29] Hamburg Testimony, *supra* note 4, at 63-64.
[30] *Id.* at 137.
[31] E-mail from Redaction to Mass. Bd. of Registration in Pharmacy (May 26, 2004, 6:16 PM).
[32] *Id.*
[33] E-mail from Susan Manning, Counsel to Mass. Bd. of Registration in Pharmacy, to Charles Young, Exec. Dir., Mass. Bd. of Registration in Pharmacy (May 27, 2004, 9:49 AM).
[34] *See* E-mail from Compliance Officer, New England Dist. Off., FDA, to Kathleen Anderson, Acting Team Leader, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA (June 23, 2004, 12:42 PM).
[35] *See* E-mail from Compliance Officer, New England Dist. Off., FDA, to Kathleen Anderson (Feb. 27, 2004, 10:49 AM).

questions about whether NECC was operating as a traditional compounding pharmacy or as a drug manufacturer. It was apparently the complaints related to trypan blue that prompted CDER to send the NWE-DO an inspection assignment for NECC on June 2, 2004, "to obtain information about the firm's compounding practices, especially as they relate to the compounding of trypan blue products."[36] Included in the inspection assignment was an acknowledgement that section 503A of the FDCA had been invalidated by the *Western States* decision so the inspection was being conducted in accordance with the 2002 CPG. It listed a number of questions that "are consistent with that guidance" for the inspector to answer based on information obtained from NECC.[37] The Ninth Circuit's invalidation of section 503A, therefore, did not preclude FDA from inspecting NECC and, as described in the 2002 CPG, from considering enforcement actions if "the scope and nature of [the] pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act."[38]

Pursuant to FDA's observations during this inspection, which began in September 2004 and was again conducted with State inspectors, NECC was issued a Warning Letter more than two years later, on December 4, 2006. The Warning Letter listed a number of practices that FDA inspectors observed during the inspection of NECC, or which were otherwise brought to the agency's attention, that indicated the company was operating as a manufacturer. In particular, the Warning Letter stated that the firm was compounding copies of commercially available products, pointing to the fact that trypan blue had since been approved by the FDA in December 2004; compounding standardized anesthetic drug products, which was outside the scope of traditional pharmacy compounding; repackaging Avastin, a sterile injectable product being used to treat macular degeneration; and reportedly informing physicians' offices that using a staff member's name on prescriptions would suffice, rather than submitting prescriptions to be filled based on the needs of an identified patient.[39] FDA concluded the Warning Letter by informing the President and co-owner of NECC, Barry Cadden, that "[f]ailure to promptly correct these deviations may result in additional regulatory action without further notice, including seizure or injunction against you and your firm."[40]

In December 2006, FDA warned Mr. Cadden that a subsequent inspection would be conducted. FDA failed to do so. When asked about this, Commissioner Hamburg testified in November: "We have also been reviewing actions taken in the past with regard to NECC. From our view thus far, we have no reason to believe that any of the specific actions in question, a more timely issuance of the 2006 Warning Letter, or inspectional follow-up, would have prevented this tragedy."[41] She elaborated, "It is very hard to know if any one action that we might have taken could have stopped this terrible tragedy. I wish that I could identify what that would be."[42]

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[36] Inspection Request from Kathleen Anderson to Dir., Investigations Branch, New England Dist. Off., FDA (June 2, 2004).
[37] *Id.*
[38] 2002 CPG, *supra* note 13, at 3.
[39] Warning Letter (NEW-06-07W) from Gail T. Costello, Dist. Dir., New England Dist. Office, FDA, to Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center (Dec. 4, 2006) [hereinafter, "FDA Warning Letter"].
[40] *Id.* at 5.
[41] Hamburg Statement, *supra* note 3.
[42] Hamburg Testimony, *supra* note 4, at 138.

What Commissioner Hamburg did not discuss was the fact that complaints about NECC continued well after the Warning Letter; that they were often associated with issues different in nature and scope than those addressed in the Warning Letter; that they were at times related to the safety and potency of NECC products; that FDA failed to inform the State about the complaints; and that FDA considered—but never conducted—several additional inspections of NECC and related enforcement actions that very well may have averted this tragedy. Parts II(B) and (C) detail these complaints and contemplated actions.

B. After Issuing the 2006 Warning Letter to NECC, FDA Receives More Complaints About NECC Products and Practices

Following FDA's September 2004 inspection of NECC to investigate the trypan blue complaints, FDA continued to receive new complaints about the company's products and practices. On January 14, 2006, Steven Silverman, then-Director of CDER's Division of New Drugs and Labeling Compliance (DNDLC), was forwarded an email from an individual in Texas detailing NECC's distribution of multiple-use vials of injectable methotrexate, a drug being used to treat certain types of arthritis and rheumatic conditions. The email stated, "In order to process an order they only need the physician's name and telephone number. . . . They do not need or desire to have the patient[']s name."[43] On a subsequent but related exchange, he attached Samia Nasr, then-Team Leader of CDER's Compounding Team, and stated, "As we discussed, NECC is a repeat player, so it might deserve attention that other operations wouldn't merit. But the team is caught up with a range of high-profile issues, so this may need to wait (especially absent reported injury)."[44] No substantive reply to this email was produced to the Committee, though on February 24, 2006, Ms. Nasr was forwarded another NECC solicitation from a consumer safety officer in CDER. This time, in addition to highlighting the firm's Avastin repackaging services, NECC was offering several compounded sterile injectable products.[45]

In forwarding the solicitation, the consumer safety officer stated, "The scope of their manufacturing seems to be beyond the limited concern we have already identified with the Avastin manipulation!" and "in light of the new information suggesting that the scope of drug manufacturing operations at this firm are expanding, the issuance of the directed inspection request is appropriate."[46] Ms. Nasr responded, "I do not have any problem with the inspection, we will know what is going on. I think what we were thinking is that if we send a [Warning Letter] now . . . [FDA] will not be able to send a second one. I do not think OCC [Office of the Chief Counsel or Chief Counsel's Office] will allow us to do that, correct?"[47]

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[43] E-mail from Redaction to Steven Silverman, Dir., DNDLC, Off. of Compliance, CDER, FDA, et al. (Jan. 14, 2006, 6:49 PM).
[44] E-mail from Steven Silverman to Dep. Dir., Div. of Manufacturing & Product Quality, Off. of Compliance, CDER, FDA, et al. (Jan 17, 2006, 11:20 AM).
[45] *See* E-mail from Supervisory Consumer Safety Officer, DNDLC, Off. of Compliance, CDER, FDA, to Samia Nasr, Team Leader, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, et al. (Feb. 24, 2006, 1:08 PM).
[46] *Id., and* E-mail from Supervisory Consumer Safety Officer to Samia Nasr et al. (Mar. 1, 2006, 9:30 AM).
[47] E-mail from Samia Nasr to Supervisory Consumer Safety Officer, et al. (Mar. 2, 2006, 6:05 AM).

The Warning Letter was ultimately sent in December 2006. NECC responded one month later, noting that "the Warning Letter is based on an inspection of NECC that started on September 23, 2004, approximately twenty-eight months ago" and that "[s]ome of the letter's assertions no longer apply to NECC's operations."[48] After disputing FDA's authority over compounded drugs, Mr. Cadden stated that "NECC does not compound copies of FDA-approved commercially available drugs, introduce unapproved new drugs into interstate commerce, does not need approved [New Drug Applications] before dispensing its compounded medications, and does not process or repackage approved drugs in a manner that would subject us to FDA regulation. Nor are our compounded medications misbranded. NECC dispenses compounded medications upon the receipt of valid prescriptions."[49]

After reviewing NECC's letter, Mr. Silverman emailed several colleagues in CDER on January 9, 2007, including Ms. Nasr and CDER's Director of Compliance at the time, Deborah Autor. He stated, "In my view, NECC's response is unacceptable. . . . If you disagree, let's discuss. Otherwise, we need a response to this letter. And given the comments about the timeliness of the Warning Letter (OCC's fault), we need a response within a reasonable time frame."[50]

FDA's response letter was not ultimately sent until October 31, 2008. Soon after the Warning Letter was issued in 2006, however, new complaints about NECC had already begun to arrive. It is apparent from documents produced to the Committee that FDA considered additional inspections and potential enforcement activities throughout this time period, but FDA's failure to issue a timely response to NECC's January 2007 reply letter thwarted any agency action.

Soon after FDA received NECC's response, on February 22, 2007, a compliance officer in the NWE-DO received an envelope of documents from an anonymous sender. The compliance officer forwarded copies of the documents to several of her colleagues in the District Office stating, "It appears from the words she highlighted on the documents, that she wants me to know about other violations of NECC [than those described in the Warning Letter]. . . . I will send the information to CDER. Note that all the documents she sent me pre-date the [Warning Letter]; however, this information can be used for the [Warning Letter] follow-up inspection assignment."[51] Similar to the NECC solicitation FDA had been forwarded a year earlier, in addition to the Avastin repackaging services being offered, the documents included advertisements for a number of compounded sterile injectable products.

While these complaints did not involve patients being harmed by NECC products, they did provide FDA with additional knowledge about the nature and scope of the company's operations. On June 25, 2007, however, FDA did receive an adverse event report directly implicating Avastin that had been repackaged by NECC and administered to a patient to treat

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[48] Letter from Barry J. Cadden, Dir. of Pharmacy, NECC, to Compliance Officer, New England Dist. Off., FDA, et al, at 1 (Jan. 5, 2007).
[49] *Id.* at 3.
[50] E-mail from Steven Silverman to Deborah Autor, Dir., Off. of Compliance, CDER, FDA, et al. (Jan. 9, 2007, 3:20 PM).
[51] E-mail from Compliance Officer, New England Dist. Off., FDA, to Mutahar Shamsi, Dir., Compliance Branch, New England Dist. Off., FDA, et al. (Feb 22, 2007, 11:30 AM).

macular degeneration. According to the report, the patient had received six monthly doses of Avastin without incident until April 21, 2007, when "the patient developed severe endopthalmitis" and had to undergo emergency eye surgery.[52] The report stated, "The Avastin dose administered prior to event onset was provided to the [reporting physician] by the New England Compounding Center."[53] No communications referring or relating to this complaint were produced to the Committee by FDA. It is not apparent, based on a review of the documents, that FDA did anything in response—let alone re-inspect NECC—despite primarily detailing these very concerns in the Warning Letter: "We are especially concerned with the potential microbial contamination associated with splitting Avastin – a single-use, preservative-free, vial – into multiple doses. When used intravitreaily, microbes could cause endophtalmitis, which has a high probability for significant vision loss."[54]

The decision over whether FDA would re-inspect NECC pursuant to the new complaints was clearly being influenced by the agency's inability to send a timely response to NECC's January 2007 letter replying to the Warning Letter. Further, the outstanding response was also influencing FDA's decision whether to inspect Ameridose, NECC's sister company. On May 21, 2007, CDER drafted an inspection request for the NWE-DO based on a MedWatch report FDA received associated with Ameridose, which made similar complaints to those FDA had already received about NECC. The complaint stated that "Ameridose is engaged in the manufacture of unapproved intravenous solutions that are not dispensed pursuant to a prescription. . . ."[55] When one of the inspectors in the District Office received the request from CDER, he emailed his supervisor asking, "Do we want to inspect with the state this new location under the same or similar management/ownership prior to responding to the NECC response of January 7, 2007?"[56] The supervisor responded that CDER was "aware of the relationship between NECC and Ameridose" but that they "still want[ ] you to go to Ameridose" after calling them to discuss the approach.[57] However, the Ameridose inspection did not ultimately occur until December 2007. Prior to the inspection, the District Office inspector contacted an individual on CDER's Compounding Team who asked him to obtain information during the inspection to "elaborate on their business relationship/model and anything else that may potentially cause some inspectional hurdles."[58] This inspection and decisions surrounding it, as well as additional issues with Ameridose and the relationship between the two entities, are subsequently addressed in greater detail in Part IV of this memorandum.

Meanwhile, new complaints directly associated with the safety of NECC products continued. On December 6, 2007, FDA's Office of Emergency Operations received a call from a

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[52] FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) (June 25, 2007).
[53] *Id.*
[54] FDA Warning Letter, *supra* note 39, at 3.
[55] Inspection Request from Staff Fellow, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Michael Kravchuk, Dir., Investigations Branch, New England Dist. Off., FDA, (May 21, 2007).
[56] E-mail from Drug Pre-Approval Manager, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA (June 7, 2007, 9:05 AM).
[57] E-mail from Compliance Officer, New England Dist. Off., FDA, to Drug Pre-Approval Manager, New England Dist. Off., FDA (June 7, 2007, 11:49 AM).
[58] E-mail from Reg. Operations Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Drug Pre-Approval Manager, New England Dist. Off., FDA (Dec. 4, 2007, 10:55 AM).

"physician pain specialist who treats patients with epidural injections."[59] The caller stated that "[f]or a period of time, he was treating fibromyalgia patients with epidural injections of betamethasone manufactured by New England Compounding Center" and that "between August 22 and October 5 he noticed that some vials of product were discolored (which he discarded) but others, which appeared normal, were administered and his patients started having problems."[60]

Based on a memorandum drafted by a consumer safety officer in FDA's New Orleans District Office (NOL-DO) assigned to investigate the complaint, she first visited the physician's office on December 11, 2007.[61] The memorandum detailed a series of meetings and interviews conducted with the physician and several patients through January 2008, which raised numerous concerns about the activities of the physician and his practices. While the physician failed to produce certain records, dates, and patient information requested, he did state that "greater than 100 patients that were treated with the betamethasone began complaining of increased fibromyalgia pain and moderate to severe flu-like symptoms"; that he noticed "some of the vials of betamethasone appeared to be discolored"; and that "particles [were] floating in the bottom of the vial."[62] He also said that "the lots in question were received on 8/20/07, 9/17/07, and 9/28/07"[63] and provided the FDA investigator with "vials of the questionable betamethasone"[64] he had not discarded from one of these lots, which she retained for sampling. She ultimately referred the complaint to the NWE-DO "for follow-up as appropriate" on February 25.[65]

It is apparent from subsequent District Office communications produced to the Committee that FDA tested the vials provided by the physician, but those tests did not detect the presence of any bacterial endotoxins and the samples met "FDA requirements for assay and ID."[66] After reviewing the memorandum and the test results, the NWE-DO compliance officer forwarded the information to Ms. Nasr in CDER on April 1, 2008, and followed up on May 22 asking, "Any decision on any type of follow-up?"[67] No response from Ms. Nasr was produced to the Committee, though this conversation between the District Office and CDER continued for some time.[68] FDA did not re-inspect NECC pursuant to this complaint. Further, based on documents produced to the Committee, it does not appear as though FDA contacted the company or informed the State about these new concerns with NECC's betamethasone injections.

FDA's decision not to re-inspect NECC based on this complaint is troubling, given that the initial inspection of NECC in 2002 was triggered by adverse event reports associated with patients experiencing similar symptoms after receiving the same drug. FDA's delay in resolving the 2006 Warning Letter appears to have influenced the agency's response. For example, on

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[59] E-mail from Emergency Coordinator, Off. of Crisis Mgmt., Off. of Emergency Operations, FDA, to Supervisor, New Orleans Dist. Off., FDA (Dec. 6, 2007, 1:53 PM).
[60] *Id.*
[61] *See* Memorandum from Consumer Safety Officer, New Orleans Dist. Off., FDA, to Supervisory Consumer Safety Officer, New Orleans Dist. Off., FDA (January 9, 2008) (note that Memorandum is accidentally dated 2007).
[62] *Id.* at 2.
[63] *Id.*
[64] *Id.* at 3.
[65] *Id* at 1.
[66] E-mail from Compliance Officer, New England Dist. Off., FDA, to Samia Nasr (Apr. 1, 2008, 2:44 PM).
[67] May 22, 2008 email from Ota to Nasr.
[68] *See* May 29, 2008 email from Ota to Anderson.

June 17, 2008, FDA received separate, though related, information about betamethasone being made and distributed by NECC. Representatives of a pharmaceutical distributor met with NOL-DO staff to express concerns about compounded betamethasone "being injected in the spinal synovial fluid."[69] Three different sizes of NECC vials were shared with NOL-DO staff who forwarded the information to the NWE-DO.[70] Once the NWE-DO compliance officer responsible for NECC received it on June 24, he forwarded it to Ms. Nasr in CDER stating, "The District usually follows up with these memos by inspecting the firms listed in the memo but the NECC [Warning Letter case] is still open and we do not usually re-inspect until an adequate response is received from the firm. I know the last time we spoke you expressed that you might want to issue an assignment to inspect NECC. Please advise on follow-up to the memo?"[71] Ms. Nasr responded, "We received information also about NECC compounding mesotherapy products[72] and we were thinking about inspection. Can we set up a call with you and others to discuss?"[73]

Ms. Nasr informed Mr. Silverman, who at this point had been promoted to Assistant Director of CDER's Office of Compliance, and Kathleen Anderson, Deputy Director of the DNDLC, that she had spoken with NWE-DO staff about the inspection and the question came up about what they would do "if they find violations and we end up needing to issue another warning letter."[74] Ms. Anderson replied, "Typically we do not issue a firm a warning letter for the same violation (unless it has been many years since the initial warning letter). Sometimes we issued more than one warning letter to a firm if the letters are to address different unrelated issues. If we have issued multiple letters, for the same or similar problems then we should be considering seizure or injunction rather than another warning letter."[75]

CDER decided to go forward with the inspection of NECC and began drafting an assignment for the District Office. On June 27, 2008, Ms. Nasr spoke with the compliance officer in the NWE-DO responsible for NECC. The compliance officer informed Mutahar Shamsi, then-Director of Compliance in the District Office, "Today Samia [Nasr] called me and she said she talked with people in [CDER] and they said if the firm is still compounding then we will enjoin the firm."[76] The assignment was ultimately issued on September 16, 2008, and stated, "The purpose of this inspection request is to investigate the site's compounding practices, particularly relating to the production of mesotherapy/lipodissolve products."[77] It is clear from the assignment that in addition to the mesotherapy-specific issues, the inspector was to follow-up on the observations documented in the December 2006 Warning Letter and to investigate the firm's compounding operations in general. In particular, as indicated by a list of questions for

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[69] Memorandum from Compliance Officer, New Orleans Dist. Off., FDA, to File (June 17, 2008).
[70] *See id.*
[71] E-mail from Compliance Officer, New England Dist. Off., FDA, to Samia Nasr (June 24, 2008, 11:38 AM).
[72] Mesotherapy products have been advertised as an alternative to liposuction. They have been compounded with phosphatidylcholine. Although phosphatidylcholine is approved by the FDA as a dietary supplement, compounders have prepared the product for injection.
[73] E-mail from Samia Nasr to Compliance Officer (June 24, 2008, 11:42 AM).
[74] E-mail from Samia Nasr to Kathleen Anderson, et al. (June 25, 2008, 6:43 AM).
[75] E-mail from Kathleen Anderson to Samia Nasr (June 25, 2008, 8:48 AM).
[76] E-mail from Compliance Officer, New England Dist. Off., FDA, to Mutahar Shamsi (June 27, 2008, 1:15 PM).
[77] Inspection Request, Sample Collection from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Michael Kravchuk & Gail Costello, at 1 (Sept. 16, 2008).

the inspector to address, sterility was a concern: "Are drug products and supplies stored under appropriate temperature, light, moisture, sanitation, and ventilation conditions?"; "Are sterile products made in an environment that prevents contamination?"; and "What type of in-process or finished product testing [is] performed and at what frequency?" The assignment concluded, "Based on the determination if the firm is operating as [a] manufacturer or as [a] traditional compounding pharmacy, an enforcement action is likely if the firm is operating as [a] manufacturer."[78]

Once Mr. Shamsi received the assignment on September 18, 2008, he forwarded it to Deborah Autor in CDER asking, "Did you want to get involved also at the beginning? Since the firm has already received a Warning Letter, further violations should (I hope) lead to a judicial action."[79] After hearing from several of her colleagues in CDER, Ms. Autor replied on September 25, "I'm told the [CDER] compounding team is now talking to and collaborating with the District on this hybrid mesotherapy/general compounding inspection. Let me see if the GMP side of my office also wants to engage now to prepare for that part of the inspection."[80] She proceeded to reach out to then-Director of CDER's Division of Manufacturing and Product Quality, Rick Friedman, asking for his thoughts, to which he replied, "[W]e could assist with manufacturing and sterility assurance issues in a pre-inspection briefing[.]"[81]

While CDER appeared ready to go forward with the inspection—despite the fact that the agency had yet to send NECC a response to its January 2007 letter objecting to the findings in the Warning Letter—it is apparent that Mr. Shamsi began to question whether it was wise to inspect the facility prior to issuing the response. On October 1, 2008, he emailed Ms. Autor stating, "I'm wondering whether our lack of a response would hinder any further regulatory action against NECC (if OGC is reluctant to respond to a [Warning Letter], how would they respond to an injunction request?)[.]"[82] To a certain extent, Mr. Shamsi's concerns were shared by the NECC compliance officer in the NWE-DO: "If we re-inspect there is no second [Warning Letter.] Next step is to enjoin the firm. . . . Injunctions have time frames and have to be processed quickly. If OCC and CDER cannot agree on a response letter can they agree on an injunction[?]"[83]

By this point, documents produced to the Committee reveal that FDA staff was frustrated with the time it was taking the FDA Chief Counsel's Office to approve a response to NECC. In fact, in January 2008, Mr. Silverman had asked whether anyone in CDER was having any particularly frustrating interactions with OCC they would like addressed.[84] On January 28, Ms. Nasr responded that the Compounding Team was concerned about the "length of time to get

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[78] *Id.* at 6.
[79] E-mail from Mutahar Shamsi to Deborah Autor (Sept. 18, 2008, 1:44 PM).
[80] E-mail from Deborah Autor to Mutahar Shamsi (Sept. 25, 2008, 11:29 PM).
[81] E-mail from Rick Friedman, Dir., Div. of Manufacturing & Product Quality, Off. of Compliance, CDER, FDA, to Deborah Autor (Sept. 26, 2008, 12:31 AM).
[82] E-mail from Mutahar Shamsi to Deborah Autor (Oct. 1, 2008, 8:19 AM).
[83] E-mail from Compliance Officer, New England Dist. Off., FDA, to Mutahar Shamsi (Oct. 2, 2008, 9:15 AM).
[84] *See* E-mail from Consumer Safety Officer, FDA, to Samia Nasr, et al. (Jan. 28, 2008, 11:39 AM).

anything cleared by OCC" and specifically cited the NECC response draft that CDER had sent to OCC on August 29, 2007.[85]

While discussions about inspecting NECC prior to issuing the response letter were ongoing, on October 9, 2008, FDA's Los Angeles District Office received a complaint about a patient being hospitalized after having been intravenously administered phosphatidylcholine made by NECC.[86] Phosphatidylcholine injections are mesotherapy products, which FDA had concerns about NECC making and distributing prior to any adverse event reports having been received. According to the complaint report, after the initial infusion period, the patient "developed [a] burning sensation" and a "swollen arm and hand."[87] After the patient was discharged, he could not swallow food or liquid, vomited, and urinated blood.[88] He was "admitted to an emergency room three more times" and "[t]he physician found blood clots in his arm and hand."[89] FDA collected a sample "to be analyzed for microbiological analysis and analyzed for potency and chemical contamination."[90] The NWE-DO was informed about the situation on October 16, 2008. On October 17, Mr. Shamsi emailed the District compliance officer responsible for NECC stating, "We need to make sure the investigator follows up on this."[91] However, according to the compliance officer's notes from a meeting that took place two days prior, involving officials from CDER, OCC, and the NWE-DO, including Mr. Shamsi, it had already been decided that "OCC will get a response letter to the firm before we do an inspection."[92]

On October 31, 2008, more than four years after the underlying inspection and almost two years after NECC responded to the Warning Letter, OCC finally signed off on FDA's response. The letter "acknowledge[d] and apologize[d] for the significant delay in this correspondence."[93] Like the agency detailed in the Warning Letter, FDA presented an extensive summary of its authority over compounded drugs and the factors the agency would consider in determining whether to exercise enforcement discretion. FDA concluded by stating, "We agree that the length of intervening period was unusual. This in no way diminishes our serious concerns about your firm's operation. Your firm must promptly correct the violations noted in the December 4, 2006, Warning Letter, and establish procedures to assure that such violations do not occur. Its failure to do so may result in enforcement action including seizure of the firm's products and/or an injunction against the firm and its principals. In a future inspection, we will confirm the commitments that you made in your response. We also will verify that your firm's compounding practices are consistent with the policy articulated in the [2002] CPG, and that your firm's operation is not otherwise at odds with the conditions under which the agency exercises enforcement discretion towards pharmacy compounding."[94] FDA, however, never

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[85] E-mail from Samia Nasr to Consumer Safety Officer, FDA, (Jan. 28, 2008, 11:45 AM). *See also* E-mail from Samia Nasr to Consumer Safety Officer, FDA (Jan. 28, 2008, 12:12 PM).
[86] *See* FDA, CONSUMER COMPLAINT/INJURY REPORT, at 1 (Oct. 9, 2008).
[87] *Id.*
[88] *See id.*
[89] *Id.*
[90] *Id* at 3.
[91] E-mail from Mutahar Shamsi to Compliance Officer, New England Dist. Off., FDA (Oct 17, 2008, 7:11AM).
[92] Memo of Meeting, Compliance Officer, New England Dist. Off., FDA (Oct. 15, 2008).
[93] Letter from Compliance Officer, New England Dist. Off., FDA, to Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center, at 1 (Oct. 31, 2008).
[94] *Id.* at 4.

returned to the firm until the 2012 meningitis outbreak, despite receiving new complaints about NECC's products and practices.

C. *After Closing Out the 2006 Warning Letter, FDA Continues to Receive New Complaints About the Safety of NECC Products and the Company's Practices*

Now that FDA's response to NECC had been sent, based on communications among FDA staff, there should have been no barrier to FDA conducting an inspection of NECC, especially in light of the additional issues and complaints that had been brought to the agency's attention while it worked on a response to NECC's January 2007 letter. On November 4, 2008, however, Mr. Shamsi informed the Director of the NWE-DO Investigations Branch at the time that "CDER would like us to hold off for now" on the inspection that would have covered issues relating to mesotherapy products and general compounding practices.[95] No explanation for this new delay is apparent from the documents produced to the Committee, although FDA staff resumed its debate in February 2009 when the results from the tests of the phosphatidylcholine associated with the hospitalization in California had come back showing the samples were superpotent and displayed signs of degradation.[96]

With further evidence that NECC's practices were continuing to result in unsafe products, FDA finally seemed prepared to take decisive action. On February 11, 2009, after receiving the test results, the same District compliance officer emailed a number of his colleagues, "CDER wants us to immediately (today) go [to] NECC to determine if the firm is willing to recall the Phosphatidyl choline [*sic*] injection it compounds. The drug is superpotent and not approved and should be recalled. We want to determine the batch size, and where distributed. The recall part should be done immediately and can be separate from the inspection."[97]

Based on a review of the documents, however, it does not appear as though a recall ever happened. According to a memorandum dated February 17, 2009, a conference call was held with CDER and NWE-DO staff. This memorandum indicates that NECC had yet to be informed about the results of the phosphatidylcholine sample.[98] Apparently, FDA had decided to wait and inform NECC of the test results during an inspection, which was scheduled to take place "around March 23, 2009."[99] On March 18, however, Ms. Nasr once again informed the District compliance officer to "hold off [on] the inspection."[100] Ms. Nasr explained that she had spoken with OCC and that "she is working on an inspection assignment to cover 503A and [the] CPG so [we] don't have to do 2 inspections."[101] According to the District compliance officer, Ms. Nasr

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[95] E-mail from Mutahar Shamsi to Michael Kravchuk, et al. (Nov. 4, 2008, 4:30 PM).
[96] Jan 30, 2009, memo from Dunn to Nasr.
[97] E-mail from Compliance Officer, New England Dist. Off., FDA, to Mutahar Shamsi, et al. (Feb. 11, 2009, 7:39 AM).
[98] *See* DRAFT Memo of Conference Call, Compliance Officer, New England Dist. Off., FDA, *New England Compounding Center Inspection* (Feb. 17, 2009).
[99] *Id.* at 1.
[100] E-mail from Compliance Officer, New England Dist. Off., FDA, to Investigator, New England Dist. Off., FDA (March 18, 2009, 11:28 AM).
[101] E-mail from Compliance Officer, New England Dist. Off., FDA, to Investigator, New England Dist. Off., FDA, et al. (March 19, 2009, 9:25 AM).

"said she is afraid if [the] inspection [is] outside [the] 5th District [the] firm will file [a] petition against [the] FDA."[102] It is apparent from this email and additional documents produced to the Committee that in anticipation of having to defend an enforcement action—such as a seizure of products or injunction against the firm—in court, FDA wanted to ensure that observations during an inspection not only addressed the factors listed in the CPG but clearly established that NECC fell outside the safe harbor provided to traditional compounding pharmacies under section 503A.

FDA has confirmed to the Committee that no further inspection of NECC occurred until after the meningitis outbreak had commenced. Towards the end of 2009, FDA received complaints about NECC's solicitation and distribution of erythromycin without patient-specific prescriptions[103] and NECC's sale of sodium tetradecyl sulfate to a physician in North Carolina for use in treating varicose veins, when there was only one commercially available product indicated for such treatment.[104] According to this last complaint report, CDER was aware of "NECC compounding sodium tetradecyl sulfate and will be issuing an assignment for NECC in the future."[105] One year later, in September 2010, Ms. Nasr was informed by an individual with CDER's Drug Shortage Program about NECC soliciting a certain antibiotic during a shortage, along with a number of other products. This individual stated, "[D]on't know if there is anything that can be done but thought I would forward it on." Ms. Nasr replied, "Yes, NECC is under our radar."[106]

Based on a review of the documents produced to the Committee, the next complaint associated with NECC was one discussed at some length during the November 2012 hearing with Commissioner Hamburg. On May 10, 2011, FDA's Denver District Office informed the NWE-DO about a Cease and Desist Order the Colorado Board of Pharmacy issued to NECC "regarding their illegal distribution of compounded drugs to hospitals in the Denver metropolitan area."[107] When Ms. Nasr was made aware of this information on May 11, she forwarded it to others in CDER stating, "Good news."[108]

The same day FDA's Denver District Office informed the New England office of the Cease and Desist Order, the New England District compliance officer responsible for NECC spoke to an optometrist with the U.S. Department of Veterans Affairs who was inquiring about whether they could use NECC to repackage Avastin for them into single dose units. This communication is significant, because it once again confirms that FDA understood that NECC was acting more like a manufacturer than a traditional compounding pharmacy. He forwarded a summary of his conversation to Ms. Nasr, copying several of his colleagues, one of whom responded, "I didn't think they could use firms if profiles were unacceptable? NECC Framingham is profiled as a manufacturer (because we determined they are a manufacturer not a

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[102] *Id.*

[103] *See* E-mail from Redaction to Samia Nasr (Sept. 14, 2009, 3:26 PM). *See also* E-mail from Samia Nasr to Anderson, et al. (Sept. 14, 2009, 3:34 PM).

[104] *See* E-mail from Compliance Officer, New England Dist. Off., FDA, to Samia Nasr, et al. (Sept. 29, 2009, 6:27 AM).

[105] FDA, CONSUMER COMPLAINT/INJURY REPORT, at 3 (Sept. 17, 2009).

[106] E-mail from Samia Nasr to Associate Dir., CDER Drug Shortage Program (Sept. 14, 2010, 2:44 PM).

[107] E-mail from Senior Case Review Expert, Denver Dist. Off., FDA, to Supervising Consumer Safety Officer, New England Dist. Off., FDA, et al. (May 10, 2011, 4:19 PM).

[108] E-mail from Samia Nasr to Kathleen Anderson, et al. (May 11, 2009, 6:17 AM).

compounding pharmacy)[.]"[109] The compliance officer replied, "You are right. I didn't think of profiles. And you are right about the repacking, manufacturing, registering, listing and GMPs. I just spoke to Samia Nasr and she said the same thing about repacking that you did that it[']s manufacturing and not compounding."[110]

The understanding FDA had reached with the Massachusetts Board in February 2003 that the State would take the lead in making sure that NECC improved its practices was based on their determination that NECC was operating as a compounding pharmacy. By 2011, FDA was well aware of the fact that this was no longer the case. Though it should have been occurring all along, it was during this time period that communication with the State would have been particularly valuable, as FDA had compiled a list of specific issues and complaints associated with NECC's practices and products that needed to be addressed. In her written testimony for the November 2012 hearing, Commissioner Hamburg pointed to the fact that "[t]he Massachusetts Board of Pharmacy reinspected NECC in 2011 in response to a letter from the firm indicating that NECC was 'updating its facility and moving into adjacent space'"; that the "inspection included a tour of the facility, security review, licensing review, and inspection of NECC's sterile and non-sterile processing areas"; and that the MBP "found the facility to be 'Satisfactory'."[111]

Commissioner Hamburg neglected to mention that by 2011, FDA knew that NECC was operating like a manufacturer and the agency had failed to pass along any information to the Massachusetts Board that would have allowed it to conduct a more informed inspection. The MDPH has asserted to Committee staff that all communications with FDA pertaining to NECC and/or Ameridose have been produced. There is no evidence from any documents produced to the Committee that FDA even knew the State inspection was taking place. Further, in the same section of inspection notes from which Commissioner Hamburg quoted, the Massachusetts Board inspector stated that he left a voicemail for Mr. Cadden on April 22, 2011, prior to the inspection taking place; that Mr. Cadden called him back on April 28 "pushing off" the inspection by two weeks; and that it was ultimately conducted on May 24, 2011—giving NECC more than a month to prepare.[112] Given that NECC employees were allegedly instructed to drop everything and clean after the firm's management became aware that FDA would be inspecting the facility in connection with the meningitis outbreak, Mr. Cadden's actions are concerning.[113]

On July 16, 2012, FDA's Denver District Office again reached out to the NWE-DO, this time informing them that NECC had violated the Colorado Board of Pharmacy's Cease and Desist Order. The same compliance officer told his colleague that he would "forward this to CDER to see if they want us to do anything."[114] He continued: "OCC at the moment is not

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[109] E-mail from Compliance Officer, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA, et al. (May 11, 2011, 11:02 AM).
[110] E-mail from Compliance Officer, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA, et al. (May 11, 2011, 11:13 AM).
[111] Hamburg Statement, *supra* note 3.
[112] MASS. DEP'T OF PUB. HEALTH, INSPECTION REPORT, at 9 (May 24, 2011).
[113] *See 60 Minutes. Lethal Medicine*. (CBS television broadcast Mar. 10, 2013) (transcript available at http://www.cbsnews.com/8301-18560_162-57573470/lethal-medicine-linked-to-meningitis-outbreak/?pageNum=4.
[114] E-mail from Compliance Officer, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA (July 17, 2012, 8:19 AM).

doing anything with compounding pharmacies because of the recent losses in the southwest. . . . CDER said last year we may do something at the end of this year with compounding pharmacies. I recently had a meeting with OCI [FDA's Office of Criminal Investigations] based on a complaint they received and they may be doing something with Ameridose. I invited CDER to the meeting and they were on the speakerphone. They did not want us going to the firm."[115]

Three things are apparent from this email: 1) FDA continued to grapple with the implications of the Circuit Court split several years after the Fifth Circuit decision in *Medical Center Pharmacy*, and until agency officials agreed on a path forward, oversight would be minimal; 2) the relationship between NECC and Ameridose was well understood by FDA staff; and 3) the complaints about NECC's sister company, Ameridose, were serious in nature and magnified those already made about NECC. Part IV of this memorandum addresses these points.

PART IV: OVERSIGHT OF NECC'S SISTER COMPANY, AMERIDOSE: 2006 – 2012

Like NECC, its sister company, Ameridose, had a significant history with FDA. FDA was well aware of the firms' shared ownership and management. On several occasions, this factored into FDA's decision-making about whether and when to take certain actions related to one of the companies. As FDA's actions pursuant to the meningitis outbreak indicate, a recent inspection of one firm may very well have triggered an inspection of the other.

As Part IV will detail, from an enforcement perspective, FDA's inaction with respect to Ameridose may be even more egregious than in the case of NECC. Ameridose was different from NECC in one, fundamental way: it had registered with FDA as a manufacturer and repackager of drug products. Ameridose's website states that the company is "[a]n FDA registered manufacturer" that meets both U.S. Pharmacopeia (USP) compounding standards and current good manufacturing practice (cGMP) requirements.[116] In addition to being registered with FDA, the firm was also registered in Massachusetts as a retail pharmacy and had Drug Enforcement Administration licenses as a manufacturer and retail pharmacy for controlled substances.[117] According to FDA, Ameridose first registered with the agency in September 2006.[118]

A. After Two Inspections Reveal Problems at Ameridose, FDA's Plan to Issue a Warning Letter to the Company is Ultimately Rejected.

Within a year of the company having registered with FDA, the agency "received a report through its MedWatch system alleging Ameridose is engaged in the manufacture of unapproved

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[115] *Id.*
[116] http://www.ameridose.com/about-ameridose/.
[117] FDA, ESTABLISHMENT INSPECTION REPORT, at 1 (Jan. 22, 2008) [hereinafter, "Jan. 22, 2008, ESTABLISHMENT INSPECTION REPORT"].
[118] *See* Memorandum from FDA to Committee staff, *Timeline of FDA Interactions with NECC and Ameridose,* at 2 (produced to Committee staff on Feb. 1, 2013, per request of Oct. 12, 2012) [hereinafter, "FDA Timeline"].

intravenous solutions that are not dispensed pursuant to a prescription."[119] The complainant who filed the MedWatch report asked FDA to investigate and "determine whether this company is making these products on a sound basis, or whether, as I strongly suspect, they are ignoring cGMPs when preparing these intravenous products. I fear a large-scale epidemic of serious infections may occur caused by these products."[120]

At the same time FDA was examining an NECC complaint forwarded by an anonymous sender, on May 22, 2007, CDER issued an inspection request to the New England District Office for Ameridose. Since FDA's reply to NECC's response to the December 2006 Warning Letter was still pending, NWE-DO staff asked whether this would be an impediment to the Ameridose inspection. Samia Nasr, then-Team Leader of CDER's Compounding Team, informed the primary compliance officer in the District that CDER was "aware of the relationship between NECC and Ameridose" and that they still wanted to proceed with the inspection.[121] According to the draft inspection request for Ameridose, the goal of the assignment was "to obtain current information about the firm's compounding practices, especially as they relate to the compounding of injectable medications."[122]

Despite having drafted an inspection request in May, by September 2007, the FDA inspection of Ameridose had yet to occur. Steven Silverman, then-Assistant Director of CDER's Office of Compliance, emailed Michael Rogers, then-Director of the Division of Field Investigations in FDA's Office of Regulatory Affairs, and Michael Chappell, then-Acting Associate Commissioner for Regulatory Affairs, a list of the "inspections that are the most critical."[123] Mr. Silverman suggested that these inspections had been stalled and noted the impact that failing to inspect could have on the public health. He requested "[a]ny help that you or others can provide in breaking these assignments loose" and stated that "[t]hese are all matters for which we're prepared to take enforcement action and moving them forward will directly benefit public health."[124] Mr. Silverman listed six "compounding inspection assignments"—Ameridose was second on the list.[125]

The Ameridose inspection finally took place in December 2007, though not before additional concerns about the firm's practices were reported to FDA. On November 21, 2007, a representative from the Ohio Board of Pharmacy forwarded CDER a solicitation that Ameridose had sent to hospitals in his State. The Ohio Board representative noted the link between Ameridose and NECC stating, "I have a company named Ameridose (which appears to be a subsidiary or an associate of New England Compounding Center – same or similar corporate officers) who is offering to sell pre-filled syringes to hospitals . . . who have purchased . . .

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[119] Inspection Request from Staff Fellow, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Michael Kravchuk, Dir., Investigations Branch, New England Dist. Off., FDA, at 1 (May 21, 2007) [hereinafter, "May 21, 2007, Inspection Request"].
[120] FDA, MEDWATCH REPORT, at 2 (May 2, 2007).
[121] E-mail from Compliance Officer, New England Dist. Off., FDA, to Drug Pre-approval Manager, New England Dist. Off. (June 7, 2007, 11:49 AM).
[122] May 21, 2007, Inspection Request, *supra* note 119.
[123] E-mail from Steven Silverman to Michael Rogers, Dir., Div. of Field Investigations, Off. of Reg. Affairs, FDA, et al. (Sept. 5, 2007, 4:52 PM).
[124] *Id.*
[125] *Id.*

infusions pumps."[126] He concluded, "[T]his appears to be just another episode of drug manufacturing being self-classified as compounding in order to make everything appear to be legitimate."[127] After several exchanges with an individual in CDER's Division of Drug Information, the representative from the Ohio Board informed the CDER employee, "I had a conversation with a Greg Conigliaro from Ameridose on Wednesday after I sent you the message. I think he said he was the President of Ameridose. . . . He said that Ameridose, of course, thinks that their preparation of syringes for use in these pumps is perfectly legal. I told him I didn't think so unless he did it on a patient specific basis by prescription. That did not make him happy[.]"[128] These exchanges were forwarded to Ms. Nasr and others in CDER.

Several days before the Ameridose inspection began on December 7, 2007, CDER raised the company's connection with NECC and asked the inspector in the NWE-DO to obtain information during the inspection to "elaborate on their business relationship/model and leadership structure and anything else that may potentially cause some inspectional hurdles."[129] The inspection report that was ultimately filed, however, did not address the question of the companies' relationship in any depth, other than to list Ameridose's management structure. The inspection report revealed that Ameridose was engaged in manufacturing activities in that the firm had "made over 610 Lots of products and 38 batches of products of Admixtures for hospitals and packaged them into IV bags, syringes, and vials since they opened in 2006."[130] This finding prompted an employee on the Compounding Team in CDER to email the Director of the NWE-DO Investigations Branch on March 3, 2008, and request an inspection, stating that "the scope and nature of Ameridose's activities are outside the bounds of traditional pharmacy practice and more consistent with that of a drug manufacturer. Therefore, as per our conversation today we would like The District to do a full GMP inspection of Ameridose LLC as soon as possible."[131]

This second inspection of Ameridose did not begin until four months later, in July 2008. In the meantime, the Ohio Board of Pharmacy again reached out to CDER about Ameridose on May 12, this time regarding other sterile injectable products. The Executive Director of the Board stated, "Before the Board issues a Cease & Desist letter to [Ameridose], telling them to stop shipping manufactured products into Ohio under the guise of compounding, I wonder if you could verify for me whether or not this is a legitimately manufactured product that is made by an FDA approved manufacturer?"[132] No substantive reply to this email was produced to the Committee, though the email was forwarded to Ms. Nasr, at which point she notified several of her colleagues that "Ameridose is a pharmacy that we inspected recently and we are waiting for the District to go back for GMP re-inspection."[133]

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[126] E-mail from Redaction to CDER DRUG INFO (Nov. 21, 2007, 2:02 PM).
[127] *Id.*
[128] E-mail from Redaction to CDER DRUG INFO (Nov. 23, 2007, 12:55 PM).
[129] E-mail from Reg. Operations Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Drug Pre-Approval Manager, New England Dist. Off., FDA (Dec. 4, 2007, 10:55 AM).
[130] Jan. 22, 2008, ESTABLISHMENT INSPECTION REPORT, *supra* note 117.
[131] E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Michael Kravchuk (Mar. 3, 2008, 3:27 PM).
[132] E-mail from Exec. Dir., Ohio St. Bd. of Pharmacy, to CDER DRUG INFO (May 12, 2008, 1:49 PM).
[133] E-mail from Samia Nasr to Kathleen Anderson, et al. (July 16, 2008, 9:15 AM).

FDA began its second inspection of Ameridose on July 21, 2008. According to the inspection report, Ameridose had been labeled a "High Risk facility" in advance. Since the previous inspection only seven months before, Ameridose's operations had considerably expanded. The report stated, "The firm currently markets over 600 products including 7 Antibiotic class, 15 Class II, 1 Class III, 2 Class IV and many Class VI products"[134] and that their customers include "approximately 500 Hospital Pharmacies located in 49 of the 50 states."[135] Summarizing the firm's operations, the FDA inspector stated, "The firm ships 75% of their product outside of Massachusetts. [Ameridose] stated that all their customers that order the products are affiliated with hospitals. The firm manufactures small orders in Lot sized batches and combines multiple orders of one specific product into Batches of finished product. None of their manufactured or repackaged products are linked to a specific patient prescription."[136]

In addition to concerns about the nature of the company's operations, the FDA inspector also observed several objectionable practices in Ameridose's facility that were then documented in a Form 483 that FDA issued to the company on August 6, 2008. While all were troubling, the first observation was particularly egregious. According to the Form 483, Ameridose was not waiting to receive test results confirming the strength or sterility of their products before shipping them to customers. Specifically, the Form 483 stated, "Testing and release of drug product for distribution [does] not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release."[137] Further, FDA found that there was "no potency or identity test done on the finished drug product, and the product is shipped immediately and prior to the 14 day sterility test results are received by the firm."[138] One example provided by the inspector was fentanyl, a narcotic injectable many times more potent than morphine. The inspector retained samples of this product for testing.[139]

Several individuals in the NWE-DO were alarmed by the Ameridose inspection findings. After reviewing the report, one compliance officer emailed her colleague in the District: "This case bothers me the more I think of it. . . . [T]he firm doesn't conduct potency testing on ANY finished product (only the stock solution, which they subsequently dilute) so I have serious concerns with the potency [of] all their products. Perhaps we should be thinking of getting a health hazard evaluation and getting the firm to recall as many of their products as we can or going out to get more finished product samples. A vast majority of their products are sterile injectable opioids, super potency is a serious concern."[140]

By September 10, 2008, the results from the fentanyl samples showed that the product was, in fact, superpotent.[141] The following day, a compliance officer in the NWE-DO informed

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[134] FDA, ESTABLISHMENT INSPECTION REPORT, at 4 (Aug. 22, 2008) (page numbers correspond with narrative report attachment).
[135] *Id.* at 5.
[136] *Id.* at 3.
[137] FDA, AMERIDOSE LLC FORM FDA 483, at 1 (Aug. 6, 2008).
[138] *Id.*
[139] *See* FDA Timeline, *supra* note 118.
[140] E-mail from Compliance Officer, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA (Sept. 9, 2008, 7:23 PM).
[141] *See* E-mail from Compliance Officer, New England Dist. Off., FDA, to Supervisory Consumer Safety Officer, New England Dist. Off., FDA (Sept. 10, 2008, 9:31 AM).

Sophia Pasedis, the Vice President of Regulatory Affairs at Ameridose, about the results. According to a memorandum of the telephone call, the compliance officer told Ms. Pasedis that "FDA is very concerned" and asked what Ameridose was "going to do with the product in the market."[142] According to a memorandum of the conversation, "She said she was going to call her accounts to see if there were any reactions and if there was any product out there. I told her if she was going to [do a] voluntary recall she could call our recall coordinator. She said she would like to first make some calls and then she would call me back."[143] Ms. Pasedis did call him back and, according to the compliance officer, "[She] said 155 bags were made and sent to 5 different facilities. She said all the facilities have ordered the product multiple times. She said one firm ordered 100 bags. She did not think she had to do anything further."[144] When he informed her that Ameridose should consider issuing a recall notice, "She said she could not make a decision until she speaks with one of her bosses and none are answering their cell phones." [145] After stating that he informed Ms. Pasedis they needed to speak first thing in the morning, the compliance officer concluded his memorandum: "The person[ ] did not appear to know what a recall is and we may have problems tomorrow. . . ."[146]

On September 12, FDA spoke with Gregory Conigliaro, co-owner of Ameridose. According to the FDA memorandum summarizing this telephone call, the compliance officer "told Mr. Conigliaro that it was his responsibility as a manufacturer to manufacture a safe and effective product. [He] told Mr. Conigliaro the product fails potency and his product is now adulterated. . . . Mr. Conigliaro said he would do the right thing and send the recall notification to the 5 accounts."[147] The recall was conducted that day.[148] On September 15, 2008, the recall notice was sent to Michael Levy, who succeeded Steven Silverman as the Director of the DNDLC in CDER's Office of Compliance. He stated in response, copying Samia Nasr and Kathleen Anderson, "Thanks. We have a history with this firm. . . . Maybe it's time for reinspection and possible follow up enforcement action?"[149] During this time period, Mr. Levy was also engaged in discussions about the NECC inspection being considered. On September 19, Samia Nasr emailed him and noted the firms' relationship, stating, "Please remember that [A]meridose and NECC are owned by two brothers."[150]

Even prior to the fentanyl recall, based on observations included in the August 2008 inspection report and corresponding Form 483, CDER had already made the determination that a Warning Letter should be sent to Ameridose and that it "should include both new drug cha[r]ges

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[142] Memo of Telephone Conversation between Compliance Officer, New England Dist. Off., FDA, and Sophia Pasedis, Vice President of Reg. Affairs, Ameridose LLC (Sept. 11, 2008).
[143] *Id.*
[144] E-mail from Compliance Officer, New England Dist. Off., FDA, to Recall Coordinator, New England Dist. Off., FDA (Sept. 11, 2008, 5:12 PM).
[145] *Id.*
[146] *Id.*
[147] Draft Memo of Telephone Call between Compliance Officer, New England Dist. Off., FDA, and Gregory Conigliaro, Co-owner, Ameridose (Sept. 12, 2008).
[148] *See* E-mail from Compliance Officer, New England Dist. Off., FDA, to Mutahar Shamsi, et al. (Sept. 12, 2008, 10:34 AM).
[149] E-mail from Michael Levy, Dir., DNDLC, Off. of Compliance, CDER, FDA, to Rick Friedman, Dir., Div. of Manufacturing & Product Quality, Off. of Compliance, CDER, FDA (Sept. 15, 2008, 8:40 PM).
[150] E-mail from Samia Nasr to Michael Levy (Sept. 19, 2008, 7:28 AM).

and GMP charges."[151] According to the documents, CDER reviewed the NWE-DO's draft Warning Letter for several months and ultimately cleared it for Chief Counsel's Office review in February 2009. Before it was cleared, there were a number of discussions among CDER officials about the nature of Ameridose's operations and how they would impact potential enforcement actions. For example, after reviewing the latest draft of the Warning Letter on January 23, 2009, Michael Levy asked his Deputy, Kathleen Anderson, whether Ameridose was "a hospital outsourcer like CAPS [Central Admixture Pharmacy Services]? If so, haven't we avoided bringing new drug charges against these firms?"[152] Ms. Anderson replied, "Yes, it appears to be a type of outsourcer, but Ameridose has several important differences. We haven't brought new drug charges against outsourcers that are manipulating/reconstituting FDA approved drugs as a hospital pharmacy typically does and that are not making copies of FDA approved drugs. Ameridose on the otherhand [*sic*] is using bulk APIs to make stock solutions of their own versions of drugs, including many that are copies of approved drugs."[153] Levy responded, "OK, got it. Thanks."[154]

On March 4, 2009, one of the lawyers in the Chief Counsel's Office informed CDER and the NWE-DO that they would approve the Warning Letter to Ameridose, but that "OCC's clearance is on hold pending . . . a final determination as to whether clarifications are needed" to a paragraph discussing FDA's enforcement policy with respect to entities located outside the Fifth Circuit.[155] This issue had yet to be resolved six months later, at which point CDER made the decision to disapprove the Warning Letter on September 1, 2009.[156] When the NWE-DO compliance officer responsible for Ameridose informed Mutahar Shamsi, then-Director of Compliance in the NWE-DO, of the decision, he noted the impact that the Circuit Court split and the resulting delay had on FDA's willingness to issue a Warning Letter to Ameridose, stating, "The activity notes say the [Warning Letter] case was put on hold due to conflicting court rulings related to Pharmacy Compounding and CDER is not proceeding with issuance of this [Warning Letter] because it has now been 1 year since the district[']s inspection of the firm."[157]

Angered by the news that the Warning Letter would not be issued because CDER and OCC could not agree on a path forward, Mr. Shamsi emailed Alyson Saben, FDA's Deputy Director of Enforcement, and other officials in the agency, asking whether they could discuss the decision and stating, "NWE-DO spent a lot of time developing this case last year and having it 'closed' for nebulous reasons is troubling. . . . This is quite frustrating since I thought we had a good [Warning Letter]. I've told our [Investigations Branch] *to not bother inspecting compounding pharmacies if we aren't going to act on the violations*."[158] Ms. Saben forwarded

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[151] E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Compliance Officer, New England Dist. Off., FDA (Sept. 9, 2008, 11:00 AM).
[152] E-mail from Michael Levy to Kathleen Anderson, Dep. Dir., DNDLC, Off. of Compliance, CDER, FDA (Jan. 23, 2009, 10:21 PM).
[153] E-mail from Kathleen Anderson to Michael Levy (Jan. 24, 2009, 7:53 AM).
[154] E-mail from Michael Levy to Kathleen Anderson (Jan. 24. 2009, 9:55 AM).
[155] E-mail from General Attorney, Office of the Chief Counsel (OCC), FDA, to Michal Levy, et al. (Mar. 4, 2009, 5:49 PM).
[156] *See* E-mail from Div. of Info. Resources Mgmt. to Compliance Officer, New England Dist. Off., FDA, et al. (Sept. 1, 2009, 11:13 AM).
[157] E-mail from Compliance Officer, New England Dist. Off., FDA, to Mutahar Shamsi (Sept. 1, 2009, 11:27 AM).
[158] E-mail from Mutahar Shamsi to ORA DCB Advisory Comm. (Sept. 1, 2009, 11:52 AM) (emphasis added).

Mr. Shamsi's email to Michael Levy, copying Deborah Autor and others in CDER. She stated, "As I recall . . . CDER was moving forward with developing a prioritized list of ongoing/open pharmacy compounding cases for which we are prepared to move forward/refresh the evidence in light of [then-Acting Commissioner of FDA] Dr. Sharfstein's decision to proceed with 503A. At that time, we discussed that CAPS [Central Admixture Pharmacy Services], Phar[MED]ium and Ap[o]the[C]ure were on the short list. Could you provide us with a status check on your current thinking and what this means for other cases such as Ameridose?"[159]

After hearing about the decision on Ameridose, Douglas Stearn, then-Director of the Division of Compliance Policy in FDA's Office of Enforcement, reached out to Mr. Shamsi on September 2, and indicated that FDA might be prepared to initiate enforcement actions against compounding operations. Mr. Stearn stated, "CDER is changing on this issue. Now is an ideal time to push."[160] The next day, Mr. Stearn emailed Michael Levy and Kathleen Anderson and noted, "There are a number of districts that have voiced concerns about some compounders that had previous OAI [Official Action Indicated] inspections. One thing that I have heard is that some of these compounders have serious sterility issues, which I understand . . . *CDER sees as a central public health issue*. It seems to me these districts would welcome the opportunity to work with CDER on choosing and focusing on compounding firms that have the issues CDER has identified."[161]

FDA's indecision about how to address compounding operations in light of the Fifth Circuit's decision in *Medical Center Pharmacy* significantly deterred enforcement actions against companies, including Ameridose, even when the agency knew they were engaged in manufacturing and jeopardizing public health in the process.

B. From 2009-2012, FDA Fails to Take Action While Complaints about Ameridose's Products and Practices Continue to Mount

It is apparent from documents produced to the Committee that senior officials at FDA were discussing how to address growing concerns about Ameridose and similar companies while also grappling with what the Fifth Circuit's decision to uphold the non-speech related provisions of section 503A meant for the agency. FDA considered at length whether the agency should apply section 503A only in the Fifth Circuit and continue to exercise enforcement discretion elsewhere, or whether it should uniformly apply section 503A nationwide, except in the Ninth Circuit, where the agency would exercise enforcement discretion regarding compounding that satisfies the criteria in section 503A. While the agency has since asserted that the former course

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[159] E-mail from Alyson Saben, Dep. Dir., Off. of Enforcement, Off. of Reg. Affairs, FDA, to Deborah Autor, et al. (Sept. 2, 2009, 12:11 PM). On February 10, 2012, the Department of Justice, at the request of FDA-OCI, charged AphotheCure Inc., a company located in Dallas, TX, with two misdemeanor criminal violations of the FDCA in connection with their interstate shipment of two lots of misbranded injectable products that led to the deaths of three people in 2007. After the meningitis outbreak, in February and March 2013, FDA inspected four PharMEDium Services, LLC facilities, and four CAPS facilities, issuing Form 483s in each instance. *See* http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/ucm340853.htm.

[160] E-mail from Douglas Stearn, Dir., Div. of Compliance Policy, Off. of Enforcement, Off. of Reg. Affairs, FDA, to Mutahar Shamsi, et al. (Sept. 2, 2009, 4:17 PM).

[161] E-mail from Douglas Stearn to Kathleen Anderson, et al. (Sept. 3, 2009, 8:54 AM) (emphasis added).

of action would be followed, based on a review of the documents, it is apparent that FDA ultimately made the decision to pursue the latter. Prior to formally announcing this new agency position, however, FDA determined that new guidance and regulations needed to be drafted to provide a clear framework that FDA would use to differentiate between pharmacy compounding and drug manufacturing—a process that was still ongoing several years later and which was almost completed at the time of the fungal meningitis outbreak in September 2012. Unfortunately, enforcement actions stalled while the agency debated whether and how to conduct inspections or bring actions against compounding operations in the interim.

Meanwhile, CDER and NWE-DO staff was becoming increasingly concerned about Ameridose. On October 27, 2009, CDER received an anonymous email from an informant within the company: "July/August 2008 the FDA came to Ameridose LLC in [F]ramingham, [MA] for an inspection. The company performed illegal and unethical actions. They directed the testing facilities they use to change reports, based on the drug[ ] results. They forged documents, forced employees to direct others to do so. . . . [Gregory Conigliaro] silently directs people to change results, doctor the findings but hides in his office. . . . VP is Sophia Pasedis, Pharm D all licenses are in her name, she too is frauduelent [*sic*]."[162] FDA's Office of Criminal Investigations (OCI) ultimately forwarded the email to Mutahar Shamsi on December 7, who replied, copying Samia Nasr, "Thanks for the info. We are waiting for an assignment from CDER to go out and will follow up on this. Ameridose has been on our radar for quite some time."[163]

Based in part on this complaint, FDA documents demonstrate that the agency was preparing to inspect Ameridose, though the inspection would again be delayed. After further discussing the informant's claims with Ms. Nasr over the telephone, Mr. Shamsi emailed several individuals in the NWE-DO and OCI, stating that "CDER will be issuing an assignment for Ameridose after an outsourcing guidance document has been cleared through CDER."[164] He then decided, "Let's wait until we get an assignment from CDER before we proceed on our side because if we forward anything down to OCC it will not proceed quickly. Obviously if we get information of an imminent health hazard we'll have to go out. I don't see that here yet."[165]

The documents indicate that CDER did not begin drafting the inspection request until April 2010 and that it was primarily to follow up on the issues raised in the Form 483 and the draft Warning Letter, both of which were based on the previous GMP inspection in 2008.[166] The assignment was received by the NWE-DO on April 28, 2010, though it was not scheduled to take place until July.[167] In the interim, CDER received another new complaint about Ameridose in

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[162] E-mail from druginfo@fda.hhs.gov to CDER DRUG INFO (Oct. 27, 2009, 6:47 PM).
[163] E-mail from Mutahar Shamsi to Resident Agent in Charge, Off. of Crim. Investigations (OCI), FDA, et al. (Dec. 7, 2009, 4:54 PM).
[164] E-mail from Mutahar Shamsi to Compliance Officer, New England Dist. Off., FDA, et al. (Dec. 8, 2009, 11:54 AM).
[165] *Id.*
[166] *See* E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA to Samia Nasr (Apr. 15, 2010, 2:44 PM).
[167] *See* E-mail from Investigator, New England Dist. Off., FDA, to Supervisory Consumer Safety Officer, New England Dist. Off., FDA (Apr. 29, 2010, 10:36 AM).

early June that altered the focus of the discussions. This complaint was made by a manufacturer and related to "Ameridose's pre-mixed nicardipine injection products."[168]

The new complaint complicated FDA's previously planned inspection of Ameridose. On July 6, 2010, a member of CDER's Compounding Team reached out to the primary compliance officer in the District Office informing him that CDER was "still trying to discuss with [the Office of the Chief Counsel] on how to approach the firm" and asking that he keep CDER up to date on whether the state independently "decide[s] to inspect [the] site in regards to the nicardipine."[169] It is clear from the documents that a decision was made to accompany the State to Ameridose on July 8, but the FDA inspector was told to focus exclusively on the commercial complaint related to the nicardipine injections. According to the FDA inspector's report, "This inspection did not include review of corrective actions to the previous FDA 483. This was a directed inspection specifically to cover the admixing and distribution of Nicardipine IV."[170] The inspector's report and her related comments indicate that she questioned whether Ameridose was in fact a compounding pharmacy, as the assignment referenced. Throughout the report, the inspector used the terms "manufactures" and "manufacturing" and her statement of jurisdiction held that the "firm currently repacks and manufactures prescription drug products which are FDA regulated drug products."[171] While forwarding her colleague notes from the inspection, the inspector stated, "I was looking on their website to see if they identify themselves as a compounding pharmacy – they don't. It states in multiple places that they are an FDA registered manufacturer. I didn't see 'compounding' anywhere."[172]

Soon after the inspection, the NWE-DO received an anonymous complaint from a "pharmacist in the manufacturing department" at Ameridose. The informant specifically raised concerns about the safety of Ameridose products.[173] This individual contacted the District Office about his concerns on at least three separate occasions in July and August 2010. During this initial call, "He explained that he recently became aware of some potential GMP issues and he wanted to bring them to our attention."[174] According to a memorandum of the call, the informant raised concerns about contamination, stating that "[approximately] a week and a half ago, they were making a batch of succinylcholine. . . . He stated that after a few lots, someone observed particulates in the bag. He stated that they determined the particulates to be 'angel hair' and pieces of the bag itself. He stated that he was not sure if the previous lots made from the same batch were released."[175] According to the related complaint report, it was also the informant's "opinion that the quality assurance program [had] been downsized and deprioritized."[176]

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[168] E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Supervisory Consumer Safety Officer, New England Dist. Off., FDA (June 9, 2010, 4:12 PM).
[169] E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Compliance Officer, New England Dist. Off., FDA (July 6, 2010, 9:10 AM).
[170] FDA, ESTABLISHMENT INSPECTION REPORT, at 1 (July 8, 2010).
[171] *Id* at 3.
[172] E-mail from Investigator, New England Dist. Off., FDA, to Investigator, New England Dist. Off., FDA (July 9, 2010, 2:58 PM).
[173] *See* Memorandum of Teleconference between Redaction and Compliance Officer, New England Dist. Off., FDA (July 13, 2010).
[174] *Id.*
[175] *Id.*
[176] FDA, CONSUMER COMPLAINT/INJURY REPORT (July 13, 2010).

After the inspection limited to the nicardipine complaint was completed, the District compliance officer responsible for Ameridose asked CDER about the broader inspection assignment that was issued in April and scheduled to begin on July 26, 2010. CDER's response was that it "should be put on hold for now" and that they "need[ed] to resolve the nicardipine issue with the firm first before we do a full inspection."[177]

On June 8, July 7, and at least one more time on July 22, 2010, an attorney for the company who had filed the commercial complaint about Ameridose's nicardipine distribution reached out to Deborah Autor, then-Director of Compliance at CDER, asking why FDA had yet to take any action against Ameridose.[178] On July 23, Ms. Autor forwarded the chain of emails to Kathleen Anderson and Samia Nasr, copying other CDER officials, and asking, "What's your assessment of this situation?"[179] Ms. Anderson replied that the New England District Office had just inspected Ameridose pursuant to the nicardipine complaint but acknowledged there were other issues with the company that needed to be addressed, which would factor into the agency's course of action. She explained, "It is my understanding that Ameridose is a state licensed pharmacy and it's [*sic*] operation is similar to CAPS. We will determine next steps based on what is found during the inspection, whether the firm is operating outside of 503A and the CPG, what the state plans, and the status of the nicardipine issue, etc."[180]

While this debate ensued within the agency, FDA continued to receive complaints associated with the safety of Ameridose products. On July 23, 2010—the same day of the exchange between Ms. Anderson and Ms. Autor—FDA received a MedWatch report about a nurse administering half of a syringe of dextrose 50% made by Ameridose to a patient before noticing "a white precipitate below the rubber plunger" which "extended about ¾ inch along the plunger's base."[181] No additional details were provided and no related communications were produced to the Committee regarding this complaint. Again, based on the documents produced to the Committee, it appears as though the complaint essentially went unnoticed.

A few weeks later, on August 16, 2010, the Ameridose informant again contacted the NWE-DO but this time raised new and more alarming concerns about Ameridose's practices and their potential impact on the safety of the company's products. At least one of his claims, documented in a District Office memorandum, was shockingly similar to the violations FDA found when it inspected both NECC and Ameridose after the fungal meningitis outbreak began. According to the memorandum, the informant alleged that not only was the Ameridose sales team "assisting in labeling operations in a clean room" but that "one of the 3 clean rooms had a *positive result for mold growth*."[182] The informant also alleged that Ameridose was tampering with its sampling procedures, stating that the company would "clean the area first before taking

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[177] E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Compliance Officer, New England Dist. Off., FDA (July 14, 2010, 8:56 AM).
[178] *See* Letter from Counsel to Deborah Autor (June 8, 2010) *and* Letter from Counsel to Deborah Autor (July 8, 2010). *See also* E-mail from Counsel to Deborah Autor (July 22, 2010, 11:28 AM).
[179] E-mail from Deborah Autor to Samia Nasr, et al. (July 23, 2010, 4:32 PM).
[180] E-mail from Kathleen Anderson to Deborah Autor (July 23, 2010, 4:59 PM).
[181] FDA, MEDWATCH REPORT (July 23, 2010).
[182] Memorandum of Teleconference between Redaction and Compliance Officer, New England Dist. Off., FDA, at 1 (Aug. 16, 2010) (emphasis added).

the [environmental] sample[s]."[183] Although the informant admitted that he was not aware of any illnesses or complaints resulting from these activities, he also stated that "he would not be in a position to know this type of information" and some of the information he had provided FDA was second or third hand."[184] The compliance officer wrote, "I explained that FDA takes complaints such as his very seriously and that we would need to evaluate the information he provided. I asked if he was aware of any other issues that would cause a public health safety concern. He said no, but that he would contact us if he became aware of similar issues. I asked if he contacted any other offices such as the State of MA or the Board of Pharmacy. He stated he had not but would plan on doing so. We discussed that FDA is still seeking jurisdiction over compounding pharmacies."[185]

The compliance officer sent her memorandum to several of her District Office colleagues, even though it was her understanding that "FDA may not be in a position to follow-up at this time[.]"[186] In an email, the compliance officer specifically asked if they should share the information with the state.[187] This email, along with the memorandum, was forwarded to Samia Nasr in CDER. Ms. Nasr questioned the informant's claims, stating that she was "not sure about his complaint since he said that this information was second or third hand. What's this mean? [H]e heard it from someone else? [A]nd I am wondering when he says manufacturing area, does he mean[s] no prescriptions?"[188] The compliance officer responded, "Yes, 2nd hand means he heard i[t] from someone else which is unreliable."[189]

Four days later, on August 20, 2010, the informant contacted the District Office again, this time to provide "additional information regarding the mold finding at Ameridose on 8/5/10."[190] According to a memorandum of the call, the informant stated that the mold was found in "the hood in which operations took place."[191] Again, this information was forwarded to Samia Nasr in CDER who, in response, asked the compliance officer, "Would it help if I set up a meeting with OCC to discuss possibility of full inspection?"[192] The compliance officer replied, "I don't think so because in his second call he stated he is not directly involved with these findings and is obtaining his information from someone at the firm."[193] Ms. Nasr simply stated, "Ok, thanks."[194]

Based on documents produced to the Committee, it does not appear that FDA took any steps to investigate or follow up on these claims, nor is there any evidence that FDA referred them to the State. FDA was still determining, though, what it should do in response to the

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[183] *Id.*
[184] *Id.* at 2.
[185] *Id.*
[186] E-mail from Compliance Officer, New England Dist. Off., FDA, to Supervisory Consumer Safety Officer, New England Dist. Off., FDA, et al. (Aug. 17, 2010, 8:02 AM).
[187] *See id.*
[188] E-mail from Samia Nasr to Compliance Officer, New England Dist. Off., FDA (Aug. 17, 2010, 10:34 AM).
[189] E-mail from Compliance Officer, New England Dist. Off., FDA, to Samia Nasr (Aug. 17, 2010, 10:42 AM).
[190] Memorandum of Teleconference between Redaction and Compliance Officer, New England Dist. Off., FDA (Aug. 20, 2010).
[191] *Id.*
[192] E-mail from Samia Nasr to Compliance Officer, New England Dist. Off., FDA (Aug. 23, 2010, 11:00 AM).
[193] E-mail from Compliance Officer, New England Dist. Off., FDA, to Samia Nasr (Aug. 23, 2010, 11:06 AM).
[194] E-mail from Samia Nasr to Compliance Officer, New England Dist. Off., FDA (Aug. 23, 2010, 11:38 AM).

nicardipine situation. On October 15, 2010, the attorney who had previously reached out to Deborah Autor on several occasions emailed her again and expressed his frustration with FDA's failure to take action against Ameridose in regard to the nicardipine complaint. The attorney pointed out that "[i]t has now been more than four months since we called this serious situation to your attention, yet to date we have seen no evidence that the agency has taken any enforcement action to protect patients and preserve the integrity of FDA's drug review and approval system. In the meantime, Ameridose continues to expand its production and distribution of its unapproved drug product, thus increasing the potential risks to patients."[195]

Three days later, on October 18, 2010, Ms. Autor received an unrelated letter from an attorney representing PharMEDium Services LLC, regarding Ameridose's practices and requesting that the agency "clarify its policies with respect to this category of compounding pharmacies."[196] PharMEDium's letter makes plain that other companies with large-scale compounding operations were well aware of Ameridose's efforts to skirt regulation and were trying to distance themselves from Ameridose's practices, understanding the impact such practices could have on patient safety. According to PharMEDium's attorney, "A principal issue is whether such compounders may utilize active pharmaceutical ingredients (API) (bulk powders) in lieu of commercially available injectable drug products (sterile vials) from approved new drug manufacturers or registered old drug manufacturers, as starting materials in this process. If those providing compounding services are permitted to do this, it will drastically change the way such preparations are compounded nationwide and *put the manufacture of large quantities of sterile drugs for use in compounding in the hands of those who are not approved or 'regulated' to perform that operation.*"[197] The letter went on to detail Ameridose's compounding practices and—in PharMEDium's view—FDA's inaction in response. It concluded in part, "Ameridose and others starting with bulk API can no longer be considered outsourcers when their compounding operations bear no resemblance to those of a hospital pharmacy, and instead resemble drug manufacturing."[198]

If there was ever any doubt, by the end of 2010, it should have been abundantly clear to FDA that Ameridose was not operating as a traditional compounding pharmacy. Not only did FDA understand the nature and scope of Ameridose's practices, it was well aware of the dangers they were posing. Based on the documents produced to the Committee, FDA officials reacted as though Ameridose was a nuisance it could not figure out how to resolve, rather than a ticking time bomb.

C. Despite an Increasing Number of Complaints, FDA Decides to Further Delay Action against Ameridose until after New 503A Guidance is Drafted

While FDA worked to resolve the issues raised by the nicardipine complaint, the agency had effectively tabled conducting a broader inspection of Ameridose to follow up on the concerning observations documented in the previous inspections and to investigate the issues raised by the company informant, among the other complaints. Once FDA was informed on

[195] E-mail from Counsel to PharMEDium Services LLC to Deborah Autor (Oct. 15, 2010, 4:37 PM).
[196] Letter from Counsel to Deborah Autor, at 1 (Oct. 18, 2010).
[197] *Id.* (emphasis added).
[198] *Id.* at 3.

January 14, 2011, that a settlement had been reached between Ameridose and the commercial complainant in the nicardipine matter,[199] the agency turned its attention to the various other complaints that it had received since the July 2008 inspection and failed to address. After learning of the nicardipine settlement on January 20, Samia Nasr noted that CDER staff was scheduled "to meet with OCC in two weeks to discuss full inspection of Ameridose since we have several complaints regarding its practice."[200] This February 4, 2011, meeting between representatives from CDER, OCC, and the NWE-DO was the first of several discussions to address the "[c]ompilation of complaints towards Ameridose."[201] Less than two weeks later, they would have another complaint to add to the list.

A representative from the Institute of Safe Medication Practices (ISMP) informed FDA on February 15, 2011, of an issue ISMP had been made aware of during an ongoing shortage of 23.4% sodium chloride, a common electrolyte replenisher.[202] According to a medication error report, which had been submitted to ISMP's website with a photocopied Ameridose label, the pharmacist complainant had "great concerns over the safety" of the sodium chloride product.[203] The complainant stated that the "drug is filled into an empty Hospira bag. This bag can be directly attached to any IV line and infused undiluted into a patient. The warning says 'May need to dilute'. There is no circumstance where this product would not need to be diluted prior to infusion. The commercial product is filled into vials and the cap reads 'MUST BE DILUTED'. It is not labeled as Sodium Chloride USP, nor does it say that it is sterile. *As a practicing pharmacist, I am shocked that such a product would be allowed to be distributed for use in the United States.*"[204]

The patient safety implications of the latest Ameridose complaint were immediately clear to Michael Levy, then-Director of the DNDLC in CDER's Office of Compliance. Upon receiving the complaint, he forwarded it Samia Nasr and asked her to have someone look into it, stating that "it should be a priority."[205] Ms. Nasr responded to Mr. Levy, copying Kathleen Anderson, and informed him that CDER was "trying to get OCC to let us go and inspect Ameridose."[206]

A member of CDER's Compounding Team echoed Mr. Levy's concerns about patient safety to Ms. Nasr. In an email dated February 16, 2011, the Compounding Team member explained the nature of the risk posed, noting that "[t]he 100 ml bags of 23.4% NaCl that Ameridose is compounding [are] *extremely dangerous*. . . . How is Ameridose even obtaining these empty Hospira 100mg bags? The way that these bags appear and are labeled is very misleading. To me it appears that these bags are made by Hospira. . . . And to say that 'Caution Concentration: may need dilute' is an understatement. This must be diluted! And they should

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[199] *See* Letter from Counsel to Deborah Autor (Jan. 14, 2011).
[200] E-mail from Samia Nasr to Kathleen Anderson, et al. (Jan. 20, 2011, 1:56 PM).
[201] E-mail from Reg. Operations Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Samia Nasr, et al. (Feb. 4, 2011, 11:07 AM).
[202] *See* E-mail from President, ISMP, Dir., Div. of Medication Errors Prevention and Analysis, Off. of Surveillance and Epidemiology, CDER, FDA, et al. (Feb. 15, 2011, 9:59 AM).
[203] E-mail from ISMP Mailsender to Pharmacy Technician Analyst, ISMP (Feb. 14, 2011, 5:00 PM).
[204] *Id.* (emphasis added).
[205] E-mail from Michael Levy to Samia Nasr (Feb. 15, 2011, 6:00 PM).
[206] E-mail from Samia Nasr to Michael Levy, et al. (Feb. 16, 2011, 6:13 PM).

further warn that this bag should not be directly infused to the patient. This is unbelievable! *I think this is a disaster waiting to happen.*"[207] In a subsequent exchange, Ms. Nasr stated, "Let us see if OCC agrees on inspecting."[208]

Before OCC could weigh in on the ISMP complaint, ISMP informed FDA later that day that they had reached out to Ameridose and the company had agreed to revise the label.[209] According to the Compounding Team employee who was alarmed by what she had learned earlier in the day, "The labeling looks much better."[210] While she still had concerns "[g]iven Ameridose's past history," she felt as though they could be addressed "when we do a full inspection of the firm in the future."[211] Whether such an inspection would ever occur, however, was still an open question at the agency.

After a March 4, 2011, discussion about Ameridose between CDER, OCC, and the NWE-DO, an employee on CDER's Compounding Team sent an email to the group titled, "Reasons to go inspect Ameridose," which listed many of the concerns FDA had with the company, including its labeling, its lack of patient-specific prescriptions, and its practices as they relate to sterile injectable products.[212] Documents produced to the Committee show that lawyers in the Chief Counsel's Office were debating which concerns CDER had already detailed could constitute actionable violations under the FDCA, in advance of the full inspection being considered. The debate about whether FDA should even conduct such an inspection of Ameridose, however, would continue throughout the summer of 2011. Finally, on September 15, 2011, a Compounding Team employee emailed others in CDER, noting that they had decided to hold off on the Ameridose inspection. According to this email, FDA would not proceed with an inspection "until we issue the 503A guidance. . . . Plan is to re-inspect Ameridose 6 months after issuance of a 503A guidance."[213] FDA's decision to assert its authority under section 503A of the FDCA, except in the Ninth Circuit, was previously touched upon and will be subsequently addressed in greater detail, particularly with respect to the impact it had on FDA's oversight of NECC and Ameridose.

While FDA turned its attention to working on the 503A guidance, the complaints about Ameridose continued. In fact, on August 9, 2011, a new series of anonymous phone calls from

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[207] E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Samia Nasr (Feb. 16, 2011, 10:01 AM) (emphasis added).
[208] E-mail from Samia Nasr to Consumer Safety Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA (Feb. 16, 2011, 10:42 AM).
[209] *See* E-mail from President, ISMP, to Dir., Div. of Medication Errors Prevention and Analysis, Off. of Surveillance and Epidemiology, CDER, FDA, et al. (Feb. 16, 2011, 2:34 PM).
[210] E-mail from Consumer Safety Officer, Compounding Team, DNDLC, Off. of Complian ce, CDER, FDA, to Samia Nasr (Feb. 16, 2011, 2:56 PM).
[211] *Id.*
[212] *See* E-mail from Reg. Operations Officer, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Samia Nasr, et al. (Mar. 4, 2011, 10:12 AM).
[213] E-mail from Consumer Safety Officer, Compounding & Pharmacy Practices Team, Div. of Prescription Drugs, Off. of Unapproved Drugs & Labeling Compliance (OUDLC), Off. of Compliance, CDER, FDA, to Consumer Safety Technician, OUDLC (Sept. 15, 2011, 3:46 PM). By September 2011, the Office of Compliance appears to have been restructured, resulting in the Compounding Team—formerly within the Division of New Drugs and Labeling Compliance—being renamed the Compounding and Pharmacy Practices Team within the Office of Unapproved Drugs and Labeling Compliance, Division of Prescription Drugs.

an Ameridose employee had begun. It is not clear whether this was the same informant who had spoken with NWE-DO staff on several occasions a year earlier. According to the initial NWE-DO report, the anonymous Ameridose employee stated that "when packages are dropped on the floor employees are told to pick up and ship" and that "the bubble wrap is stored directly on the floor and that this room is dirty and is never cleaned."[214] The NWE-DO employee who received the complaint labeled the firm in question "Manufacturer" and marked it "Surveillance Information for Next [Establishment Inspection]."[215] This informant would continue to contact FDA with new concerns through mid-November, though that informant was not the only person doing so.

Based on a review of the documents, since November 2010, individuals from the California Health Department and Board of Pharmacy had been in contact with FDA's Los Angeles District Office about concerns they had with Ameridose shipping repackaged succinylcholine, a neuromuscular blocking agent used in surgery. According to the State representatives, Ameridose was shipping the product with significantly different expiration dates than the branded product and doing so without corresponding package inserts.[216] The issue resurfaced in September 2011, when an employee from the Department of Public Health had asked FDA whether "Ameridose received premarket approval for the succinylcholine product" and noted that they were "concerned with microbial contamination, as well as stability of product, associated with the repackaging (from the original manufacturers) of the Ameridose products."[217] These concerns were shared with Tamara Ely, the new leader of CDER's Compounding Team, on September 28, 2011.[218]

One month later, the documents indicate that an anonymous Ameridose employee had also contacted FDA's Office of Criminal Investigations regarding similar concerns as those previously raised with the NWE-DO. On October 21, 2011, Amber Wardwell, who succeeded Mutahar Shamsi as NWE-DO Compliance Branch Director, informed her colleagues that "OCI has sent over a referral for a[n] informant at Ameridose in Westboro [*sic*]" which involved allegations that "sales people [were] in [the] clean area filling product" and that Ameridose "continue[d] to repack Avastatin [*sic*] without FDA license."[219] Nonetheless, CDER was steadfast in its position that it would not inspect Ameridose and investigate complaints until the compounding guidance was finalized. For example, when the District compliance officer primarily responsible for Ameridose reached out to CDER's Compounding Team on October 24 to discuss the informant's claims, one of the Compounding Team employees asked Tamara Ely whether she should "schedule something and let him know that we aren't actively pursuing

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[214] FDA, CONSUMER COMPLAINT/INJURY REPORT, at 1 (Aug. 9, 2011).
[215] *Id.* at 3.
[216] *See* E-mail from Supervising Inspector, Cal. Bd. of Pharmacy, to Supervisory Consumer Safety Officer, Los Angeles Dist. Off., FDA (Nov. 18, 2010, 9:03 AM).
[217] E-mail from Pharmaceutical Consultant, Cal. Dep't. of Public Health, to Supervisory Consumer Safety Officer, Los Angeles Dist. Off., FDA (Sept. 20, 2011, 9:43 AM).
[218] *See* E-mail from Tamara Ely, Team Leader, Compounding & Pharmacy Practices Team, Div. of Prescription Drugs, OUDLC, Off. of Compliance, CDER, FDA, to Supervisory Consumer Safety Officer, Los Angeles Dist. Off., FDA (Sept. 28, 2011, 5:51 AM).
[219] E-mail from Amber Wardwell, Compliance Branch Director, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA (Oct. 21, 2011, 11:22 AM).

anything at this time. . . ?"[220] Ms. Ely responded, "I will handle it so you can focus on all things 503[A] [guidance]."[221] According to a subsequent email from the District compliance officer to Amber Wardwell, Ms. Ely informed the compliance officer that "CDER is in the process of drafting guidance on compounding and manufacturing" and that no inspections would be conducted until it was issued.[222] Ms. Ely directed the compliance officer to interview the informant and forward the notes from the interview, but acknowledged that the District Office "should not immediately follow-up but wait until the guidance is out, and then inspect as directed by CDER." The compliance officer concluded: "*She said no compounding facility is slated to be inspected in 2012.*"[223]

The next day, October 25, 2011, the compliance officer had his colleague contact the informant to set up an interview, as directed by Ms. Ely. Although the informant agreed to meet with the compliance officer and several of his colleagues on October 31,[224] the interview was ultimately postponed until November 3 and, in the end, was brief. According to the interview notes, the informant was "concern[ed] about [the] consequences of speaking w/ FDA [in terms of] retaliation, future employment, personal safety – legal expenses if [it] goes to court, personal law suit."[225] Although FDA staff agreed to look into whistleblower protections,[226] the Ameridose informant decided not to meet with them again after speaking with his lawyer.[227]

On November 17, 2011—only one day after the informant declined to meet with FDA again—the agency received an adverse event report associated with an Ameridose product. This report stated that three pregnant women who were in labor had complained of poor pain control after receiving epidural fentanyl injections subsequently determined to have been made and distributed by Ameridose. The women ultimately had C-sections.[228] The reporting physician or hospital pharmacist stated that they had "[n]otified [Ameridose] for investigation" and had "attempted to contact Ameridose numerous times over the last several weeks to find the outcome of the investigation."[229] On January 24, 2012, FDA received an additional report associated with fentanyl produced and distributed by Ameridose. This time, the complaint related to confusing labeling resulting in "2 near misses" where nurses had stated that "they almost gave their patient's [*sic*] 100mcg instead of 50mcg."[230]

The next day, January 25, 2012, FDA received another report via its adverse event reporting system, this time involving a heparin product. According to the complaint, a hospital

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[220] E-mail Reg. Operations Officer, Compounding & Pharmacy Practices Team, Div. of Prescription Drugs, OUDLC, Off. of Compliance, CDER, FDA, to Tamara Ely (Oct. 24, 2011, 9:30 AM).
[221] E-mail from Tamara Ely to Reg. Operations Officer, Compounding & Pharmacy Practices Team, Div. of Prescription Drugs, OUDLC, Off. of Compliance, CDER, FDA (Oct. 24, 2011, 9:34 AM).
[222] E-mail from Compliance Officer, New England Dist. Off., FDA, to Compliance Branch Director, New England Dist. Off., FDA (Oct. 24, 2011, 10:07 AM).
[223] *Id.* (emphasis added).
[224] Notes of Investigator, New England Dist. Off., FDA (Oct. 25, 2011, 9:30 AM).
[225] Notes of Investigator, New England Dist. Off., FDA (Nov. 3, 2011, 3:00 PM).
[226] *See id.*
[227] E-mail from Supervisory Consumer Safety Officer, New England Dist. Off., FDA, to Chris van Twuyver, Dir., Investigations Branch, New England Dist. Off., FDA (Nov. 16, 2011, 4:10 PM).
[228] *See* FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) (Nov. 17, 2011).
[229] *Id.*
[230] FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) (Jan. 24, 2012).

"had a patient that the doctor had ordered a Heparin drip for. The patient had a bag and the labs came back that their level had not changed. They increased the drip and rechecked labs [and] still no change. They changed the bag [and followed the] same processes and still not level. Pharmacy had lab test the . . . 2 bags . . . and neither bag had any Heparin in [it]. These bags were made by Ameridose, a compounding pharmacy in Framingham, MA."[231]

On March 12, 2012, another adverse event report was submitted to FDA, again involving potency issues with pain medications produced by Ameridose. Again, according to the complaint, "Ameridose was contacted about the potential problem and is conducting an investigation."[232] Less than two weeks later, on March 23, 2012, FDA received yet another report involving another "Hospital Close-call" associated with confusing Ameridose labeling.[233]

No other documents or communications related to this five-month string of adverse event reports associated with Ameridose products were produced to the Committee, suggesting that FDA did not take any further steps to investigate them, let alone re-inspect the company's facilities. Based on the MDPH's assertion to Committee staff, none of these complaints were forward to the State either.

On May 24, 2012, one of the inspectors from the NWE-DO who had previously visited Ameridose was contacted by a special agent in FDA's OCI. According to notes from the call, the agent was "interested in setting up [a] meeting to discuss Ameridose."[234] The inspector then emailed a supervisor in the District Office informing her that "[OCI] had recently received a complaint for Ameridose" and that the agent "would like to set up a time to meet with me to discuss what I saw at the firm and ask a few other questions about our inspection there."[235] The compliance officer primarily responsible for Ameridose informed his contact at CDER about the request, who replied by copying Pamela Lee—"the new [Team Leader] for the compounding team."[236] It is apparent from the documents that a teleconference was scheduled and ultimately occurred on June 5, 2012. Representatives from OCI, CDER, and the NWE-DO participated.[237] Based on notes from the call, the "anonymous complaint" that generated the discussion was "from HHS [U.S. Department of Health and Human Services] IG" and involved "drugs [being] misbranded, [and] not complying with GMPs."[238] The notes also indicate that Ms. Lee informed the group that CDER was "revising guidelines so enforcement actions [were] on hold unless [there was] clear harm or fraud."[239] After the call, Pamela Lee followed up with one of the participating NWE-DO compliance officers about the discussion. She asked what the compliance officer "meant when [she] said Ameridose did not have patient-specific prescriptions

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[231] *Id.*
[232] FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) (Jan. 25, 2012).
[233] FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) (Mar. 23, 2012).
[234] Notes of Investigator, New England Dist. Off., FDA (May 24, 2012, 1:20 PM).
[235] E-mail from Investigator, New England Dist. Off., FDA, to Supervisory Consumer Safety Officer, New England Dist. Off., FDA (May 24, 2012, 10:01 AM).
[236] E-mail from Reg. Operations Officer, Compounding & Pharmacy Practices Team, Div. of Prescription Drugs, OUDLC, Off. of Compliance, CDER, FDA, to Compliance Officer, New England Dist. Off., FDA (May 29, 2012, 9:58 AM).
[237] *See* Notes of Investigator, New England Dist. Off., FDA (June 5, 2012).
[238] *Id.*
[239] *Id.*

for approximately 99% of their drugs but instead had 'physician orders."[240] The compliance officer responded by clarifying that aside from certain dialysis patients, "The[re] are no patient/physician orders. There is nothing signed by MD's except for the dialysis orders."[241]

It is unclear from the documents whether anything associated with the underlying complaint that had been raised with HHS IG was resolved prior to the meningitis outbreak beginning in late September 2012. However, on July 17, 2012, after the NWE-DO was informed of NECC violating the Colorado Cease and Desist Order, the District compliance officer primarily responsible for NECC informed his colleague about the news and stated that "CDER said last year we may do something at the end of this year with compounding pharmacies. I recently had a meeting with OCI based on a complaint they received and they may be doing something with Ameridose. I invited CDER to the meeting and they were on the speakerphone. They did not want us going to the firm."[242] The compliance officer then forwarded the information received from FDA's Denver District Office to Pamela Lee and asked, "Based on past conversations that we may start enforcing compounding pharmacies at the end of this year do you want us to wait until you issue an assignment to go to [NECC]?"[243] Ms. Lee's reply, if there was one, was not produced to the Committee.

At this point in time, NECC had already shipped two of the three batches of fatal methylprednisolone acetate to facilities across the country. The meningitis outbreak started to unfold in late September. After it was determined that NECC was the responsible entity, FDA initiated an inspection of the facility, along with the State, on September 26, 2012. On October 10, 2012 FDA and the State began an inspection of Ameridose because, according to FDA, "Ameridose and NECC of Framingham, Mass. share some of the same managers."[244]

Prior to the inspection of Ameridose, on October 5, 2012, the NWE-DO received a new complaint from an anonymous employee at Ameridose. According to the report, the informant stated that, approximately one year ago, NECC had received a large order for a product used to prevent nausea and vomiting associated with chemotherapy. He explained that since NECC did not have the capacity to fill this order, "a couple batches containing a couple thousand syringes were produced at Ameridose for NECC" and that "it wasn't documented because it was not supposed to be done this way and illegal." According to the NWE-DO report, the informant concluded by stating that "the same people that own NECC also own Ameridose" and that the informant was "instructed by management to keep quiet as Ameridose does not want to be associated with NECC."[245]

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[240] E-mail from Pamela Lee, Senior Regulatory Operations Officer, Compounding & Pharmacy Practices Team, Div. of Prescription Drugs, OUDLC, Off. of Compliance, CDER, FDA, to Compliance Officer, New England Dist. Off., FDA (June 5, 2011, 3:21 PM).
[241] E-mail from Compliance Officer, New England Dist. Off., FDA, to Pamela Lee (June 5, 2011, 3:34 PM).
[242] E-mail from Compliance Officer, New England Dist. Off., FDA, to Compliance Officer, New England Dist. Off., FDA (July 17, 2012, 8:19 AM).
[243] E-mail from Compliance Officer, New England Dist. Off., FDA, to Pamela Lee, et al. (July 17, 2012, 8:35 AM).
[244] FDA, *Questions and Answers on Ameridose Recall* (Nov. 1, 2012) [hereinafter, "Ameridose Q&A"], *available at* http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm326471.htm.
[245] FDA, CONSUMER COMPLAINT/INJURY REPORT (Oct. 5, 2012).

On November 1, 2012, FDA announced that Ameridose was conducting a voluntary recall of all of its unexpired products in circulation based on "the preliminary results of the FDA's ongoing inspection, which has raised concerns for the FDA about a lack of sterility assurance. . . ."[246] On November 9, 2012, FDA issued Gregory Conigliaro a Form 483, documenting the agency's observations during the inspection of Ameridose beginning on October 10.[247] The observations included in this twenty-page document are too numerous to address in this memorandum. In summarizing the document, one FDA spokesperson stated that the firm "fails to test finished product for potency, failed to investigate complaints for ineffective products, failed to investigate violations of their own environmental sampling plan and fails to adequately maintain equipment and facilities used to manufacture sterile drug products."[248] For more reasons than one, this statement does not even begin to tell the whole story.

PART V: CONCLUSION

It can and should be stipulated that the fungal meningitis outbreak would not have occurred if not for a company whose management was willing to consistently cut corners and prioritize the expansion of their business over the safety of their products. That being said, NECC was not operating in the shadows. NECC had been on FDA's radar since 2002 and never left.

One of FDA's fundamental reasons for existence is to protect the public health by assuring the safety of our nation's drug supply. With respect to NECC and Ameridose, documents produced to the Committee raise serious questions about whether FDA repeatedly failed in its core mission. The documents also indicate that it was by sheer chance that NECC products caused these deaths and illnesses, as opposed to products produced and distributed by Ameridose. FDA employees were well aware of the link between these two companies. The agency's inaction in the face of years of complaints and red flags associated with the safety of both companies' products and underlying practices had a tragic ending. While nobody could have fully anticipated the scope of this terrible outbreak, FDA was on notice that something like this might occur.

Issues with the safety of NECC and Ameridose products and practices aside, by 2012 FDA had a deep understanding of the nature and scope of the companies' business; the agency knew that both NECC and Ameridose were engaged in activities that strongly suggested they were operating as drug manufacturers. Had the companies long ago crossed any line FDA could conceivably have drawn in the sand to differentiate pharmacy compounding from drug manufacturing? Even if FDA was so unsure of its authority to initiate enforcement actions against these companies after the Circuit Court split, was there anything in the law that precluded them from informing the State about the litany of complaints the agency had independently

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[246] FDA, Ameridose Q&A, *supra* note 244.

[247] *See* FDA, AMERIDOSE, LLC, FORM FDA 483, *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM327729.pdf.

[248] Elizabeth Weise, *FDA finds contamination at Ameridose*, USA Today, Nov. 13, 2012, *available at* http://www.usatoday.com/story/news/nation/2012/11/12/fda-ameridose-meningitis/1700589/.

received about NECC and Ameridose and strongly encouraging State action for the sake of patients across the country?

The Committee is committed to ensuring that something like this never happens again. If additional legislation is needed so FDA can adequately enforce the pertinent provisions of the FDCA with respect to companies that label themselves compounding pharmacies, yet are engaged in large-scale manufacturing and distribution activities, the Committee will work on such legislation. That being said, additional authority will not necessarily solve the fundamental issues within FDA that allowed this tragedy to unfold right under the agency's nose. Guidance documents will always need to be updated. Clarifying regulations will always need to be drafted. Statutory authority will always need to be defended. How many complaints, red flags, and close calls does FDA need to accumulate before protecting the public health outweighs any of these other activities?

DEPARTMENT OF HEALTH AND HUMAN SERVICES

OFFICE OF INSPECTOR GENERAL

WASHINGTON, DC 20201

APR 10 2013

TO: Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

/S/

FROM: Stuart Wright
Deputy Inspector General
for Evaluation and Inspections

SUBJECT: Memorandum Report: *High-Risk Compounded Sterile Preparations and Outsourcing by Hospitals That Use Them*, OEI-01-13-00150

This memorandum report provides information about the extent to which acute-care hospitals used compounded sterile preparations (CSPs) and purchased them from outside sources in 2012. It also describes the steps that hospitals take to ensure the quality of CSPs.

SUMMARY

We surveyed a nationally representative sample of acute-care hospitals that participated in Medicare in 2012. This survey focused on hospital use of compounded sterile preparations (CSPs). CSPs are sterile compounded drugs that are generally administered to patients via injection or infusion. We found that in 2012, 92 percent of hospitals used CSPs. Of those hospitals that used CSPs, 92 percent used sterile-to-sterile products and only 25 percent used higher risk nonsterile-to-sterile products. Nonsterile-to-sterile products composed less than 1 percent of CSPs used in 2012. Of the hospitals that used nonsterile-to-sterile CSPs, 85 percent outsourced at least some of these products (i.e., purchased them from outside pharmacies).

Ensuring an adequate supply of CSPs was very important to hospitals when determining whether to outsource CSPs. Many hospitals cited shortages of commercial products (68 percent), the availability of CSPs with extended shelf lives (62 percent), and CSP stability (69 percent) as very important factors when deciding whether to outsource CSPs. Also, hospitals took limited steps to ensure the quality of outsourced CSPs but had few problems with the quality of products from outside pharmacies. Few hospitals (11 of 236 hospitals in our sample) reported problems with product contamination; however, as shown by the meningitis outbreak in the fall of 2012, any instance of product contamination has the potential for serious consequences. Finally, we found that 56 percent of hospitals made changes or planned to make changes to CSP sourcing practices in response to that meningitis outbreak.

BACKGROUND

A recent nationwide meningitis outbreak caused by contaminated injections, which were compounded by the New England Compounding Center (NECC), raised major concerns about the use of compounded drugs supplied by outside pharmacies.[1] The meningitis outbreak and its aftermath revealed a gap in information about hospitals' use of drugs supplied by such pharmacies. Hospitals may have outsourcing arrangements with multiple outside pharmacies and may also compound drugs within their own pharmacies.

Pharmaceutical compounding is the creation of a prescription drug tailored to meet the needs of an individual patient. For example, a compounding pharmacist may produce a version of a drug without an ingredient to which a patient may be allergic, or the pharmacist might create a liquid form of a drug for a patient who is unable to swallow a pill. Traditionally, pharmacies compounded a drug upon receipt of a prescription for an individual patient. However, recent trends in drug compounding have included the large-scale production of certain drugs to help ease shortages of drugs approved by the Food and Drug Administration (FDA) and to meet the sourcing needs of some hospitals.[2]

Compounded Drugs

There are two broad categories of compounded drugs: nonsterile preparations and sterile preparations. (In this report, we refer to the latter as compounded sterile preparations, or CSPs.) Nonsterile preparations, such as ointments applied to the skin or capsules or pills that a patient takes orally, are lower risk products. Their production is subject to less stringent standards than those for sterile preparations.

CSPs are higher risk products that are generally administered to patients via injection or infusion. Preparation of CSPs requires more expertise and more extensive safety measures. Risks associated with CSP preparation include the use of the wrong medium or the wrong concentration for mixture, contamination with pathogens, and human error. CSPs may be divided into two types based on their components and the method of preparation:

- Sterile-to-sterile CSPs are prepared from sterile products, which a pharmacist constitutes. Sterile-to-sterile products are considered to carry a high risk of contamination in their preparation.
- Nonsterile-to-sterile CSPs carry the highest risk of contamination. These products are prepared from one or more nonsterile ingredients that must be mixed together and then sterilized. The products from NECC that led to the outbreak fell into this category. Nonsterile-to-sterile compounding requires extensive safety precautions, including specialized staff training, positive and negative flow sterile rooms, sterile laminar hoods, and daily cleaning and disinfection.

[1] In this report, the term "outside pharmacy" refers to any outside compounding pharmacy from which a hospital or medical center purchases compounded drugs.
[2] S. Tavernise, "FDA Chief Seeks Expanded Authority to Improve Safety of Drug Compounders," *The New York Times*, November 14, 2012.

Because of CSPs' greater risk, this study focuses on hospital use of both kinds of CSPs, rather than the lower risk nonsterile preparations, such as ointments and capsules.

United States Pharmacopoeia

The United States Pharmacopoeia (USP) is an official compendium of drug standards in the United States.[3] The USP chapter 797 (USP 797) provides product safety and quality standards for preparing CSPs.[4] Pharmacies have widely adopted USP 797 standards.[5] FDA has limited authority to inspect pharmacies and enforce compliance with current standards for good manufacturing practices; therefore, it largely defers to the States for regulating and inspecting pharmacies.[6]

METHODOLOGY

We identified 4,867 acute-care hospitals operating in 2012 that participated in Medicare.[7] From this population we selected a simple random sample of 300 hospitals. After we eliminated 2 ineligible hospitals, the sample consisted of 298 acute-care hospitals. We developed and used an online questionnaire to determine the extent and nature of hospital use of CSPs and outsourcing, including the extent to which hospitals outsource versus prepare onsite, and challenges in outsourcing and preparing CSPs. In January 2013, we mailed a letter to the director of pharmacy services for each sampled hospital requesting that he/she complete the online questionnaire.[8] We followed up with each nonrespondent with a reminder letter and telephone calls. We received responses from 236 hospitals, an overall response rate of 79 percent.

In addition, we interviewed stakeholders, including four practicing hospital pharmacists and officials of the trade association that represents hospital pharmacists.

Appendix A contains the sample sizes, point estimates, and 95-percent confidence intervals for all statistics in this report, as well as other data gathered in the survey.

Limitations

All data in this report are self-reported, and we did not independently verify them.

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[3] The Federal Food, Drug, and Cosmetic Act §§ 201(j) and (g)(1)(A) (21 U.S.C. §§ 321(j) and (g)(1)(A)) (defining the terms "official compendium" and "drug").

[4] The United States Pharmacopeial Convention. "USP-NF General Chapter 797 Pharmaceutical Compounding—Sterile Preparations." *The United States Pharmacopoeia and the National Formulary*, ch. 797 (copyright 2011).

[5] American Society of Health-System Pharmacists (ASHP), *The ASHP Discussion Guide on USP Chapter 797 for Compounding Sterile Preparations.* Accessed at www.ashp.org on December 13, 2012.

[6] FDA, *Compliance Policy Guidance for FDA Staff and Industry, Section 460.200 Pharmacy Compounding* (reissued May 29, 2002). Accessed at www.fda.gov on December 13, 2012.

[7] Pursuant to Section 1861 of the Social Security Act, to participate in Medicare, hospitals must demonstrate that they meet the Medicare Conditions of Participation during onsite inspections conducted by State survey and certification agencies and hospital accreditors with Medicare deeming authority.

[8] Because of a law enforcement request, we did not contact six acute-care hospitals.

Standards
This study was conducted in accordance with the *Quality Standards for Inspection and Evaluation* issued by the Council of the Inspectors General on Integrity and Efficiency.

RESULTS

In 2012, only one-quarter of hospitals used higher risk nonsterile-to-sterile CSPs, whereas almost all hospitals used sterile-to-sterile products

Overall, 92 percent of hospitals used CSPs in 2012. Hospitals of all sizes used CSPs and some used them extensively (Table 1). For example, we interviewed a pharmacy director of a large teaching hospital who reported that his hospital uses around 2,500 doses of CSPs per day. Ninety-two percent of hospitals used sterile-to-sterile CSPs. Twenty-five percent of hospitals used higher risk nonsterile-to-sterile CSPs.

Table 1: Use of Compounded Sterile Preparations by Hospital Size, 2012

Hospital Size	Number of Doses of CSPs Administered in Hospitals Mean (95% Confidence Interval (CI))	Number of Doses of Nonsterile-to-Sterile CSPs Administered in Hospitals Mean (95% CI)	Number of Doses of Sterile-to-Sterile CSPs Administered in Hospitals Mean (95% CI)
Fewer Than 50 Beds (n=81)	3,065 (1,878–4,252)	67 (10–124)	2,947 (1,766–4,127)
50–99 Beds (n=40)	18,008 (6,930–29,086)	*	18,001 (6,925–29,077)
100–299 Beds (n=69)	45,378 (33,803–56,952)	158 (43–273)	45,222 (33,658–56,785)
300 Beds and Above (n=43)	206,086 (111,647–300,526)	666 (310–1,021)	205,421 (111,080–299,761)

Source: Office of Inspector General survey of acute-care hospitals participating in Medicare, 2013.
*We were unable to project an estimate for this data field because we did not have a valid 95-percent confidence interval.

Nonsterile-to-sterile preparations composed less than 1 percent of CSPs used in hospitals in 2012. Only 16 percent of hospitals with fewer than 50 beds used these products. Nonsterile-to-sterile CSPs have a higher risk of contamination than other CSPs because pharmacists prepare them from nonsterile components that must be sterilized prior to administration. When we asked hospitals which kinds of nonsterile-to-sterile CSPs they commonly used, they named both product types and modes of administration. Hospitals in our sample commonly used nonsterile-to-sterile opioids, steroids, electrolytes, and diuretics. Hospitals in our sample also reported using nonsterile-to-sterile CSPs for intrathecal pain pumps and epidurals.

Sterile-to-sterile preparations composed over 99 percent of CSPs used by hospitals in 2012. When asked about commonly used sterile-to-sterile CSPs, hospitals in our sample reported using antibiotics, opioids, epidurals, oxytocics, total parenteral nutrition, and cardioplegic solutions.

Of the hospitals that used higher risk CSPs in 2012, 85 percent purchased at least some of these products from outside sources

Of the hospitals that used nonsterile-to-sterile CSPs in 2012, only 36 percent prepared any of these products onsite (Table 2). USP 797 standards for preparing nonsterile-to-sterile CSPs are more stringent than those for sterile-to-sterile CSPs, and a few hospitals in our sample (5 out of 236) reported that they cannot make these products onsite because their facilities do not meet USP 797 standards. Overall, most hospitals (75 percent) that used any CSPs used a combination of outsourcing and onsite preparation to obtain these products.

Table 2: Hospital Sourcing of Compounded Sterile Preparations, 2012

Product Type	Percentage of Hospitals That Outsourced	Percentage of Hospitals That Prepared Onsite	Percentage of Hospitals That Both Outsourced And Prepared Onsite
All CSPs (n=218 Hospitals That Used CSPs)	79.4% (74.1%−84.6%)	95.0% (92.1%−97.8%)	74.7% (69.2%−80.4%)
Nonsterile-to-Sterile CSPs (n=59 Hospitals That Used Nonsterile-to-Sterile CSPs)	84.7% (75.8%−93.7%)	35.6% (23.7%−47.5%)	20.3% (10.3%−30.3%)
Sterile-to-Sterile CSPs (n=216 Hospitals That Used Sterile-to-Sterile CSPs)	76.9% (71.4%−82.3%)	95.4% (92.6%−98.1%)	72.2% (66.4%−78.0%)

Source: Office of Inspector General (OIG) survey of acute-care hospitals participating in Medicare, 2013.

Of the hospitals that purchased nonsterile-to-sterile CSPs from outside pharmacies, 63 percent contracted with one pharmacy, 20 percent contracted with two, and 16 percent with three (see Table A4 in Appendix A).[9] Most hospitals (67 percent) that purchased nonsterile-to-sterile CSPs from outside pharmacies used at least one pharmacy located in another State.[10]

For those hospitals that used sterile-to-sterile CSPs, 77 percent purchased sterile-to-sterile products from at least one outside pharmacy. Of these hospitals that purchased sterile-to-sterile CSPs from outside pharmacies, 41 percent contracted with one outside pharmacy, 50 percent contracted with two or three pharmacies, and 9 percent contracted with four or five pharmacies (see Table A5 in Appendix A). As with nonsterile-to-sterile products, most of these hospitals purchased sterile-to-sterile CSPs from at least one out-of-State pharmacy: 45 percent used one out-of-State pharmacy, 41 percent used two or three out-of-State pharmacies, and 3 percent used four or five out-of-State pharmacies.

[9] The 95-percent confidence intervals for these three percentage estimates are 50.1 to 76.4 percent, 9.4 to 31.4 percent, and 6.2 to 26.4 percent, respectively.
[10] The 95-percent confidence interval for the 67-percent estimate is 54.6 to 80.1 percent.

Hospitals consider factors related to ensuring an adequate supply of CSPs as very important when determining whether to outsource CSPs

Hospitals cited shortages of commercial products as a very important factor when deciding whether to outsource CSPs (see Table A6 in Appendix A). Outsourcing CSPs may be necessary to ensure the ready availability of products during such shortages. A few hospitals in our sample (15 of 236) indicated that they outsource CSPs only when commercial products are unavailable because of a shortage and the cost of producing the CSP onsite would be prohibitive. One pharmacy director stated that his hospital had outsourced more CSPs in 2012 than in previous years because of growing shortages of commercially available products.

When asked how an abrupt shortage of CSPs from outside pharmacies would affect delivery of care and risk to patients, 48 percent of hospitals stated that a shortage of outsourced CSPs would have a non-life-threatening but great impact on delivery of care in their hospitals (see Table A8 in Appendix A). An additional 11 percent responded that such a shortage would cause life-threatening, major disruptions.

Hospitals also regarded CSP stability[11] and the need for CSPs with extended shelf lives as very important factors when deciding whether to outsource CSPs. A pharmacy's ability to provide products with extended shelf lives was also important to hospitals when selecting a particular outside pharmacy (see Table A7 in Appendix A). This suggests that hospitals rely on outsourcing to provide commonly used products for which the exact demand may be unpredictable. According to pharmacists with whom we spoke, CSPs prepared onsite often have limited shelf lives or must be refrigerated. In many cases, outside pharmacies can provide products that have undergone stability testing and have extended shelf lives. Outsourcing these CSPs enables hospitals to have product on hand when needed with less waste. A few hospitals in our sample (6 out of 236) noted that the option of outsourcing CSPs with extended shelf lives is particularly important because they do not have pharmacies that operate 24 hours a day.

In deciding to outsource, hospitals considered other factors as important in ensuring a supply of CSPs. Hospitals cited the ability to prepare CSPs onsite, such as lack of necessary equipment, shortage of trained staff, and lack of physical facilities to prepare CSPs as important when deciding whether to outsource CSPs (see Table A6 in Appendix A). In fact, only 56 percent of hospitals had a USP 797-compliant clean room for preparing CSPs. When deciding whether to outsource, hospitals also considered whether CSPs were high risk or required nonsterile-to-sterile preparation.

Hospitals took limited steps to ensure the quality of outsourced CSPs, but they also rarely had problems with CSP quality

Most hospitals that outsourced CSPs required that outside pharmacies comply with USP 797 (83 percent) and reviewed quality reports provided by outside pharmacies (71 percent, Table 3). Of the hospitals that outsourced CSPs, few conducted their own site visits at outside pharmacies (22 percent) or reviewed independent quality

[11] The term "CSP stability" refers to the extent to which the preparation retains the same properties and characteristics that it possessed at the time of its preparation throughout its period of storage and use.

assessments of the outside pharmacies used (27 percent). Some hospitals in our sample (14 out of 236) also reported that they lacked the resources, access, or expertise to assess the quality of outside pharmacies and therefore must rely on State Boards of Pharmacy to assess them.

Table 3: Steps That Hospitals That Outsourced Compounded Sterile Preparations Took To Ensure Quality in 2012

Quality Step	Percentage of Hospitals That Reported Taking Quality Step for Some or All Outside Pharmacies They Contracted With
Required Compliance With USP 797	83%
Reviewed Quality Reports Provided by the Outside Pharmacy	71%
Reviewed Quality Reports Provided by a Third Party	27%
Conducted Onsite Visits at the Outside Pharmacy	22%
Tested CSPs Provided by Outside Pharmacy	9%

Source: OIG survey of acute-care hospitals participating in Medicare, 2013.

Although hospitals took limited steps to ensure the quality of outsourced CSPs, 42 percent of hospitals were very confident that the steps taken were adequate. An additional 47 percent were only somewhat confident that these steps were adequate. However, 12 percent of hospitals were not at all confident in the quality of products from outside pharmacies.[12] Most hospitals (64 percent) that outsourced CSPs had no problems or concerns with outside pharmacies in 2012, and of those that had problems, many were related to product availability (73 percent).[13] Few hospitals (11 of 236 hospitals) in our sample reported problems with product contamination; however, as shown by the meningitis outbreak in fall 2012, any instance of product contamination has the potential for serious consequences.

Half of all hospitals made changes or planned to make changes to CSP sourcing practices in response to the fall 2012 meningitis outbreak

Overall, 56 percent of hospitals made changes to CSP sourcing practices in 2012 or plan to make changes in 2013. This includes hospitals that use only sterile-to-sterile products and hospitals that use higher risk nonsterile-to-sterile products. Some changes were related to the way in which hospitals outsource CSPs (see Table A14 in Appendix A). Outsourcing changes that hospitals made or plan to make included decreasing CSP outsourcing, requesting more information on product quality from outside pharmacies, and contracting with different outside pharmacies.

Hospitals also made or planned changes to the way they prepare CSPs in-house. Many hospitals increased or plan to increase quality control mechanisms in the hospital pharmacies and hospital capacity to prepare CSPs in-house. Making such changes while complying with USP 797 may be resource intensive for hospitals. About half of hospitals ranked cost (47 percent) and space limitations (49 percent) as major challenges to

[12] Percentages for hospital confidence in the quality of CSPs purchased from outside sources add up to 101 percent because of rounding. See Table A10 in Appendix A for exact percentages.
[13] The 95-percent confidence interval for the 73-percent estimate is 61.8 to 83.4 percent.

USP 797 compliance. A few hospitals in our sample (6 out of 236) reported that becoming fully compliant with USP 797 would require a building redesign or new construction.

CONCLUSION

Our review shows that the use of compounded sterile products is widespread in hospitals, although the use of the highest risk products—those involving preparation of sterile products from nonsterile components—is limited to about one-quarter of hospitals, most commonly larger facilities.

Although most hospital pharmacies prepared sterile-to-sterile products onsite, hospitals outsource most nonsterile-to-sterile CSPs. Hospitals tend to rely upon a limited number of external pharmacies for these CSPs, especially for nonsterile-to-sterile products. Often these pharmacies are located in other States.

Many factors go into a hospital pharmacy's decision to outsource CSPs. Among these are the need to ensure a ready supply of products in the event of shortages and the need for products with extended shelf lives, which require sophisticated equipment and testing that may not be readily available on the hospital premises.

The meningitis outbreak in the fall of 2012 has spurred hospital pharmacies to make some changes, such as seeking additional information from outside pharmacies about quality practices, or even expanding their own internal compounding capacity. For the most part, hospitals remain confident about the quality of outsourced CSPs. Nevertheless, the meningitis outbreak raises questions about whether this confidence is well placed and emphasizes the need to stay vigilant about procedures for compounding and outsourcing CSPs.

OIG will pursue additional work to further examine the safety and quality of pharmaceutical compounding in hospitals, including work examining Federal oversight mechanisms.

This report is being issued directly in final form because it contains no recommendations. If you have comments or questions about this report, please provide them within 60 days. Please refer to report number OEI-01-13-00150 in all correspondence.

APPENDIX A

Complete Results From Office of Inspector General Survey of Acute-Care Hospitals That Participated in Medicare in 2012

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Table A1: Hospital Demographic Information, 2012

	Sample Size	Percentage of Hospitals (95% Confidence Interval (CI))
Hospital Size	233	
Fewer Than 50 Beds		34.8% (28.8%−40.7%)
50–99 Beds		17.2% (12.5%−21.9%)
100–299 Beds		29.6% (23.9%−35.3%)
300 Beds and Above		18.5% (13.6%−23.3%)
Operating Room in Hospital	235	91.5% (88.0%−95.0%)
Intensive Care Unit in Hospital	234	72.6% (67.1%−78.2%)
Dialysis Performed at Hospital	235	47.7% (41.4%−53.9%)

Source: Office of Inspector General (OIG) survey of acute-care hospitals participating in Medicare, 2013.

Table A2: Use of Compounded Sterile Preparations by Hospital Size, 2012

	Sample Size	Hospitals That Used Compounded Sterile Preparations (CSPs) Percentage (95% CI)	Hospitals That Used Nonsterile-to-Sterile CSPs Percentage (95% CI)	Hospitals That Used Sterile-to-Sterile CSPs Percentage (95% CI)
All Hospitals	236	92.4% (89.1%−95.7%)	25.1%* (19.7%−30.5%)	91.5% (88.1%−95.0%)
Hospitals by Size				
Fewer Than 50 Beds	81	81.5% (73.2%−89.7%)	16.0% (8.8%−25.9%)	79.0% (68.5%−87.3%)
50−99 Beds	40	95.0% (88.4%−100.0%)	5.0% (0.6%−16.9%)	95.0% (83.1%−99.4%)
100−299 Beds	69	98.6% (95.8%−100.0%)	25.0% (15.3%−37.0%)	98.6% (92.2%−100.0%)
300 Beds and Above	43	100.0% (91.8%−100.0%)	60.5% (46.2%−74.7%)	100.0% (91.8%−100.0%)

Source: OIG survey of acute-care hospitals participating in Medicare, 2013.
*The sample size for this estimate is 235.

Table A3: Total Doses of Compounded Sterile Preparations Used in 2012

	Percentage of Total CSPs (95% CI)
Total Doses of CSPs (n=236)	
Nonsterile-to-Sterile CSPs (n=235)	0.34% (0.2%−0.5%)
Sterile-to-Sterile CSPs (n=236)	99.6% (99.5%−99.8%)

Source: OIG survey of acute-care hospitals participating in Medicare, 2013.

Table A4: Use of Outside Pharmacies by Hospitals Outsourcing Nonsterile-to-Sterile Compounded Sterile Preparations in 2012

Number of Outside Pharmacies Used	Sample Size	Hospitals That Outsourced Nonsterile-to-Sterile CSPs Percentage (95% CI)
All Outside Pharmacies	49	
1		63.3% (50.1%−76.4%)
2		20.4% (9.4%−31.4%)
3		16.3% (6.2%−26.4%)
Out-of-State Pharmacies	49	
0		32.7% (19.9%−45.4%)
1		51.0% (37.4%−64.7%)
2		14.3% (5.9%−27.2%)
3		2.0% (0.1%−10.9%)

Source: OIG survey of acute-care hospitals participating in Medicare, 2013.

Table A5: Use of Outside Pharmacies by Hospitals Outsourcing Sterile-to-Sterile Compounded Sterile Preparations in 2012

Number of Outside Pharmacies Used	Sample Size	Hospitals That Outsourced Sterile-to-Sterile CSPs Percentage (95% CI)
All Outside Pharmacies	165	
1		40.6% (33.3%−47.9%)
2		36.4% (29.2%−43.5%)
3		13.9% (8.8%−19.1%)
4		6.7% (3.0%−10.4%)
5		2.4% (0.1%−4.7%)
Out-of-State Pharmacies	163	
0		11.0% (6.4%−15.7%)
1		44.8% (37.3%−52.2%)
2		33.1% (26.1%−40.2%)
3		8.0% (3.9%−12.0%)
4		1.8% (0.4%−5.3%)
5		1.2% (0.1%−4.4%)

Source: OIG survey of acute-care hospitals participating in Medicare, 2013.

Table A6: Factors Important to Hospitals When Deciding Whether To Outsource Compounded Sterile Preparations

Factor	Sample Size	Very Important Percentage (95% CI)	Somewhat Important Percentage (95% CI)	Not Important Percentage (95% CI)
Stability of CSP	226	68.6% (62.7%−74.5%)	19.9% (14.8%−25.0%)	11.5% (7.5%−15.6%)
Shortages of Commercial Products	229	68.1% (62.2%−74.0%)	22.7% (17.4%−28.0%)	9.2% (5.5%−12.8%)
Need for Ready-to-Administer Form of CSP	227	67.0% (61.0%−72.9%)	20.7% (15.6%−25.8%)	12.3% (8.2%−16.5%)
Need for Product With Extended Shelf Life	226	61.9% (55.8%−68.1%)	23.5% (18.1%−28.8%)	14.6% (10.1%−19.1%)
Product-Testing Requirements	228	61.4% (55.2%−67.6%)	23.2% (17.9%−28.6%)	15.4% (10.8%−19.9%)
Product Is High Risk or Problem Prone To Prepare	229	53.7% (47.4%−60.0%)	27.5% (21.9%−33.1%)	18.8% (13.8%−23.7%)
Inability of Hospital Pharmacy To Produce CSPs in Quantity Needed	228	46.9% (40.6%−53.2%)	27.2% (21.6%−32.8%)	25.9% (20.3%−31.4%)
CSP Requires Nonsterile-to-Sterile Preparation	227	47.1% (40.8%−53.5%)	18.1% (13.2%−22.9%)	34.8% (28.8%−40.8%)
Need for Specialized Products	228	45.6% (39.3%−51.9%)	30.7% (24.9%−36.5%)	23.7% (18.3%−29.1%)
Lack of Necessary Equipment To Prepare CSP in-House	229	38.9% (32.7%−45.0%)	23.6% (18.2%−28.9%)	37.6% (31.4%−43.7%)
Amount of Time Needed To Produce CSP in-House	229	39.3% (33.1%−45.5%)	36.7% (30.6%−42.8%)	24.0% (18.6%−29.4%)
Predictability of Demand for CSP	229	35.4% (29.3%−41.4%)	45.0% (38.7%−51.3%)	19.7% (14.6%−24.7%)
Lack of Physical Facilities To Prepare CSP in-House	227	34.8% (28.8%−40.8%)	26.9% (21.3%−32.5%)	38.3% (32.2%−44.5%)
Workflow Management	229	33.6% (27.7%−39.6%)	38.4% (32.3%−44.6%)	27.9% (22.3%−33.6%)
Prior Problems With Outsourced CSPs	223	27.8% (22.1%−33.5%)	22.0% (16.7%−27.3%)	50.2% (43.8%−56.6%)
Cost of Producing Product in-House	229	27.5% (21.9%−33.1%)	49.8% (43.5%−56.1%)	22.7% (17.4%−28.0%)
Shortage of Staff Trained to Prepare CSP	228	26.8% (21.2%−32.4%)	33.8% (27.8%−39.8%)	39.5% (33.3%−45.7%)
Prior Problems Preparing CSP in-House	225	20.0% (14.9%−25.1%)	21.8% (16.5%−27.0%)	58.2% (51.9%−64.5%

Source: OIG survey of acute-care hospitals participating in Medicare, 2013.

Table A7: Factors Important to Hospitals When Selecting a Particular Outside Pharmacy

Factor	Sample Size	Very Important Percentage (95% CI)	Somewhat Important Percentage (95% CI)	Not Important Percentage (95% CI)
Quality of Product	228	88.6% (84.6%−92.6%)	3.1% (0.9%−5.3%)	8.3% (4.8%−11.8)
Pharmacy Expertise in Preparing Product	228	87.3% (83.1%−91.5%)	5.3% (2.4%−8.1%)	7.5% (4.1%−10.8%)
Pharmacy Reputation	229	83.8 % (79.2%−88.5%)	9.6% (5.9%−13.3%)	6.6% (3.4%−9.7%)
Pharmacy Accreditation	229	79.0% (73.9%−84.2%)	13.5% (9.2%−17.9%)	7.4% (4.1%−10.7%)
Inspection History With State Board of Pharmacy	227	77.5% (72.2%−82.8%)	13.2% (8.9%−17.5%)	9.3% (5.6%−12.9%)
Product Availability	229	75.5% (70.1%−81.0%)	17.0% (12.3%−21.8%)	7.4% (4.1%−10.7%)
Pharmacy's Ability To Provide Products With Extended Shelf Life	228	71.1% (65.3%−76.8%)	18.9% (13.9%−23.8%)	10.1% (6.3%−13.9%)
Pharmacy Responsiveness	228	66.7% (60.7%−72.6%)	25.0% (19.5%−30.5%)	8.3% (4.8%−11.8%)
Pharmacy's Delivery Schedule	229	50.7% (44.3%−57.0%)	37.6% (31.4%−43.7%)	11.8% (7.7%−15.9%)
Product Cost	227	37.4% (31.3%−43.6%)	48.5% (42.1%−54.8%)	14.1% (9.7%−18.5%)
Hospital's Own Site Inspection of Pharmacy	226	23.5% (18.1%−28.8%)	39.8% (33.6%−46.0%)	36.7% (30.6%−42.8%)
Medical Staff Preference	228	3.5% (1.2%−5.8%)	31.1% (25.3%−37.0%)	65.4% (59.3%−71.4%)

Source: OIG survey of acute-care hospitals participating in Medicare, 2013.

Table A8: Hospital Beliefs About the Effect of an Abrupt Shortage or Loss of Supply of Compounded Sterile Preparations From Outside Pharmacies on Risk to Patients and Delivery of Care in the Hospital (n=235)

Perceived Level of Risk to Patients and Disruption of Care	Percentage of Hospitals (95% CI)
Life-Threatening, Major Disruptions	11.5% (7.5%−15.5%)
Not Life-Threatening, But Still Great Impact	48.1% (41.9%−54.3%)
Little Impact, an Inconvenience	16.6% (12.0%−21.2%)
No Impact at All	23.8% (18.5%−29.1%)

Source: OIG survey of acute-care hospitals participating in Medicare, 2013.

Table A9: Steps That Hospitals Outsourcing Compounded Sterile Preparations To Ensure Quality in 2012

Quality Step	Sample Size	Performed Quality Step for All Outside Pharmacies Percentage (95% CI)	Performed Quality Step for Some Outside Pharmacies Percentage (95% CI)	Did Not Perform Quality Step Percentage (95% CI)	Not Applicable Percentage (95% CI)
Required Compliance With USP 797	172	76.7% (70.6%−82.9%)	6.4% (2.8%−10.0%)	14.0% (8.9%−19.0%)	2.9% (0.5%−5.4%)
Reviewed Quality Reports Provided by Outside Pharmacy	171	48.5% (41.2%−-55.8%)	22.8% (16.7%−28.9%)	26.3% (19.9%−32.7%)	2.3% (0.1%−4.5%)
Reviewed Quality Reports Provided by Third Party	170	16.5% (11.0%−21.9%)	10.0% (5.6%−14.4%)	67.6% (60.8%−74.5%)	5.9% (2.4%−9.3%)
Conducted Onsite Visits at Outside Pharmacy	172	7.0% (3.3%−10.7%)	15.1% (9.9%−20.3%)	72.7% (66.2%−79.2%)	5.2% (2.0%−8.5%)
Tested CSPs Provided by Outside Pharmacy	171	5.8% (2.4%−-9.3%)	3.5% (0.8%−6.2%)	86.0% (80.9%−91.0%)	4.7% (1.6%-7.8%)

Source: OIG survey of acute-care hospitals participating in Medicare, 2013.

Table A10: Hospital Confidence in Steps Taken To Ensure Quality of Compounded Sterile Preparations Purchased From Outside Pharmacies in 2012 (n=221)

Level of Confidence	Percentage of Hospitals (95% CI)
Very Confident	41.6% (35.3%−48.0%)
Somewhat Confident	46.6% (40.2%−53.0%)
Not at All Confident	11.8% (7.6%−15.9%)

Source: OIG survey of acute-care hospitals participating in Medicare, 2013.

Table A11: Hospitals That Outsourced Compounded Sterile Preparations and Had Problems or Concerns With Outside Pharmacies in 2012

Problems or Concerns	Sample Size	Had Problem or Concern Percentage (95% CI)	Did Not Have Problem or Concern Percentage (95% CI)
Any Problem or Concern With Outside Compounding Pharmacies	171	35.7% (28.7%−42.7%)	64.3% (57.3%−71.3%)
Lack of Product Availability	62	72.6% (61.8%−83.4%)	27.4% (16.6%−38.2%)
Problems With Product Delivery	61	42.6% (30.5%−54.7%)	57.4% (45.3%−69.5%)
Product Contamination	61	18.0% (8.6%−27.4%)	82.0% (72.6%−91.4%)
Problems With Product Potency	61	8.2% (1.5%−14.9%)	91.8% (85.1%−98.5%)

Source: OIG survey of acute-care hospitals participating in Medicare, 2013.

Table A12: Hospital Ability to Prepare Compounded Sterile Preparations Onsite, 2012

	Sample Size	Percentage of Hospitals (95% CI)
Hospitals With a USP 797-Compliant Clean Room	235	56.2% (50.0%−62.4%)
Hospitals With a Barrier Isolator for Preparing CSPs	236	54.2% (48.0%−60.4%)
Hospital Compliance With USP 797 Requirements for Risk Level of CSPs Prepared Onsite	228	
Fully Compliant		59.6% (53.4% −65.9%)
Mostly Compliant		29.8% (24.0% −35.6%)
Somewhat Compliant		6.1% (3.1%−9.2%)
Not at All Compliant		4.4% (1.8% −7.0%)

Source: OIG survey of acute-care hospitals participating in Medicare, 2013.

Table A13: Hospital-Identified Challenges To Meeting Compliance With USP 797 Standards

	Sample Size	Major Challenge Percentage (95% CI)	Minor Challenge Percentage (95% CI)	Not a Challenge Percentage (95% CI)
Space Limitations	226	49.1% (42.8%−55.5%)	27.0% (21.4%−32.6%)	23.9% (18.5%−29.3%)
Cost	228	47.4% (41.1%−53.7%)	30.3% (24.5%−36.1%)	22.4% (17.1%−27.6%)
Access to Needed Equipment	228	25.4% (19.9%−30.9%)	35.5% (29.5%−41.6%)	39.0% (32.9%−45.2%)
Number of Staff	228	22.4% (17.1%−27.6%)	43.4% (37.2%−49.7%)	34.2% (28.2%−40.2%)
Staff Skill Set	228	11.0% (7.0%−14.9%)	45.6% (39.3%−51.9%)	43.4% (37.2%−49.7%)

Source: OIG survey of acute-care hospitals participating in Medicare, 2013.

Table A14: Hospitals That Have Made or Plan To Make Changes to Sourcing Practices for Compounded Sterile Preparations in Response to the Fall 2012 Meningitis Outbreak

	Sample Size	Percentage of Hospitals (95% CI)
Hospitals That Either Changed or Plan To Change CSP Sourcing Practices	232	56.0% (49.8%−62.3%)
Hospitals That Changed CSP Sourcing Practices in 2012	233	45.9% (39.7%−52.2%)
Changes Made		
Decreased Outsourcing of CSPs	106	78.3% (70.7% −85.9%)
Requested More Information From Outside Compounding Pharmacies on Product Quality	105	61.9% (52.9%−71.0%)
Increased Quality Control Mechanisms in Hospital Pharmacy	104	54.8% (45.5% −64.1%)
Increased Hospital Capacity To Prepare CSPs Onsite	106	51.9% (42.6%−61.2%)
Contracted With Different Outside Pharmacy	105	50.5% (41.2%−59.8%)
Hospitals That Plan To Change CSP Sourcing Practices in 2013	234	38.5% (32.4%−44.5%)
Planned Changes		
Request More Information From Outside Compounding Pharmacies on Product Quality	88	84.1% (76.6%−91.5%)
Increase Quality Control Mechanisms in Hospital Pharmacy	87	74.7% (65.8%−83.6%)
Decrease Outsourcing of CSPs	88	56.8% (46.7%−66.9%)
Increase Hospital Capacity To Prepare CSPs Onsite	88	54.5% (44.4%−64.7%)
Contract With Different Outside Pharmacy	89	51.7% (41.6%−61.8%)

Guidance for FDA Staff and Industry

Marketed Unapproved Drugs – Compliance Policy Guide

Sec. 440.100
Marketed New Drugs Without Approved NDAs or ANDAs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 19, 2011
Compliance

Guidance for FDA Staff and Industry

Marketed Unapproved Drugs Compliance Policy Guide

Sec. 440.100
Marketed New Drugs Without
Approved NDAS or ANDAs

Additional copies are available from:
Office of Communications
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10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 19, 2011
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APPENDIX **9**

Guidance for FDA Staff and Industry[1]
Marketed Unapproved Drugs —
Compliance Policy Guide
Chapter 4
Subchapter 440

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This Compliance Policy Guide (CPG) describes how we intend to exercise our enforcement discretion with regard to drugs marketed in the United States that do not have required FDA approval for marketing. This is a revision of a guidance of the same name that was issued in June 2006. The guidance has been revised to state that the enforcement priorities and potential exercise of enforcement discretion discussed in the guidance apply only to unapproved new drugs (including new drugs covered by the Over-the-Counter (OTC) Drug Review), except for licensed biologics and veterinary drugs, that are commercially used or sold[2] prior to September 19, 2011.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Reason for This Guidance

For historical reasons, some drugs are available in the United States that lack required FDA approval for marketing. A brief, informal summary description of the various

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.
[2] For the purposes of this guidance, the term "commercially used or sold" means that the product has been used in a business or activity involving retail or wholesale marketing and/or sale.

categories of these drugs and their regulatory status is provided in Appendix A as general background for this document. The manufacturers of these drugs have not received FDA approval to legally market their drugs, nor are the drugs being marketed in accordance with the OTC drug review. The new drug approval and OTC drug monograph processes play an essential role in ensuring that all drugs are both safe and effective for their intended uses. Manufacturers of drugs that lack required approval, including those that are not marketed in accordance with an OTC drug monograph, have not provided FDA with evidence demonstrating that their products are safe and effective, and so we have an interest in taking steps to either encourage the manufacturers of these products to obtain the required evidence and comply with the approval provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) or remove the products from the market. We want to achieve these goals without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market.

The goals of this guidance are to (1) clarify for FDA personnel and the regulated industry how we intend to exercise our enforcement discretion regarding unapproved drugs and (2) emphasize that illegally marketed drugs must obtain FDA approval.

B. Historical Enforcement Approach

FDA estimates that in the United States today perhaps as many as several thousand drug products are marketed illegally without required FDA approval.[3] Because we do not have complete data on illegally marketed products, and because the universe of such products is constantly changing as products enter and leave the market, we first have to identify illegally marketed products before we can contemplate enforcement action. Once an illegally marketed product is identified, taking enforcement action against the product would typically involve one or more of the following: requesting voluntary compliance; providing notice of action in a *Federal Register* notice; issuing an untitled letter; issuing a Warning Letter; or initiating a seizure, injunction, or other proceeding. Each of these actions is time-consuming and resource intensive. Recognizing that we are unable to take action immediately against all of these illegally marketed products and that we need to make the best use of scarce Agency resources, we have had to prioritize our enforcement efforts and exercise enforcement discretion with regard to products that remain on the market.

In general, in recent years, FDA has employed a risk-based enforcement approach with respect to marketed unapproved drugs. This approach includes efforts to identify illegally marketed drugs, prioritization of those drugs according to potential public health concerns or other impacts on the public health, and subsequent regulatory follow-up. Some of the specific actions the Agency has taken have been precipitated by evidence of safety or effectiveness problems that has either come to our attention during inspections or been brought to our attention by outside sources.

[3] This rough estimate comprises several hundred drugs (different active ingredients) in various strengths, combinations, and dosage forms from multiple distributors and repackagers.

III. FDA'S ENFORCEMENT POLICY

In the discussion that follows, we intend to clarify our approach to prioritizing our enforcement actions and exercising our enforcement discretion with regard to unapproved, illegally marketed drug products.

The enforcement priorities and potential exercise of enforcement discretion discussed in this guidance apply only to unapproved drug products that are being commercially used or sold as of September 19, 2011. All unapproved drugs introduced onto the market after that date are subject to immediate enforcement action at any time, without prior notice and without regard to the enforcement priorities set forth below. In light of the notice provided by this guidance, we believe it is inappropriate to exercise enforcement discretion with respect to unapproved drugs that a company (including a manufacturer or distributor) begins marketing after September 19, 2011.

For unapproved drugs commercially used or sold as of September 19, 2011, FDA's enforcement priorities are described below.

A. Enforcement Priorities

Consistent with our risk-based approach to the regulation of pharmaceuticals, FDA intends to continue its current policy of giving higher priority to enforcement actions involving unapproved drug products in the following categories:

Drugs with potential safety risks. Removing potentially unsafe drugs protects the public from direct and indirect health threats.

Drugs that lack evidence of effectiveness. Removing ineffective drugs protects the public from using these products in lieu of effective treatments. Depending on the indication, some ineffective products would, of course, pose safety risks as well.

Health fraud drugs. FDA defines health fraud as "[t]he deceptive promotion, advertisement, distribution or sale of articles . . . that are represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes. Such practices may be deliberate or done without adequate knowledge or understanding of the article" (CPG Sec. 120.500). Of highest priority in this area are drugs that present a direct risk to health. Indirect health hazards exist if, as a result of reliance on the product, the consumer is likely to delay or discontinue appropriate medical treatment. Indirect health hazards will be evaluated for enforcement action based on section 120.500, Health Fraud - Factors in Considering Regulatory Action (CPG Sec. 120.500). FDA's health fraud CPG outlines priorities for evaluating regulatory actions against indirect health hazard products, such as whether the therapeutic claims are significant, whether there are any scientific data to support the safety and

effectiveness of the product, and the degree of vulnerability of the prospective user group (CPG Sec. 120.500).

Drugs that present direct challenges to the new drug approval and OTC drug monograph systems. The drug approval and OTC drug monograph systems are designed to avoid the risks associated with potentially unsafe, ineffective, and fraudulent drugs. The drugs described in the preceding three categories present direct challenges to these systems, as do unapproved drugs that directly compete with an approved drug, such as when a company obtains approval of a new drug application (NDA) for a product that other companies are marketing without approval (see section III.C, Special Circumstances – Newly Approved Product). Also included are drugs marketed in violation of a final and effective OTC drug monograph. Targeting drugs that challenge the drug approval or OTC drug monograph systems buttresses the integrity of these systems and makes it more likely that firms will comply with the new drug approval and monograph requirements, which benefits the public health.

Unapproved new drugs that are also violative of the Act in other ways. The Agency also intends, in circumstances that it considers appropriate, to continue its policy of enforcing the preapproval requirements of the FD&C Act against a drug or firm that also violates another provision of the FD&C Act, even if there are other unapproved versions of the drug made by other firms on the market. For instance, if a firm that sells an unapproved new drug also violates current good manufacturing practice (CGMP) regulations, the Agency is not inclined to limit an enforcement action in that instance to the CGMP violations. Rather, the Agency may initiate a regulatory action that targets both the CGMP violation and the violation of section 505 of the FD&C Act (21 U.S.C. 355). This policy efficiently preserves scarce Agency resources by allowing the Agency to pursue all applicable charges against a drug and/or a firm and avoiding duplicative action. See *United States v. Sage Pharmaceuticals, Inc.*, 210 F.3d 475, 479-80 (5th Cir. 2000).

Drugs that are reformulated to evade an FDA enforcement action. The Agency is also aware of instances in which companies that anticipate an FDA enforcement action against a specific type or formulation of an unapproved product have made formulation changes to evade that action, but have not brought the product into compliance with the law. Companies should be aware that the Agency is not inclined to exercise its enforcement discretion with regard to such products. Factors that the Agency may consider in determining whether to bring action against the reformulated products include, but are not limited to, the timing of the change, the addition of an ingredient without adequate scientific justification (see, for example, 21 CFR 300.50 and 330.10(a)(4)(iv)), the creation of a new combination that has not previously been marketed, and the claims made for the new product.

B. Notice of Enforcement Action and Continued Marketing of Unapproved Drugs

FDA is not required to, and generally does not intend to, give special notice that a drug product may be subject to enforcement action, unless FDA determines that

notice is necessary or appropriate to protect the public health.[4] The issuance of this guidance is intended to provide notice that any product that is being marketed illegally is subject to FDA enforcement action at any time.[5] The only exception to this policy is, as set forth elsewhere, that generally products subject to an ongoing DESI[6] proceeding or ongoing OTC drug monograph proceeding (i.e., an OTC product that is part of the OTC drug review for which an effective final monograph is not yet in place) may remain on the market during the pendency of that proceeding[7] and any additional period specifically provided in the proceeding (such as a delay in the effective date of a final OTC drug monograph).[8] However, once the relevant DESI or OTC drug monograph proceeding is completed and any additional grace period specifically provided in the proceeding has expired, all products that are not in compliance with the conditions for marketing determined in that proceeding are subject to enforcement action at any time without further notice (see, for example, 21 CFR 310.6).

FDA intends to evaluate on a case-by-case basis whether justification exists to exercise enforcement discretion to allow continued marketing for some period of time after FDA determines that a product is being marketed illegally. In deciding whether to allow such a grace period,[9] we may consider the following factors: (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of legally marketed products to meet the needs of patients taking the drug); (2) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application; (3) the burden on affected parties of

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[4] For example, in 1997, FDA issued a *Federal Register* notice declaring all orally administered levothyroxine sodium products to be new drugs and requiring manufacturers to obtain approved new drug applications (62 FR 43535, August 14, 1997). Nevertheless, FDA gave manufacturers 3 years (later extended to 4 (65 FR 24488, April 26, 2000)) to obtain approved applications and allowed continued marketing without approved new drug applications because FDA found that levothyroxine sodium products were medically necessary to treat hypothyroidism and no alternative drug provided an adequate substitute.

[5] For example, FDA may take action at any time against a product that was originally marketed before 1938, but that has been changed since 1938 in such a way as to lose its grandfather status (21 U.S.C. 321(p)).

[6] The Drug Efficacy Study Implementation (DESI) was the process used by FDA to evaluate for effectiveness for their labeled indications over 3,400 products that were approved only for safety between 1938 and 1962. DESI is explained more fully in the appendix to this document.

[7] OTC drugs covered by ongoing OTC drug monograph proceedings may remain on the market as provided in current enforcement policies. See, for example, CPG sections 450.200 and 450.300 and 21 CFR part 330. This document does not affect the current enforcement policies for such drugs.

[8] Sometimes, a final OTC drug monograph may have a delayed effective date or provide for a specific period of time for marketed drugs to come into compliance with the monograph. At the end of that period, drugs that are not marketed in accordance with the monograph are subject to enforcement action and the exercise of enforcement discretion in the same way as any other drug discussed in this CPG.

[9] For purposes of this guidance, the terms *grace period* and *allow a grace period* refer to an exercise of enforcement discretion by the Agency (i.e., a period of time during which FDA, as a matter of discretion, elects not to initiate a regulatory action on the ground that an article is an unapproved new drug).

immediately removing the products from the market; (4) the Agency's available enforcement resources; and (5) any special circumstances relevant to the particular case under consideration. However, as stated above, FDA does not intend to apply any such grace period to an unapproved drug that was introduced onto the market after September 19, 2011.

C. Special Circumstances — Newly Approved Product

Sometimes, a company may obtain approval of an NDA for a product that other companies are marketing without approval.[10] We want to encourage this type of voluntary compliance with the new drug requirements because it benefits the public health by increasing the assurance that marketed drug products are safe and effective — it also reduces the resources that FDA must expend on enforcement. Thus, because they present a direct challenge to the drug approval system, FDA is more likely to take enforcement action against remaining unapproved drugs in this kind of situation. However, we intend to take into account the circumstances once the product is approved in determining how to exercise our enforcement discretion with regard to the unapproved products. In exercising enforcement discretion, we intend to balance the need to provide incentives for voluntary compliance against the implications of enforcement actions on the marketplace and on consumers who are accustomed to using the marketed products.

When a company obtains approval to market a product that other companies are marketing without approval, FDA normally intends to allow a grace period of roughly 1 year from the date of approval of the product before it will initiate enforcement action (e.g., seizure or injunction) against marketed unapproved products of the same type. However, the grace period provided is expected to vary from this baseline based upon the following factors: (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of the holder of the approved application to meet the needs of patients taking the drug); (2) whether the effort to obtain approval was publicly disclosed;[11] (3) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application; (4) the burden on affected parties of removing the products from the market; (5) the Agency's available enforcement resources; and (6) any other special circumstances relevant to the particular case under consideration. To assist in an orderly transition to the approved product(s), in implementing a grace period, FDA may identify interim dates by which firms should first

[10] These may be products that are the same as the approved product or somewhat different, such as products of different strength.

[11] For example, at the Agency's discretion, we may provide for a shorter grace period if an applicant seeking approval of a product that other companies are marketing without approval agrees to publication, around the time it submits the approval application, of a *Federal Register* notice informing the public that the applicant has submitted that application. A shortened grace period may also be warranted if the fact of the application is widely known publicly because of applicant press releases or other public statements. Such a grace period may run from the time of approval or from the time the applicant has made the public aware of the submission, as the Agency deems appropriate.

cease manufacturing unapproved forms of the drug product, and later cease distributing the unapproved product.

The length of any grace period and the nature of any enforcement action taken by FDA will be decided on a case-by-case basis. Companies should be aware that a Warning Letter may not be sent before initiation of enforcement action and should not expect any grace period that is granted to protect them from the need to leave the market for some period of time while obtaining approval. Companies marketing unapproved new drugs should also recognize that, while FDA normally intends to allow a grace period of roughly 1 year from the date of approval of an unapproved product before it will initiate enforcement action (e.g., seizure or injunction) against others who are marketing that unapproved product, it is possible that a substantially shorter grace period would be provided, depending on the individual facts and circumstances.[12]

The shorter the grace period, the more likely it is that the first company to obtain an approval will have a period of de facto market exclusivity before other products obtain approval. For example, if FDA provides a 1-year grace period before it takes action to remove unapproved competitors from the market, and it takes 2 years for a second application to be approved, the first approved product could have 1 year of market exclusivity before the onset of competition. If FDA provides for a shorter grace period, the period of effective exclusivity could be longer. FDA hopes that this period of market exclusivity will provide an incentive to firms to be the first to obtain approval to market a previously unapproved drug.[13]

D. Regulatory Action Guidance

District offices are encouraged to refer to CDER for review (with copies of labeling) any unapproved drugs that appear to fall within the enforcement priorities in section III.A. Charges that may be brought against unapproved drugs include, but are not limited to, violations of 21 U.S.C. 355(a) and 352(f)(1) of the FD&C Act. Other charges may also apply based on, among others, violations of 21 U.S.C. 351(a)(2)(B) (CGMP), 352(a) (misbranding), or 352(o) (failure to register or list).

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[12] Firms are reminded that this CPG does not create any right to a grace period; the length of the grace period, if any, is solely at the discretion of the Agency. For instance, firms should not expect any grace period when the public health requires immediate removal of a product from the market, or when the Agency has given specific prior notice in the *Federal Register* or otherwise that a drug product requires FDA approval.

[13] The Agency understands that, under the Act, holders of NDAs must list patents claiming the approved drug product and that newly approved drug products may, in certain circumstances, be eligible for marketing exclusivity. Listed patents and marketing exclusivity may delay the approval of competitor products. If FDA believes that an NDA holder is manipulating these statutory protections to inappropriately delay competition, the Agency will provide relevant information on the matter to the Federal Trade Commission (FTC). In the past, FDA has provided information to the FTC regarding patent infringement lawsuits related to pending abbreviated new drug applications (ANDAs), citizen petitions, and scientific challenges to the approval of competitor drug products.

APPENDIX

BRIEF HISTORY OF FDA MARKETING APPROVAL REQUIREMENTS AND CATEGORIES OF DRUGS THAT LACK REQUIRED FDA APPROVAL[14]

Key events in the history of FDA's drug approval regulation and the categories of drugs affected by these events are described below.

A. 1938 and 1962 Legislation

The original Federal Food and Drugs Act of June 30, 1906, first brought drug regulation under federal law. That Act prohibited the sale of adulterated or misbranded drugs, but did not require that drugs be approved by FDA. In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act (the FD&C Act), which required that new drugs be approved for safety. As discussed below, the active ingredients of many drugs currently on the market were first introduced, at least in some form, before 1938. Between 1938 and 1962, if a drug obtained approval, FDA considered drugs that were identical, related, or similar (IRS) to the approved drug to be covered by that approval, and allowed those IRS drugs to be marketed without independent approval. Many manufacturers also introduced drugs onto the market between 1938 and 1962 based on their own conclusion that the products were generally recognized as safe (GRAS) or based on an opinion from FDA that the products were not new drugs. Between 1938 and 1962, the Agency issued many such opinions, although all were formally revoked in 1968 (see 21 CFR 310.100).

B. DESI

In 1962, Congress amended the Act to require that a new drug also be proven effective, as well as safe, to obtain FDA approval. This amendment also required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had approved as safe between 1938 and 1962 through the new drug approval process.

FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. The NAS/NRC created 30 panels of 6 professionals each to conduct the review, which was broken down into specific drug categories. The NAS/NRC reports for these drug products were submitted to FDA in the late 1960s and early 1970s. The Agency reviewed and re-evaluated the findings of each panel and published its findings in *Federal Register* notices. FDA's administrative implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI). DESI covered the 3,400 products specifically reviewed by the NAS/NRCs as well as the even larger number of IRS products that entered the market without FDA approval.

[14] This brief history document should be viewed as a secondary source. To determine the regulatory status of a particular drug or category of drugs, the original source documents cited should be consulted.

Because DESI products were covered by approved (pre-1962) applications, the Agency concluded that, prior to removing products not found effective from the market, it would follow procedures in the FD&C Act and regulations that apply when an approved new drug application is withdrawn:

- All initial DESI determinations are published in the *Federal Register* and, if the drug is found to be less than fully effective, there is an opportunity for a hearing.

- The Agency considers the basis of any hearing request and either grants the hearing or denies the hearing on summary judgment and publishes its final determination in the *Federal Register*.

- If FDA's final determination classifies the drug as effective for its labeled indications, as required by the FD&C Act, FDA still requires approved applications for continued marketing of the drug and all drugs IRS to it – NDA supplements for those drugs with NDAs approved for safety, or new ANDAs or NDAs, as appropriate, for IRS drugs. DESI-effective drugs that do not obtain approval of the required supplement, ANDA, or NDA are subject to enforcement action.

- If FDA's final determination classifies the drug as ineffective, the drug and those IRS to it can no longer be marketed and are subject to enforcement action.

1. Products Subject to Ongoing DESI Proceedings

Some unapproved marketed products are undergoing DESI reviews in which a final determination regarding efficacy has not yet been made. In addition to the products specifically reviewed by the NAS/NRC (i.e., those products approved for safety only between 1938 and 1962), this group includes unapproved products identical, related, or similar to those products specifically reviewed (see 21 CFR 310.6). In virtually all these proceedings, FDA has made an initial determination that the products lack substantial evidence of effectiveness, and the manufacturers have requested a hearing on that finding. It is the Agency's longstanding policy that products subject to an ongoing DESI proceeding may remain on the market during the pendency of the proceeding. See, e.g., *Upjohn Co. v. Finch*, 303 F. Supp. 241, 256-61 (W.D. Mich. 1969).[15]

2. Products Subject to Completed DESI Proceedings

[15] Products first marketed after a hearing notice is issued with a different formulation than those covered by the notice are not considered subject to the DESI proceeding. Rather, they need approval prior to marketing. Under longstanding Agency policies, a firm holding an NDA on a product for which a DESI hearing is pending must submit a supplement prior to reformulating that product. The changed formulation may not be marketed as a related product under the pending DESI proceeding; it is a new drug, and it must be approved for safety and efficacy before it can be legally marketed. See, e.g., "Prescription Drugs Offered for Relief of Symptoms of Cough, Cold, or Allergy" (DESI 6514), 49 FR 153 (January 3, 1984) (Dimetane and Actifed); "Certain Drugs Containing Antibiotic, Corticosteroid, and Antifungal Components" (DESI 10826), 50 FR 15227 (April 17, 1985) (Mycolog). See also 21 U.S.C. 356a(c)(2)(A). Similarly, firms without NDAs cannot market new formulations of a drug without first getting approval of an NDA.

Some unapproved marketed products are subject to already-completed DESI proceedings and lack required approved applications. This includes a number of products IRS to DESI products for which approval was withdrawn due to a lack of substantial evidence of effectiveness. This group also includes a number of products IRS to those DESI products for which FDA made a final determination that the product is effective, but applications for the IRS products have not been both submitted and approved as required under the statute and longstanding enforcement policy (see 21 CFR 310.6). FDA considers all products described in this paragraph to be marketed illegally.

C. Prescription Drug Wrap-Up

As mentioned above, many drugs came onto the market before 1962 without FDA approvals. Of these, many claimed to have been marketed prior to 1938 or to be IRS to such a drug. Drugs that did not have pre-1962 approvals and were not IRS to drugs with pre-1962 approvals were not subject to DESI. For a period of time, FDA did not take action against these drugs and did not take action against new unapproved drugs that were IRS to these pre-1962 drugs that entered the market without approval.

Beginning in 1983, it was discovered that one drug that was IRS to a pre-1962 drug, a high potency Vitamin E intravenous injection named E-Ferol, was associated with adverse reactions in about 100 premature infants, 40 of whom died. In November of 1984, in response to this, a congressional oversight committee issued a report to FDA expressing the committee's concern regarding the thousands of unapproved drug products in the marketplace.

In response to the E-Ferol tragedy, CDER assessed the number of pre-1962 non-DESI marketed drug products. To address those drug products, the Agency significantly revised and expanded CPG section 440.100 to cover all marketed unapproved prescription drugs, not just DESI products. The program for addressing these marketed unapproved drugs and certain others like them became known as the Prescription Drug Wrap-Up. Most of the Prescription Drug Wrap-Up drugs first entered the market before 1938, at least in some form. For the most part, the Agency had evaluated neither the safety nor the effectiveness of the drugs in the Prescription Drug Wrap-Up.

A drug that was subject to the Prescription Drug Wrap-Up is marketed illegally, unless the manufacturer of such a drug can establish that its drug is grandfathered or otherwise not a new drug.

Under the 1938 grandfather clause (see 21 U.S.C. 321(p)(1)), a drug product that was on the market prior to passage of the 1938 Act and which contained in its labeling the same representations concerning the conditions of use as it did prior to passage of that act was not considered a new drug and therefore was exempt from the requirement of having an approved new drug application.

Under the 1962 grandfather clause, the FD&C Act exempts a drug from the effectiveness requirements if its composition and labeling has not changed since 1962 and if, on the day before the 1962 Amendments became effective, it was (a) used or sold commercially in the United

States, (b) not a new drug as defined by the FD&C Act at that time, and (c) not covered by an effective application. See Public Law 87-781, section 107 (reprinted following 21 U.S.C.A. 321); see also *USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 662-66 (1973).

The two grandfather clauses in the FD&C Act have been construed very narrowly by the courts. FDA believes that there are very few drugs on the market that are actually entitled to grandfather status because the drugs currently on the market likely differ from the previous versions in some respect, such as formulation, dosage or strength, dosage form, route of administration, indications, or intended patient population. If a firm claims that its product is grandfathered, it is that firm's burden to prove that assertion. See 21 CFR 314.200(e)(5); see also *United States v. An Article of Drug (Bentex Ulcerine)*, 469 F.2d 875, 878 (5th Cir. 1972); *United States v. Articles of Drug Consisting of the Following: 5,906 Boxes*, 745 F.2d 105, 113 (1st Cir 1984).

Finally, a product would not be considered a new drug if it is generally recognized as safe and effective (GRAS/GRAE) and has been used to a material extent and for a material time. See 21 U.S.C. 321(p)(1) and (2). As with the grandfather clauses, this has been construed very narrowly by the courts. See, e.g., *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); United States *v. 50 Boxes More or Less Etc*., 909 F.2d 24, 27-28 (1st Cir. 1990); *United States v. 225 Cartons . . . Fiorinal*, 871 F.2d 409 (3rd Cir. 1989). See also Letter from Dennis E. Baker, Associate Commissioner for Regulatory Affairs, FDA, to Gary D. Dolch, Melvin Spigelman, and Jeffrey A. Staffa, Knoll Pharmaceutical Co. (April 26, 2001) (on file in FDA Docket No. 97N-0314/CP2) (finding that Synthroid, a levothyroxine sodium product, was not GRAS/GRAE).

As mentioned above, the Agency believes it is not likely that any currently marketed prescription drug product is grandfathered or is otherwise not a *new drug*. However, the Agency recognizes that it is at least theoretically possible. No part of this guidance, including the Appendix, is a finding as to the legal status of any particular drug product. In light of the strict standards governing exceptions to the approval process, it would be prudent for firms marketing unapproved products to carefully assess whether their products meet these standards.

D. New Unapproved Drugs

Some unapproved drugs were first marketed (or changed) after 1962. These drugs are on the market illegally. Some also may have already been the subject of a formal Agency finding that they are new drugs. See, e.g., 21 CFR 310.502 (discussing, among other things, controlled/timed release dosage forms).

E. Over-the-Counter (OTC) Drug Review

Although OTC drugs were originally included in DESI, FDA eventually concluded that this was not an efficient use of resources. The Agency also was faced with resource challenges because it was receiving many applications for different OTC drugs for the same indications. Therefore, in 1972, the Agency implemented a process of reviewing OTC drugs through rulemaking by therapeutic classes (e.g., antacids, antiperspirants, cold remedies). This process involves convening an advisory panel for each therapeutic class to review data relating to claims and active ingredients. These panel reports are then published in the *Federal Register*, and after

FDA review, tentative final monographs for the classes of drugs are published. The final step is the publication of a final monograph for each class, which sets forth the allowable claims, labeling, and active ingredients for OTC drugs in each class (see, e.g., 21 CFR part 333). Drugs marketed in accordance with a final monograph are considered to be generally recognized as safe and effective (GRAS/GRAE) and do not require FDA approval of a marketing application.

Final monographs have been published for the majority of OTC drugs. Tentative final monographs are in place for virtually all categories of OTC drugs. FDA has also finalized a number of *negative monographs* that list therapeutic categories (e.g., OTC daytime sedatives, 21 CFR 310.519) in which no OTC drugs can be marketed without approval. Finally, the Agency has promulgated a list of active ingredients that cannot be used in OTC drugs without approved applications because there are inadequate data to establish that they are GRAS/GRAE (e.g., phenolphthalein in stimulant laxative products, 21 CFR 310.545(a)(12)(iv)(B)).

OTC drugs covered by ongoing OTC drug monograph proceedings may remain on the market as provided in current enforcement policies (see, e.g., CPG sections 450.200 and 450.300, and 21 CFR part 330). This document does not affect the current enforcement policies for such drugs.

OTC drugs that need approval, either because their ingredients or claims are not within the scope of the OTC drug review or because they are not allowed under a final monograph or another final rule, are illegally marketed. For example, this group would include a product containing an ingredient determined to be ineffective for a particular indication or one that exceeds the dosage limit established in the monograph. Such products are new drugs that must be approved by FDA to be legally marketed.

United States Senate
Health, Education, Labor, and Pensions Committee

The Case for Clarifying FDA Authority: Large-Scale Drug Compounding and the Ongoing Risk to Public Health

Committee Staff Report

May 22, 2013

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Executive Summary

- This is the second HELP Committee staff report of the Committee's investigation into the nationwide outbreak of fungal meningitis traced to injections of contaminated drugs prepared by the Massachusetts-based New England Compounding Center. The report is based on a review of more than 30,000 pages of internal Food and Drug Administration ("FDA") documents over a six month period, as well as publicly available documents.

- Drug compounding is a traditional and longstanding activity of pharmacies, and serves an important role in our health care system. However, over the last 10 to 15 years, a number of large-scale drug compounding companies have started to produce large batches of high-risk drugs for national sale.

- Despite a scope of operations that makes these companies much more similar to drug manufacturers than pharmacies, they primarily face oversight similar to a state-licensed community pharmacy, rather than the more rigorous quality standards governing traditional drug manufacturers.

- The New England Compounding Center ("NECC") and the co-owned compounding company, Ameridose, both have lengthy track records of producing drugs of questionable sterility and potency, and both have been the subject of repeated adverse event reports and consumer complaints.

    - The Committee review of FDA documents indicates that, between 2002 and 2012, NECC was the subject of at least 52 adverse event reports that demonstrate the dangers created by its hazardous compounding practices. Documented issues include: the failure to ensure the sterility of equipment and products; the distribution of drugs containing particulate matter; the manufacture of super-potent and sub-potent drugs; the mislabeling of drugs; inaccurate beyond use dating; and the illegal distribution of drugs in the absence of patient-specific prescriptions.

    - Similarly, internal FDA documents dated between 2007 and 2012 indicate that Ameridose was the subject of at least 18 adverse event reports, with inspections documenting that Ameridose-compounded drugs displayed issues relating to sterility, potency, mislabeling, and adulteration.

- In tests of compounded drugs conducted by the FDA in 2001 and 2006, 34 and 33 percent of the drugs sampled *failed* one or more standard quality tests.

- FDA documents indicate that, between 2001 and 2011, at least 25 deaths and 36 serious injuries, including hospitalizations, were linked to large-scale drug compounding companies, including 13 deaths in 2011 alone. These numbers likely understate the actual number of adverse events, as current law does not require reporting of these events.

- Large-scale drug compounders *continue* to pose a serious risk to public health. In the eight months since the NECC-caused meningitis infections, at least 48 compounding companies have been found to be producing and selling drugs that were contaminated or created in unsafe conditions. Ten drug compounders have issued national recalls because of concerns about contamination, and 11 drug compounders have been ordered by state licensing agencies to stop producing some or all drugs.

- To reduce the risk to the public health from compounded drug products, it is essential that a clear statutory framework be enacted – one that requires compounding manufacturers to engage in good manufacturing practices, to better ensure the drugs produced are sterile and contain the correct amount of the active pharmaceutical ingredient.

Introduction

Beginning in the summer of 2012, 379 people in 19 states were infected with a rare form of fungal meningitis.[1] Fifty-five of those people died.[2] Rapid epidemiological investigative work by the Tennessee Department of Health and the Centers for Disease Control and Prevention ("CDCP") likely averted additional fatalities.[3] However, many of those infected continue to suffer debilitating side effects from the infection and the powerful drugs required to save their lives.[4] Those effects include loss of feeling in limbs, nightmare-like hallucinations, intense chronic pain, and the risk of organ failures.[5] One woman who received an injection in Michigan stated that she had been hospitalized seven separate times for a total of 75 days as a result of the infection she contracted.[6] A Florida woman remained hospitalized four months after developing meningitis.[7] Three hundred sixty-two additional cases of spinal and joint infections have also been documented.[8] The CDCP has linked those infections to injections of a fungus-contaminated drug prepared by the New England Compounding Center ("NECC"), a pharmacy based in Massachusetts.[9]

The contaminated drug linked to this outbreak was manufactured in large batch doses and distributed nationally. Neither the FDA nor the state of Massachusetts acted to enjoin the actions of the company. Because the FDA lacked clear authority over this type of pharmacy, the agency did not act to require the company to meet the good manufacturing practices or the quality standards that would have better ensured that the drugs produced were safe. Even in the wake of the NECC outbreak, and despite increased awareness of the risks posed by pharmacies operating like manufacturers, large-scale drug compounders continue to pose a serious risk to public health. Since the NECC outbreak, at least 10 separate companies have recalled compounded drugs, and at least 11 companies were ordered to stop producing some or all drugs.[10] Besides NECC and Ameridose, at least 48 other pharmacies have been found by the FDA or state regulators to be producing and selling drugs that are contaminated, were created in unsafe conditions, or otherwise violate state licensing requirements.[11]

What is Drug Compounding and How is it Regulated?

Compounding medicines is a traditional activity of pharmacies and serves an important role in our health care system. When compounding, the pharmacist alters medicines to adjust the dosing or modify the form to meet a patient-specific need. For instance, if an infant needs an antibiotic that is normally produced as a pill, a pharmacist could convert it to a liquid to be taken orally. That traditional compounding practice, by which a drug is produced in response to an individual prescription, or at most in small batches based on reasonably anticipated need, is regulated by the states. Drugs that are manufactured, in contrast, are regulated by the FDA.[12] Those drugs must be manufactured following rigorous quality controls to ensure that the drugs are not contaminated and that the dosage of the active ingredient is correct.

Over the last 10 to 15 years, a number of pharmacies have expanded operations far beyond the traditional compounding role, at least in part in response to hospital and consumer demand for otherwise unavailable drugs. Dozens, and possibly hundreds, of these large-scale drug compounding companies produce large batches of high-risk drugs, including preservative-free steroid injections and triple

anesthetic creams, for national sale. Some have specialized to become suppliers of commonly used hospital intravenous (IV) drugs like heparin, oxytocin, hydromorphone, and sodium chloride. Despite a scope of operations that makes these companies much more similar to drug manufacturers than pharmacies, they primarily face oversight similar to a state-licensed community pharmacy rather than the rigorous quality controls Americans would expect. Meanwhile, the FDA has been faced with a lack of clarity over the scope of its authority and an industry willing to challenge that authority on a regular basis. There also existed within FDA a bureaucracy hesitant to act on instances of apparent misconduct.

Over the last 10 to 15 years, dozens, and possibly hundreds, of large-scale drug compounding companies have started to produce large batches of high-risk drugs for national sale.

Congress and federal regulators have made previous efforts to establish an enforceable policy that clearly differentiates between traditional pharmacy compounding and compound drug manufacturing, but those efforts have proved to be complicated. Although Congress passed legislation designed to delineate these practices in 1997, the Supreme Court found certain provisions of this law unenforceable in 2002, and federal circuit courts split over whether the rest of the law was enforceable.[13] Also in 2002, the FDA issued a Compliance Policy Guidance setting forth when it would consider bringing an enforcement action against a compounding pharmacy.[14] However, trade associations and individual drug compounding companies continued to initiate challenges when the FDA sought to bring an enforcement action against large-scale drug compounders.[15] These cases further complicated the enforceability of the 1997 law in different parts of the country.

Although the FDA was faced with a lack of clarity in the law, and with an industry willing to challenge its authority on a regular basis, the agency responded poorly to those challenges. Officials responsible for enforcing the drug compounding guidance appear to have lacked defined inspection criteria and tracking procedures for building a strong evidentiary record for these cases. These uncertainties contributed to long delays when cases were brought to the agency Chief Counsel's office for approval, a required step before a Warning Letter or an injunction could be issued for a compounding pharmacy.[16] At least in actions relating to NECC and its co-owned compounding pharmacy, Ameridose, the Chief Counsel's office delayed decisions until the matter was so stale that it was no longer pursued.[17] Even when the agency did issue Warning Letters, as it ultimately did in the case of NECC, the agency's promised follow-through to injunction often did not materialize.[18]

By 2008, the jurisdictional issues had become so unclear that the agency appeared to be unable to balance the risk of litigation against the public health risk posed by the large-scale compounders, even though the agency continued to receive regular reports of serious adverse events, complaints from state boards of pharmacy, and consumer complaints. The result was an agency that lacked effective internal guidelines, procedures, and the leadership consensus required to regulate high-risk compounders like NECC and Ameridose.

In 2009, FDA leadership set out to develop a clear and enforceable policy that reflected the limitations of the multiple court decisions and the resulting differences in authority in various parts of the country.[19] In the fall of 2012, almost three years later, and despite additional complaints, the agency was finally

close to issuing that policy through revised Compounding Pharmacy Guidance, when the NECC-linked fungal meningitis outbreak occurred.[20]

However, had the FDA successfully implemented the revised guidance, it still would have faced serious challenges to ensuring that large-scale compounders were producing safe and effective drugs. Even under the proposed guidance, high-risk compounders would not have been required to register with the FDA, they would not have been subject to regular inspections (only to inspections following an adverse event or complaint), and additional rulemakings would have been necessary to define significant terms in the 1997 law, including what constituted compounding "regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available product."[21] It also likely would have had to litigate further to determine which circuit court's interpretation of the 1997 law would prevail.

Moreover, although the FDA's ability to inspect and bring enforcement actions against individual high-risk compounding operations would have been clarified, it is not clear that the guidance would have led many of the large-scale drug compounders that were engaged in the equivalent of manufacturing to improve quality standards. As demonstrated by the continuing safety violations documented over the past seven months, Congress needs to take action to ensure clear lines of responsibility for oversight of these companies. Drug compounding companies that are manufacturing batches of drugs in the absence of a prescription, and shipping those products to states across the country, need to adhere to an appropriate level of good manufacturing practices as determined by the FDA. These requirements are the linchpin that ensures that drugs are not contaminated and that the dosage of the active ingredient is correct.

The Public Health Risk Posed by NECC and Ameridose

As large-scale compounding manufacturers have grown over the last decades, so have concerns about the quality of the drugs produced by some of those companies. Documents produced to the Committee indicate that both NECC and co-owned Ameridose have lengthy track records of producing drugs of questionable sterility and potency, and both were the subject of repeated adverse event reports and consumer complaints.

NECC

Between 2002 and 2012, NECC was the subject of at least 52 adverse event reports exemplifying the dangers created by its hazardous compounding practices.[22] Also during this time, NECC's threat to public health was conclusively established by investigations undertaken by the FDA and state regulators, both as routine measures and in response to reports of NECC's unsafe compounding practices.[23] NECC's unsafe operations were repeatedly highlighted in the complaints of doctors, state boards of pharmacy, competitors, and consumers, some of whom suffered meningitis-like symptoms after receiving steroid injections made by NECC.[24]

As evidenced by these persistent complaints, NECC's compounding practices posed a public safety risk that was both broad in scope and egregious in nature. Among the many issues documented were

NECC's failure to ensure the sterility of equipment and products, including the distribution of drugs containing particulate matter; the manufacture of drugs that were overly strong or not strong enough ("super-potent" and "sub-potent"); the mislabeling of drugs; the inaccurate use of expiration dates (or "beyond use dates"); and the illegal distribution of drugs in the absence of patient-specific prescriptions.[25]

These deficient and unsafe practices compromised the integrity of a broad range of NECC-compounded drugs, including steroids administered for pain relief such as betamethasone epidural injections and methylprednisolone acetate injections; repackaged Avastin, a drug used to treat age-related macular degeneration; Trypan Blue, a drug used for capsular staining during cataract surgery; methotrexate; and topical anesthetic creams. Ultimately, these dangerous practices appear to have caused more than 50 patients to suffer serious illnesses, often requiring hospitalization, years in advance of the 2012 meningitis outbreak.[26] As previously documented by the Committee, both the FDA and the Massachusetts Board of Registration in Pharmacy took action against NECC, respectively issuing a Warning Letter and a Consent Decree, but neither agency moved effectively to enjoin the company from practices that placed the public health at risk.[27]

The New England Compounding Center and the co-owned compounding company, Ameridose, both have lengthy track records of producing drugs of questionable sterility and potency, and both were the subject of repeated adverse event reports and consumer complaints.

When the FDA and Massachusetts Board inspectors returned to NECC in the wake of the 2012 meningitis outbreak, their findings only amplified NECC's long history of unsound practices. The inspection demonstrated that NECC failed to comply with sterility procedures outlined in USP <797>, a widely accepted quality standard for smaller-scale compounders, and documented visible black particulate matter in vials of recalled methylprednisolone acetate.[28] Further, the FDA determined that NECC's environmental monitoring system documented 61 instances between January and August 2012 in which bacteria or mold existed in concentrations surpassing action-level thresholds.[29] Additional findings included "greenish yellow discoloration" lining one of two autoclaves used to sterilize various components and equipment; "yellow residue lining the rear return of Weigh Station 2 Hood and greenish residue lining the rear return of Weigh Station 3 Hood" which were used to "weigh active ingredients and other raw materials"; residual powder in the powder hood; tacky mats, which were used to prevent potential contaminants from entering the clean room, that were "visibly soiled with assorted debris"; and a leaking boiler that "created an environment susceptible to contaminant growth" adjacent to the clean room.[30]

Ameridose

Although regulators had already documented extensive problems concerning NECC's compounding practices, the Massachusetts Board of Registration in Pharmacy approved a license for the owners of NECC, the Conigliaro family, to open a second compounding company called Ameridose in 2006.[31] While NECC primarily manufactured drugs for purchase by pain clinics and physicians, Ameridose focused on compounding IV mixtures for use by hospitals across the country.

Between 2006 and 2012, Ameridose grew rapidly and, by the time of the NECC-caused meningitis crisis, Ameridose-compounded drugs were available to the 3,000 hospital members of Novation, the largest group purchasing organization in the country, in addition to 22,000 other providers and facilities.[32]

Ameridose engaged in many of the same unsafe compounding practices as did NECC. Between 2007 and 2012, Ameridose was the subject of at least 18 adverse event reports, in addition to a report from an employee-informant, and investigations by both federal and state authorities.[33] Findings established that Ameridose products posed considerable risks arising from issues of sterility, potency, mislabeling, adulteration, and illegal manufacturing.[34] For example, in August 2008, FDA investigators found that Ameridose products were shipped immediately without waiting for the results of sterility testing; testing for potency and dose uniformity was not routinely performed; and Ameridose failed to comply with the requirements of USP <797> in violation of Massachusetts law.[35]

A subsequent follow-up inspection resulted in sampling of Fentanyl, a drug opioid analgesic that FDA inspectors noted was already "very potent" at "80x" the potency of morphine in its standard form.[36] Testing demonstrated that Ameridose-compounded Fentanyl was concentrated at 118.4 percent the standard level, leading to a recall of that particular batch of that particular drug.[37] Following the 2008 inspections, a Warning Letter was drafted for Ameridose that enumerated many instances of illegal manufacturing of unapproved, misbranded, and adulterated drug products.[38] While the Warning Letter was tentatively cleared by the FDA's Office of the Chief Counsel in early March 2009, concerns over a single sentence delayed final approval for months.[39] In September 2009, the Warning Letter was deemed stale because it had been over a year since the initial inspections, and the letter was never sent.[40]

In 2010, an employee-informant of Ameridose described concerns such as the elimination of several product safety checks and the presence of particulate matter in a batch of Succinylcholine that was deemed acceptable for distribution.[41] The informant also related that untrained sales force personnel had assisted in labeling operations in a clean room, one of the three clean rooms was used despite a positive test result for mold growth, and employees sanitized areas before taking environmental samples.[42]

Following the 2012 meningitis outbreak, FDA investigators documented concerns at the larger-scale Ameridose that were virtually identical to those they found at the co-owned NECC facility. Among the issues discovered were failures to guarantee the sterility of drugs and the uniformity of doses, including findings that batches of drugs were not subjected to sterility testing, and that procedures to prevent microbiological contamination of sterile drugs were inadequate.[43] Further, FDA investigators found that Ameridose failed to clean or maintain equipment and utensils sufficiently to prevent contamination, lacked equipment for adequate control over air pressure, and was infested with vermin.[44]

The Scope of the Public Health Risk: Beyond NECC and Ameridose

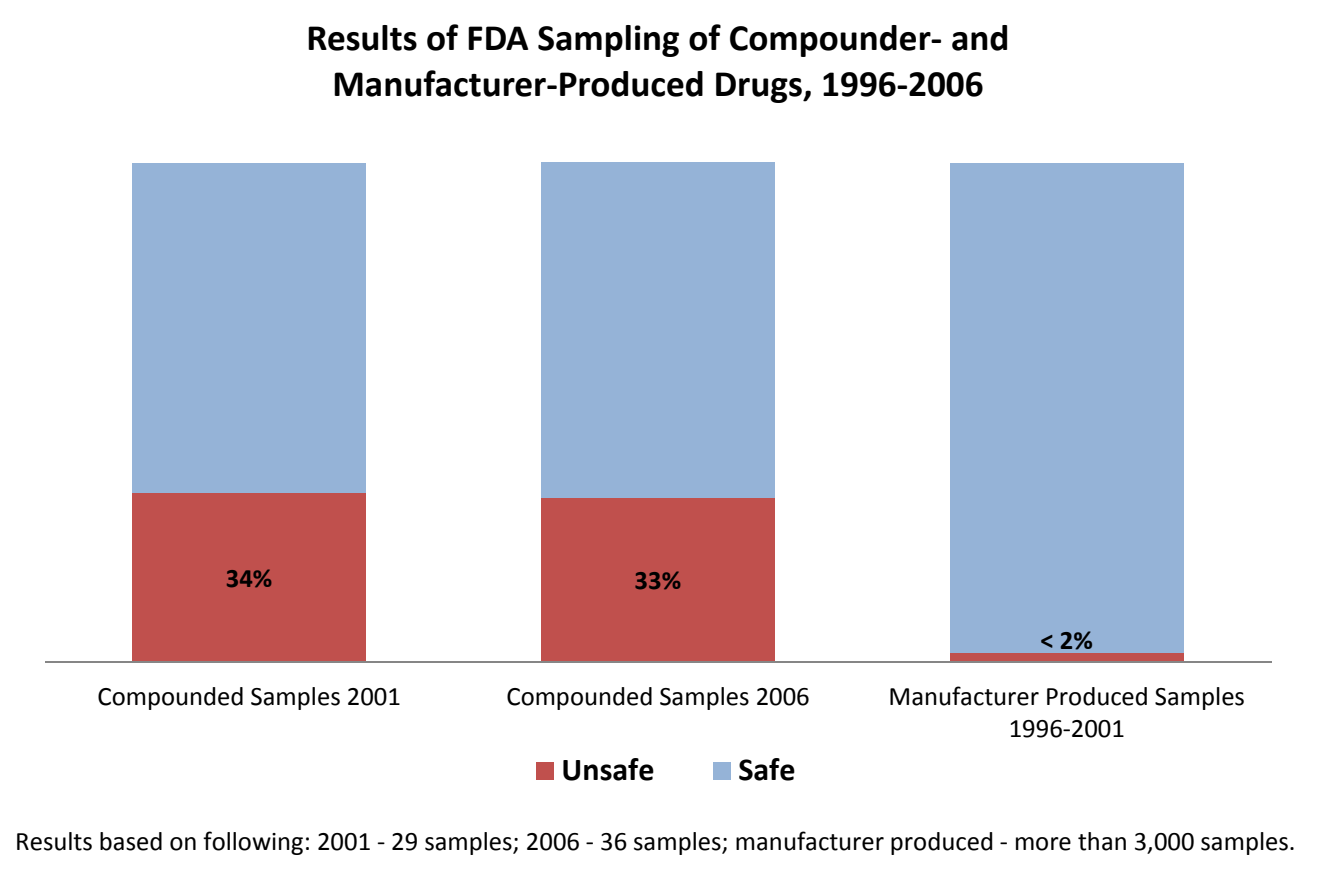
NECC and Ameridose were hardly the only companies engaged in practices that were of serious concern to the FDA. Between 2004 and 2010, the agency issued at least 46 Warning Letters to compounders documenting concerns ranging from failure to test drugs for contaminants and potency, to the use of unjustifiable beyond use dates[45] Additionally, between 2001 and 2011, an FDA document compiling

some of the most serious adverse events related to drug compounding details at least 25 deaths and 36 serious injuries, including hospitalizations, that were linked to large-scale drug compounding companies, including 13 deaths in 2011 alone.[46]

In addition, since the NECC outbreak, state boards of pharmacy, the National Association of Boards of Pharmacy, and the FDA have taken steps to understand and inspect companies engaged in large-scale drug compounding more effectively. As a result of those efforts, at least 10 companies have issued recalls for sterile drug products, many in response to documented contamination; at least 11 companies have been the subject of cease-and-desist orders by state authorities; and Iowa has initiated license revocations against at least five companies.[47]

FDA Sampling Documented Risks of Compounding

In an effort to understand better the risks posed by increasingly large drug compounding companies, the FDA undertook surveys of compounded drugs in 2001 and 2006. In 2001, the FDA purchased products from 12 companies offering products for sale online, and, in 2006, it collected samples in unannounced visits to 36 compounding pharmacies.[48] The FDA also tested the active ingredients used to compound the drugs and determined that no underlying active ingredient failed quality testing.[49]



The 2001 survey was based on standard quality testing conducted on compounded drugs, including sterile injectables, pellet implants, and ophthalmic products.[50] Ultimately, the agency was able to

complete testing on a total of 29 samples.[51] Of those, 10 of the samples, or 34 percent, *failed* one or more standard quality tests.[52] By contrast, in routine FDA samples of drug products from commercial manufacturers, the analytical testing failure for those drugs has been less than 2 percent.[53] When compared to this failure rate, the failure rate of 34 percent for compounded drugs indicates the need for better quality controls in most compounding companies. Specifically, the survey found that most of the samples that failed quality testing contained improper amounts of the active ingredient, and thus were either super-potent or sub-potent.[54] In addition, one sterile injectable was found to have an unacceptably high level of bacterial endotoxins.[55] The failed products included sterile injectable betamethasone, a drug which has resulted in meningitis infections on several occasions, and commonly used fertility drugs, including estradiol.[56]

Similarly, the 2006 survey collected samples from unannounced visits to compounding pharmacies from around the United States.[57] Quality testing was completed on 36 samples, all of which were sterile injectable drugs.[58] Of the 36 samples tested, 12, or 33 percent, failed one or more standard quality tests.[59] As in 2001, the survey found that the samples that failed quality testing were either super-potent or sub-potent.[60] Moreover, the test results were not off by small margins; in fact, the samples ranged from having 67.5 percent to 268.4 percent of the drug potency declared on the product labeling.[61] All tested drug products with the active ingredient of lidocaine and estradiol failed the analysis.[62] Since none of the active pharmaceutical ingredients that went into the final product failed testing, the FDA concluded that "the analytical failures of the finished drug products were likely related to the compounding processes at the pharmacies."[63] As the FDA concluded, "the fact that nearly one-third failed analytical testing raises public health concerns."[64]

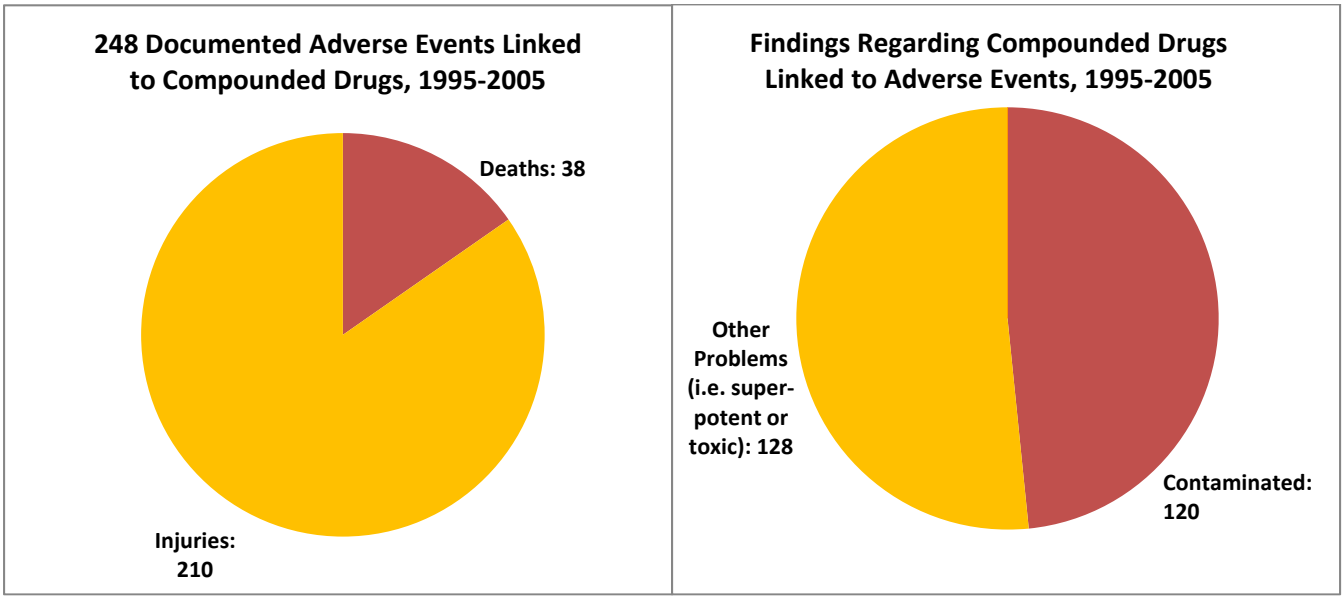
Adverse Events

The gravity of the public health threat posed by large-scale drug compounders can be better understood by examining some of the documented adverse events. Between 2001 and 2011, an FDA document compiling some of the most serious adverse events related to drug compounding details at least 25 deaths and 36 serious injuries, including hospitalizations, that were linked to large-scale drug compounding companies, including 13 deaths in 2011 alone.[65] As the FDA stated in the memo, "Based on the information presented…, we feel that there are significant public health concerns with the compounding of sterile drug products."[66]

Between 1988 and 2005, at least 38 deaths and 210 injuries were linked to compounding company drugs that were contaminated, mislabeled or caused lethal overdoses

A separate accounting of adverse events and complaints linked to drug compounding companies between 1988 and 2005 documents at least 38 deaths and 210 injuries from drugs that were contaminated, mislabeled, or caused lethal overdoses because they contained more of the active pharmaceutical ingredient than indicated.[67] These 248 tragedies included the deaths of six infants and children, and at least 18 other children paralyzed, burned, hospitalized, and suffering from other severe reactions.[68] The FDA said that these reports represented only a small percentage of total adverse events

from compounded drugs.[69] There is currently no system in place that requires adverse event reporting or accurately tracks adverse events to compounded products.



The adverse events detailed by the FDA include three 2007 deaths that were associated with compounded Colchicine from a pharmacy in Texas.[70] Colchicine, which can be very toxic when given in high doses, is used to prevent gout attacks (sudden, severe pain in one or more joints) in adults, and to relieve the pain accompanying gout attacks when they occur. Three patients died after being administered the drug by injection for back pain.[71] Within hours of receiving the injections, the patients became seriously ill and were taken to local hospitals.[72] When the FDA investigated and tested samples of the compounded product, sample potency varied from 640 percent to 62 percent of the level of Colchicine declared.[73]

Last month, on April 15, 2013, the same pharmacy announced a total recall of all lots of all sterile compounded products.[74] The company continues to operate under current law as a pharmacy not subject to good manufacturing practices, and currently manufactures numerous drug products, including hormones, thyroid and adrenal drugs, and eye drops.

Numerous other examples exist of compounding pharmacies repeatedly failing to meet high-quality safe and sterile manufacturing practices, including a California pharmacy selling contaminated compounded cardioplegia solution (used in open-heart surgery) that resulted in severe infections, sepsis, and three deaths in 2005.[75] The same compounding pharmacy produced super-potent hydromorphone in 2009, causing patients to overdose.[76] The company continues to operate under current law as a pharmacy not subject to good manufacturing practices, and it currently operates 25 locations nationwide. During recent inspections of six of these 25 locations, the FDA found such disturbing problems as potential potency issues, microorganism contamination, and pests.[77]

Similarly in 2002, several people developed fungal infections and two died after being injected with methylprednisolone made by a South Carolina pharmacy.[78] The South Carolina Board of Pharmacy found the pharmacy unsanitary and its sterilization practices inadequate.[79] It suspended the pharmacist's license for four years and fined him $10,000. Ultimately, the pharmacy closed.[80]

Findings of Recent Investigations and Inspections

In the eight months since the NECC-caused meningitis crisis, it has become clear that public health risks from large-scale drug compounding persist. As a result of increased oversight from state and federal regulators, at least 48 compounding companies have been found to be producing and selling drugs that are contaminated, were created in unsafe conditions, or otherwise violate state licensing requirements.[81] Ten companies have issued nationwide recalls of drugs compounded at their facilities.[82] In at least four cases, the recall was issued in response to documentation of actual contamination.[83] Further, 11 compounding pharmacies have been ordered to cease and desist operations, including two of those that had issued nationwide recalls.[84]

In Massachusetts, one compounding pharmacy recalled all of its sterile products after unidentified particulates were observed in five vials of drugs.[85] After producing a super-potent painkiller that caused two people to be hospitalized last year, the company was already under investigation by state authorities.[86] In November 2012, the state ordered the company to stop making a generic form of Viagra because it was found to be using "improper components."[87]

Adverse events and complaints linked to drug compounding companies between 1988 and 2005 account for at least 38 deaths and 210 injuries.

A second Massachusetts specialty pharmacy recalled allegedly sterile fertility drugs after a patient discovered an unknown substance floating in a vial of medication that had been shipped to 2,100 patients in 39 states.[88] In February 2013, state health officials issued a cease-and-desist order prohibiting the company from producing sterile compounded drugs.[89]

Similarly, in March 2013, a hospital nurse spotted debris floating in a vial of intravenous drugs.[90] Tests confirmed that the debris was a fungus and, consequently, prompted a massive recall by the New Jersey compounding pharmacy that produced the drugs.[91] Although the New Jersey Board of Pharmacy has restricted the company from compounding intravenous drugs, and the state Attorney General is seeking the revocation of the pharmacy's license, the company previously manufactured a wide variety of other sterile drugs, including antibiotics, anesthetics, and pain management medications.[92]

More recently, in April 2013, a Florida pharmacy recalled all lots of its sterile drug products after an FDA inspection revealed "black particles of unknown origin" in seven vials of an injectable steroid.[93] FDA investigators also found "a cloth-like filament of unknown origin" in one vial of chromium-chloride injections, an additive used for intravenous nutritional supplements.[94] Tests confirmed the presence of bacteria.[95]

Six additional companies also have recalled potentially contaminated drugs over the past few months, spurred by FDA inspections that identified serious quality control deficiencies resulting in the high

potential for contaminated products.[96] In addition, the FDA issued "inspectional observations" to 20 other compounding pharmacies that contained findings including inappropriate and/or inadequate clothing for sterile processing, lack of appropriate air filtration systems, insufficient microbiological testing, failure to conduct potency testing, and problems related to expiration and beyond use dates.[97]

Finally, the Iowa Board of Pharmacy has filed charges against at least five companies for violations including incorrect labeling, noncompliant sterile areas, and improper distribution of drugs.[98] These actions are the result of an ongoing series of inspections of all out-of-state pharmacies licensed in Iowa, conducted in partnership with the National Association of Boards of Pharmacy.[99] Tennessee and Florida are both surveying state compounding pharmacies in an effort to regulate these companies more effectively.[100] Other states have also been re-examining their oversight of these entities.

Conclusion

The NECC-linked meningitis crisis occurred against a backdrop of a significant increase in the number of companies that manufacture large batches of high-risk compounded drugs and market and ship them nationally. Investigations and sampling studies conducted by the FDA plainly demonstrate that many of these companies were and are not following good manufacturing standards or meeting other practice standards. At the same time, the FDA struggled to develop a clear and enforceable policy for these types of large-scale drug compounders. The agency faced numerous challenges in developing this policy, including repeated legal challenges to the agency's attempted enforcement actions against high-risk compounders, but the agency ultimately never released a workable policy.

Today, eight months after quick work by the Tennessee Department of Health and the CDCP isolated NECC-produced steroids as the source of the infections, the public health risk from compounded drugs persists. Some states have engaged in an effort to understand and inspect large-scale compounders operating in or licensed within their borders more effectively, and the FDA has similarly inspected a number of large compounders closely. That scrutiny has demonstrated the scope of the public health risk posed by large-scale compounding manufacturers and the need for well-defined lines that differentiate these companies from traditional pharmacy compounders, providing medicine for individual patients. To reduce the risk to the public health from compounded drug products, it is essential that a clear statutory framework be enacted that requires compounding manufacturers to follow the appropriate good manufacturing practices that will better ensure that the drugs produced are sterile and contain the correct amount of the active pharmaceutical ingredient.

Endnotes

[1] CDC, *Multi-State Meningitis Outbreak - Current Case Count*, May 6, 2013, http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html, (accessed May 17, 2013).
[2] Id.
[3] CDC Testimony before the Senate HELP Committee, Re: *The CDC and Public Health Response to the 2012 Fungal Meningitis and Other Infections Outbreak*, November 15, 2012 ("Their [local infectious disease officials, including state epidemiologists, healthcare associated infection (HAI) prevention coordinators, and others whose positions are directly supported through CDC's Epidemiology and Laboratory Capacity (ELC) cooperative agreement and CDC's Emerging Infections Program (EIP)] efforts at the state and local level have been extraordinary and in many cases undoubtedly contributed directly to saving the lives of exposed patients.").
[4] CDC, *Multi-State Meningitis Outbreak - Current Case Count*, May 6, 2013, http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html, (accessed May 17, 2013).
[5] *E.g.*, 60 Minutes, *"Lethal Medicine Linked to Meningitis Outbreak*," March 10, 2013, http://www.cbsnews.com/video/watch/?id=50142537n (accessed May 15, 2013); 60 Minutes, *"A Painful Road to Recovery,"* March 10, 2013, http://www.cbsnews.com/video/watch/?id=50142543n (accessed May 15, 2013).
[6] 60 Minutes, *"Lethal Medicine Linked to Meningitis Outbreak*," March 10, 2013, http://www.cbsnews.com/video/watch/?id=50142537n (accessed May 15, 2013).
[7] Jodie Tillman, *Infection adds mystery to meningitis outbreak*, TAMPA BAY TIMES, January 19, 2013, *available at* http://www.tampabay.com/news/health/infection-adds-mystery-to-meningitis-outbreak/1271439 (accessed May 20, 2013).
[8] CDC, *Multi-State Meningitis Outbreak - Current Case Count*, May 6, 2013, http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html, (accessed May 17, 2013).
[9] CDC Testimony before the Senate HELP Committee, Re: *The CDC and Public Health Response to the 2012 Fungal Meningitis and Other Infections Outbreak*, November 15, 2012 ("My remarks today will focus specifically on the identification of, and subsequent public health response to, the outbreak associated with injections of contaminated preservative-free methylprednisolone acetate (MPA), an injectable steroid produced by the New England Compounding Center (NECC).").
[10] *See, e.g.*, Iowa Board of Pharmacy, *Re: Iowa nonresident Pharmacy License of Med Quest Pharmacy, License No 3399, Statement of Charges & Notice of Hearing*, January 16, 2012; Iowa Board of Pharmacy, *Re: Iowa nonresident Pharmacy License of PharMedium Services LLC, License No 5759, Statement of Charges & Notice of Hearing*, January 16, 2012; Iowa Board of Pharmacy, *Re: Wholesale Drug License of PharMedium Services LLC, License No 3763, Statement of Charges & Notice of Hearing*, January 16, 2012; Iowa Board of Pharmacy, *Re: Iowa nonresident Pharmacy License of Talon Compounding Pharmacy, License No 4027, Statement of Charges & Notice of Hearing*, January 16, 2012; Iowa Board of Pharmacy, *Re: Iowa nonresident Pharmacy License of Unique Pharmaceuticals, LTD, License No 3265, Statement of Charges & Notice of Hearing*, January 16, 2012; Iowa Board of Pharmacy, *Re: Iowa nonresident Pharmacy License of Wedgewood Pharmacy, License No 3577, Statement of Charges & Notice of Hearing*, January 16, 2012; Massachusetts Department of Health and Human Services Press Release, *Department of Public Health Announces Update on Unannounced Pharmacy Inspections*, February 05, 2013, *available at*: http://www.mass.gov/eohhs/gov/newsroom/press-releases/dph/update-on-unannounced-pharmacy-inspections-announced.html (accessed May 21, 2013); FDA News Release, *FDA alerts health care providers of recall of all sterile drug products by Med Prep Consulting in New Jersey*, March 18, 2013, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm344314.htm (accessed May 17, 2013); FDA Recall Firm Press Release, *Clinical Specialties Compounding Pharmacy Announces Voluntary Nationwide Recall of All lots of Sterile Products Repackaged and Distributed by Clinical Specialties Compounding Due to Lack of Sterility Assurance*, March 20, 2013, *available at:* http://www.fda.gov/Safety/Recalls/ucm344786.htm (accessed May 21, 2013); FDA Recall Firm Press Release, *Green Valley Drugs Announces Voluntary Nationwide Recall of All Lots of All Sterile Products Compounded, Repackaged, and Distributed by Green Valley Drugs Due to Quality Control Concerns*, April 5, 2013, *available at:* http://www.fda.gov/Safety/Recalls/ucm347559.htm (accessed May 21, 2013; FDA News Release, *FDA issues alert about lack of sterility assurance of drug products from ApotheCure, Inc. and NuVision Pharmacy and of forthcoming recall*, April 15, 2013, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm348093.htm (accessed May 17, 2013); Lena Sun, *Balanced Solutions Compounding Pharmacy Recalls Sterile Drug Products*, THE WASHINGTON POST, April 21, 2013, *available at* http://articles.washingtonpost.com/2013-04-21/national/38717632_1_fda-new-england-compounding-center-products (accessed May 20, 2013); FDA Recall Firm Press Release, *Nora Apothecary & Alternative Therapies*

Announces a Voluntary Multi-State Recall of All Sterile Compounded Products Due to a Lack of Sterility Assurance, April 22, 2013, *available at:* http://www.fda.gov/Safety/Recalls/ucm349040.htm (accessed May 21, 2013); FDA Recall Firm Press Release, *In Cooperation with FDA, The Compounding Shop, LLC Declares a Voluntary Recall of All Lots of Sterile Compounded Products Due to a Lack of Sterility Assurance Distributed Within its Local Market Area,* May 6, 2013, *available at:* http://www.fda.gov/Safety/Recalls/ucm351841.htm (accessed May 21, 2013); Letter from FDA to PharMEDium Services, LLC, Lake Forest Illinois, February 5, 2013; Letter from Foundation Care LLC to FDA, Re: *Foundation Care LLC, Earth City, Missouri (FEIN #3005364771) Response to FDA Form 483 Issued March 19, 2013,* April 9, 2013; Letter from IVSolutions of Lubbock to FDA, Re: *FDA 483, IVSolutions of Lubbock*, April 2, 2013; Kay Lazar, *Lab Results Expected Soon on Recalled Waltham Pharmacy Fertility Drugs*, THE BOSTON GLOBE, February 27, 2013, *available at* http://www.bostonglobe.com/lifestyle/health-wellness/2013/02/26/test-results-expected-soon-recalled-fertility-drugs-from-waltham-pharmacy/6atDVwnAbNrLSr1E0dHSFJ/story.html (accessed May 16, 2013); Chelsea Conaboy, *Recalled Woburn Compounding Pharmacy Products Were Shipped to 21 States*, BOSTON.COM, March 27, 2013, *available at* http://www.boston.com/whitecoatnotes/2013/03/27/recalled-woburn-compounding-pharmacy-products-were-shipped-states/hOenagPUFpnVzthgA3PeDO/story.html (accessed May 20, 2013); FDA *Inspectional Observations*, Form FDA483, issued to: Custom Compounding Centers, LLC, Los Alamitos, California, December 13, 2012; PharMEDium Services LLC, Chester, Virginia, December 14, 2012; Central Admixture Pharmacy Services, Inc., Woburn, Massachusetts, January 29, 2013; PharMEDium Services LLC, Poland, Ohio, February 7, 2013; Wedgewood Village Pharmacy, Inc., Swedesboro, New Jersey, February 11, 2013; Central Admixture Pharmacy Services, Inc., Wallingford, Connecticut, February 19, 2013; Lee and Company, d/b/a Lee Pharmacy, Inc., Fort Smith, Arkansas, February 21, 2013; Central Admixture Pharmacy Services, Inc., Chicago, Illinois, February 22, 2013; PharMEDium Services LLC, Cleveland, Mississippi, February 22, 2013; Avella of Deer Valley, Inc., Phoenix, Arizona, February 25, 2013FDA *Inspectional Observations*, Form FDA483, issued University Pharmacy, Inc., Salt Lake City, Utah, February 26, 2013; PharMEDium Services LLC, Sugar Land, Texas, February 27, 2013; JCB Labs LLC, Wichita, Kansas, February 27, 2013; Central Admixture Pharmacy Services, Inc., Kansas City, Missouri, February 28, 2013; Central Admixture Pharmacy Services, Inc., Livonia, Michigan, February 28, 2013; PharMEDium Services LLC, Edison, New Jersey, February 28, 2013; Oakdell Pharmacy, Inc., San Antonio, Texas, March 1, 2013; Triangle Compounding, Cary, North Carolina, March 1, 2013; Home Intensive Care Pharmacy, Inc., San Antonio, Texas, March 1, 2013; PharMEDium Services LLC, Portage, Michigan, March 6, 2013; Central Admixture Pharmacy Services, Inc., Homewood, Alabama, March 7, 2013; Lowlyn Pharmacies, Inc., Blanchard, Oklahoma, March 8, 2013; College Pharmacy Incorporated, Colorado Springs, Colorado, March 15, 2013; FVS Holdings, Inc., d/b/a Green Valley Drugs, Henderson, Nevada, March 15, 2013; Foundation Care LLC, Earth City, Missouri, March 19, 2013; IV Solutions of Lubbock [sic], Lubbock, Texas, March 20, 2013; Drugs Are Us, Inc., d/b/a Hopewell Pharmacy, Hopewell, New Jersey, March 21, 2013; Lowlite Investments, Inc., d/b/a Olympia Pharmacy, Orlando, Florida, March 21, 2013; Medaus, Inc., Birmingham, Alabama, March 22, 2013; PharMEDium Services LLC, Memphis, Tennessee, March 22, 2013; Stewart Compounding Pharmacy, Fayetteville, North Carolina, March 25, 2013; Pentec Health, Inc., Boothwyn, Pennsylvania, April 1, 2013 (*hereinafter* "Recent Regulatory Actions").

[11] Recent Regulatory Actions, *supra* 10.

[12] Among other requirements, drug manufacturers are subject to a preapproval process that generally requires clinical testing. Manufacturers must also register with the agency and identify their drug products.

[13] Food and Drug Administration Modernization Act of 1997 (FDAMA); *Western States Medical Center v. Shalala*, 238 F.3d 1090 (9th Cir. 2001); *Medical Center Pharmacy v. Mukasey*, 536 F.3d 383 (5th Cir. 2008).

[14] FDA, *Guidance for FDA Staff and Industry, Compliance Policy Guides Manual, Se. 460.200, Pharmacy Compounding,* May 2002.

[15] *Medical Center Pharmacy v. Mukasey*, 536 F.3d 383 (5th Cir. 2008); *Wedgewood Village Pharmacy Inc. v. United States*, 421 F.3d 263 (3d Cir. 2005); *United States v. Franck's Lab, Inc.*, 816 F. Supp. 2d 1209 (M.D. Fla. 2011); *Medical Center Pharmacy v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006).

[16] FDA Internal Document, Re: *Procedures for Clearing FDA Warning Letters and Untitled Letters*, July 2012, *available at* http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM176965.pdf (accessed May 16, 2013). In 2001, a policy was implemented that required all Warning Letters and untitled letters to be reviewed by the FDA Chief Counsel's Office. The policy was revised in 2009, but it continues to require review for a wide range of letters, including any letter implicating compounding or other controversial legal issues.

[17] *E.g.*, FDA Internal Email, Re: *CMS Quality Control Check*, September 1, 2009 ("Ameridose's Warning Letter (Case ID 40318) was put on hold due to conflicting court rulings related to Pharmacy Compounding. We are currently not proceeding

with issuance of this warning letter because it has now been 1 [sic] year since the district's inspection of the firm. We may in the future conduct an inspection of this firm, but for now this case is closed.").

[18] *See* FDA Warning Letter, Re: *NWE-06-07W*, December 4, 2006.

[19] FDA Internal Memorandum, Re: *Draft Guidance on Compounding of Human Drugs Under Section 503A of the Federal Food, Drug, and Cosmetic Act – Compliance Policy Guide*, November 1, 2010.

[20] FDA Internal Document, Re: *Draft Revised Compliance Policy Guide Sec. 460.200*, August 15, 2012; FDA Internal Memorandum, Re: *Rationale for 503A Policy and Regulatory Strategy*, October 4, 2011.

[21] FDA Internal Document, *Draft Compounding CPG Announcing Enforcement of Section 503A of the FDCA*, October 2, 2012.

[22] Untitled Letters from Food and Drug Administration to Chairman Harkin and Ranking Member Enzi, December 6, 2012.

[23] *E.g.*, Colorado State Board of Pharmacy, *Special Report*, Re: *New England Compounding Pharmacy, Inc. (WHO 7832)*, July 20, 2012; FDA Warning Letter to NECC, December 4, 2006; Massachusetts Board of Registration in Pharmacy, *Consent Agreement* re: *Docket No. DS-03-055, PH-03-066*.

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2012, at 4.

[29] FDA *Inspectional Observations*, Form FDA483, issued to Barry Cadden, Owner, New England Compounding Pharmacy, Inc., d/b/a New England Compounding Center, October 26, 2012.

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[31] Ameridose, LLC, *Application for a New Store – 50 Fountain Street*, 2006.

[32] *See* Todd Wallack, *Ameridose faced previous safety questions*, BOSTON GLOBE, October 10, 2012, *available at* http://www.boston.com/news/local/massachusetts/2012/10/11/ameridose-faced-previous-safety-questions/9kI81p8FOEuOKG5X9rnZoM/story.html (accessed May 17, 2013). In June 2012, prior to the NECC outbreak, Novation announced that it would sever its agreement with Ameridose after the company failed an audit. During that audit, Novation found that Ameridose neglected to separate sterile products from non-sterile objects and lacked sufficient quality controls, though the agreement was not officially severed at the time of the NECC-triggered outbreak.

[33] Untitled Letters from Food and Drug Administration to Chairman Harkin and Ranking Member Enzi, December 6, 2012; FDA Consumer Complaint/Injury Report, Re: *Complaint #115569*, July 13, 2010.

[34] FDA *Inspectional Observations*, Form FDA483, issued to Gary Conigliaro, General Manager, Ameridose, LLC, August 6, 2008.

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[36] FDA Internal Email, Re: *Ameridose spl 366491*, September 10, 2008.

[37] Id.

[38] FDA Internal Memorandum, Re: *Warning Letter Recommendation*, October 6, 2008.

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[40] FDA Internal Email, Re: *CMS Quality Control Check*, September 1, 2009 ("Ameridose's Warning Letter (Case ID 40318) was put on hold due to conflicting court rulings related to Pharmacy Compounding. We are currently not proceeding with issuance of this warning letter because it has now been 1 [sic] year since the district's inspection of the firm. We may in the future conduct an inspection of this firm, but for now this case is closed."). *See also* FDA Internal Email, Re: *Compounding Pharmacy*, September 2, 2009 ("…NWE-DO spent a lot of time developing this case last year and having it 'closed' for nebulous reasons is troubling. If you look this up in CMS CDER actually concurred with our rec [sic] back in Feb. [sic]. So, I'm not sure what happened. This is quite frustrating since I thought we had a good WL. I've told our IB [sic] not to bother inspecting compounding pharmacies if we aren't going to act on the violations.").

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[42] FDA Internal Memorandum, Re: *Memorandum of Telecon, Between [Redacted] at Ameridose and Karen Archdeacon, CO, NWE-DO, re: GMP Allegations at Ameridose, Westboro, MA*, July 16, 2010 ("He indicated that personnel from their sales force were assisting in labeling operations in a clean room. He indicated that they had not been trained to perform such an operation. … He indicated that their firm was behind in orders and that this is why they needed additional personnel to assist in the manufacturing."; "On 8/5/10, he was aware that one of the 3 clean rooms had a positive result for mold growth. … He indicated that the room was used that day and that the managers performed a cleaning of the room in the event. He indicated that this cleaning was not documented."; "He also indicated that when they take environmental samples, they clean the area first before taking the sample.").
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[51] Id.
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The Boston Globe Health & wellness

Compounder sold drugs illegally in seven states

By Chelsea Conaboy | GLOBE STAFF MARCH 30, 2013

A Woburn compounding pharmacy that recalled two dozen drugs this week has said it distributed directly to patients and doctors in up to 21 states, but a Globe review found the company lacked the required license to operate as a pharmacy in at least a third of those states.

The California pharmacy board on Wednesday ordered Pallimed Solutions Inc. to stop shipping prescription drugs into that state because it had no license. Texas will consider taking similar action, the pharmacy board director said. State officials in Illinois, Maine, Wisconsin, Vermont, and Virginia — all listed on the distribution list in Pallimed's recall notice — said the company was not properly licensed to operate within their borders.

The possibility that the pharmacy was operating in states where it is not licensed points to continued gaps in the oversight of compounding pharmacies exposed last year when tainted steroids produced at New England Compounding Center caused a national crisis.

The Framingham pharmacy's drugs sickened hundreds of people and have been linked to 51 deaths. Regulators have said New England Compounding was acting more like a drug manufacturer, shipping products in bulk to providers nationwide though it didn't have a federal license.

While manufacturers are overseen by the Food and Drug Administration, it is the responsibility of compounding pharmacies to secure proper licenses for the states in which they do business.

"It's easy to see how, given the regulatory structure, these companies can go undetected," particularly if they are shipping drugs directly to patients' homes, said Dr. Michael Carome, deputy director of the Health Research Group at Public Citizen, a consumer advocacy group.

Compounders are supposed to custom make drugs for individual patients who need doses or preparations that aren't available off the shelf. Some compounders, including Pallimed and New England Compounding, specialized in mixing sterile products, which can include injections, intravenous solutions, and eye drops.

Pallimed announced on Tuesday that it is working with the FDA to recall all sterile compounded products it has dispensed since Jan. 1, after inspectors found still-unidentified contaminants in five vials of drugs at the company's Woburn pharmacy.

Many of the recalled products are injections used to treat erectile dysfunction or other conditions. No patient injuries or illnesses have been reported as a result of the recall. Pallimed has said it will continue to make products that don't require a sterile compounding process.

The company would not comment this week on how many patients might have received recalled items, where exactly it shipped its drugs, or where the pharmacy is licensed.

When asked about licensing status, Pallimed spokesman Scott Farmelant said by e-mail that "patients with out-of-state billing addresses often fill their prescriptions at Pallimed's Massachusetts facility." He declined to explain, citing the ongoing investigation. For the same reason, state and federal regulators would not comment specifically on the issue.

It is unclear at what scale Pallimed, which has a small staff and is located in the back of an office building in West Cummings Park, was operating. The state has said it is looking into whether the company has stayed within the scope of its Massachusetts license.

Carmen Catizone, executive director of the National Association of Boards of Pharmacy, said the system of making pharmacies responsible for securing their state licenses seemed to work until the fungal meningitis outbreak linked to New England Compounding.

"It wasn't troubling before, but it is troubling now," he said. "The whole game has changed."

His organization is working to build a database of pharmacy profiles, including disciplinary records, as a free resource for regulators researching a company's history in other states. The group has offered to contract with states to inspect out-of-state pharmacies that sell drugs within their borders.

According to a Globe review of records and interviews with state regulators, Pallimed has active licenses in eight states, including Massachusetts. In two states on Pallimed's distribution list, Georgia and Pennsylvania, representatives said licenses are not required for out-of-state pharmacies. Pallimed did not show up in licensing databases for several other states listed in the company recall, but state officials could not be reached for confirmation.

New York regulators did not renew Pallimed's pharmacy license in December, after the Massachusetts pharmacy board ordered Pallimed to stop making a generic form of Viagra because it was using veterinary components to fill human prescriptions. The company also was cited last year for making a too-potent batch of a painkiller that caused two people to be hospitalized.

Some officials said the licensing board in a compounding pharmacy's home state should compare the facility's product logs with its licenses to be sure it is complying with basic regulatory standards.

"Any legitimate pharmacy is going to make sure they have all the proper licenses and registrations that they need," said Ronald Klein, a pharmacist and former inspector who is executive officer of Vermont's pharmacy board.

Massachusetts wasn't making routine pharmacy inspections prior to the New England Compounding case. Governor Deval Patrick's administration has recently expanded oversight efforts, ordering surprise inspections of sterile compounding pharmacies and planning to hire more staff.

Proposals before state and federal lawmakers could further tighten regulation of the pharmacies. A federal proposal would require compounders that are acting as manufacturers to register with the FDA.

Massachusetts is one of just three states that do not require pharmacies located out of state to be licensed in Massachusetts in order to serve patients here. That means if Pallimed were based in another state, for example, it could distribute drugs here without a Massachusetts license. A bill scheduled for a legislative hearing Tuesday would change that.

Kay Lazar of the Globe staff contributed to this report. Chelsea Conaboy can be reached at cconaboy@boston.com. Follow her on Twitter @cconaboy.

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THE WIRE

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Report: Compounding Pharmacies Go Untracked (Washn)

April 14, 2013, 8:21 p.m. PDT

The Washington Post News Service

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WASHINGTON — State authorities who are supposed to oversee the type of specialized pharmacy at the heart of last fall's deadly meningitis outbreak lack the most basic information about the companies they are supposed to regulate, according to a congressional report to be released Monday.

State boards of pharmacy generally don't know which pharmacies in their state engage in compounding, the custom mixing of medications for individual patients. Nor do they know how much medication they make, how much of it is sterile and whether any products are sold across state lines. Only two states, Mississippi and Missouri, routinely track the number of compounding pharmacies in their states.

The report, by Rep. Edward Markey, D-Mass., follows up on a state-by-state examination last fall into safety issues raised when thousands of vials of steroid shots were sent to doctors' offices and clinics in 23 states by the New England Compounding Center (NECC), based in Framingham, Mass. Some of the vials were contaminated, and the outbreak killed 53 people and sickened 680 others.

The report's findings include state-by-state information on inspections, record-keeping and other aspects of compounding oversight. The information further demonstrates that states do not have the ability to effectively inspect, track or police activities within states or across state lines, Markey said.

"In states from coast to coast, compounding pharmacies are going untracked, unregulated and under-inspected, exposing patients everywhere to tainted drugs, disease and death," he said in a statement.

Markey and many other Democrats in Congress support legislation to give the Food and Drug Administration more authority over compounders. That topic is likely to be a focus Tuesday during a scheduled hearing of a House Energy and Commerce subcommittee.

Republicans are expected to question FDA Commissioner Margaret Hamburg about why the agency didn't take more forceful action against the NECC before the outbreak. Democrats on the panel want executives of the International Academy of Compounding Pharmacists, a major industry group, to testify about their two decades of lobbying Congress to limit FDA authority over compounders.

Last week, FDA officials released initial results of a targeted inspection of 30 compounding pharmacies that mix sterile drugs, considered the most high risk because any breakdown in the process can result in contamination. Federal inspectors found dozens of potentially dangerous safety problems, including unidentified black particles in vials of sterile solution, rust and mold in "clean rooms," and workers wearing torn gloves.

Hospitals, clinics and doctor's offices rely on a wide array of medications made by compounding pharmacies, including antibiotics, painkillers, and labor and delivery drugs, as well as medication for pets.

Sometimes compounders start with raw materials. Sometimes they repackage finished drugs into different forms and concentrations.

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But unlike drugs made by pharmaceutical companies, compounded drugs are not FDA-approved. Compounders do not have to meet the same standards as drug companies, even though some have grown so large that they resemble manufacturing-style operations, producing tens of thousands of doses and shipping them across state lines, often without individual prescriptions.

The FDA rarely inspects the facilities, unless the agency is responding to a complaint or a request from state authorities. State pharmacy boards are the primary regulators, but their oversight and expertise is uneven.

About a dozen states were considering legislation that would require stricter licensing requirements for compounders. Maryland and Virginia have passed bills requiring greater scrutiny of compounders who make sterile drugs.

The Markey report is based on information collected from states last month.

Among the other findings:

The majority of states allow any pharmacy to compound without a specific compounding license or permit. Forty-seven states and the District of Columbia were unable to provide an exact number of pharmacies that are authorized to compound. Only Missouri and Mississippi require a license for basic drug compounding.

Three other states — Arkansas, Maine and Oregon — ask that pharmacies indicate on their initial license application whether they plan to engage in compounding activities.

None of the states said they track the volume of medications made by compounders or whether pharmacies sell compounded drugs across state lines.

Thirty-seven state boards of pharmacy do not systematically track which pharmacies make sterile products. Among the 13 states that do track are California, Massachusetts and New Jersey.

When issues arise with pharmacies located in other states, state boards do not consistently inform each other or the FDA.

As a result, a state may discover a serious problem with the drugs produced by a pharmacy located in another state, take action to stop that pharmacy from shipping drugs into its state, but never notify the home state or any other state about the safety problem.

To address this lack of information, the Iowa pharmacy board is inspecting more than 600 out-of-state pharmacies that ship medications into Iowa, including compounders. The inspections have led to charges against five compounding pharmacies. The board is accusing the companies of failing to comply with regulations that require compounders to have prescriptions for specific patients, among other violations.

Carmen Catizone, executive director of the National Association of Boards of Pharmacy (NABP), which represents the state regulators and is helping Iowa with its inspections, said the report will help efforts underway to strengthen state oversight.

"Most of what they found we're already pushing the states to do," he said. "But we welcome any time we can get some help from Congress to identify these issues."

The NABP is putting together an electronic database accessible to all state pharmacy boards that would share detailed information about every pharmacy, including the states where it is licensed, its products, and any disciplinary action by any state, he said. He hopes to have it ready for the states by the end of the month and accessible to the public by the end of the summer.

Aaron Davis and Magda Jean-Louis contributed to this report.

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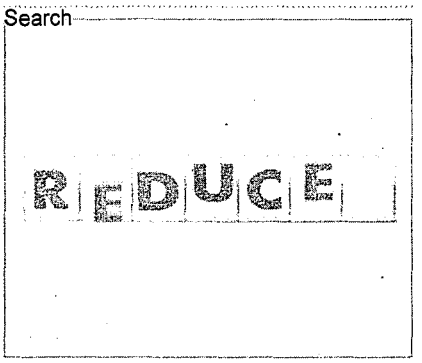

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FDA inspectors find unsanitary conditions at 30 compounding pharmacies across the US

Manuel Balce Ceneta, File/Associated Press - FILE - In this Wednesday, April 10, 2013 file photo, Food and Drug Administration (FDA) Commissioner Margaret Hamburg, foreground, with Health and Human Services Secretary Kathleen Sebelius, left, and others, speaks during a news conference at the Health and Humans Services (HHS) Department in Washington, to discuss the Health Department's fiscal 2014 budget. The Food and Drug

By Associated Press,

WASHINGTON — The Food and Drug Administration says it has uncovered potential safety problems at 30 specialty pharmacies that were inspected in the wake of a recent outbreak of meningitis caused by contaminated drugs.

The agency said its inspectors targeted 31 compounding pharmacies that produce sterile drugs, which must be prepared under highly sanitary conditions. The FDA said Thursday it issued inspection reports to all but one of the pharmacies citing unsanitary conditions and quality control problems, including: rust and mold in supposedly sterile rooms, inadequate ventilation, and employees wearing non-sterile lab coats.

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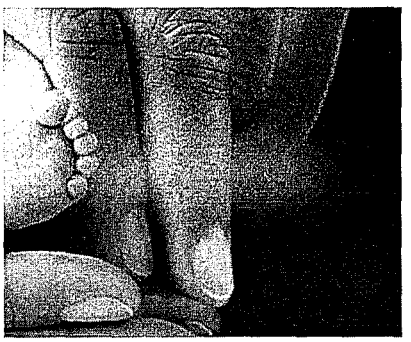
The agency generally issues such reports before taking formal action against companies. Inspectors visited pharmacies in 18 states, including Florida, Arizona, Colorado, Tennessee and New Jersey.



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The wave of inspections comes in response to a deadly fungal meningitis outbreak linked to contaminated steroids from the New England Compounding Center, a Massachusetts pharmacy. The company's injections, mainly used to treat back pain, have been linked to 53 deaths and 733 illnesses since last summer.

Compounding pharmacies are supposed to mix customized prescriptions based on individual doctors' instructions. However, some pharmacies like the New England Compounding Center have grown into larger businesses, supplying bulk quantities of injectable drugs to hospitals across the country.

The FDA has stepped up its oversight of the pharmacies since the outbreak was identified in September, but agency officials say they have been slowed by the complex overlap of various state and federal laws that govern the industry. Pharmacies are licensed and overseen by state pharmacy boards, though the FDA sometimes intervenes when major safety issues arise.

In a blog post to the FDA's website Thursday, FDA Commissioner Margaret Hamburg noted that four pharmacies initially refused to admit the agency's inspectors. In two cases the agency had to return with search warrants and U.S. marshals to complete the inspections.

"These challenges and others highlight the need for clearer authorities for FDA to efficiently protect public health," Hamburg stated.

Hamburg has asked Congress to pass new laws giving the FDA explicit oversight over large compounding pharmacies. Under the proposal, large compounders would have to register with the FDA and undergo regular inspections, similar to pharmaceutical manufacturers.

But the FDA proposal has faced pushback from some members of Congress, particularly House Republicans, who have been investigating whether the FDA could have prevented the meningitis outbreak using its existing powers.

The House Energy and Commerce Subcommittee for Oversight and Investigations will hold its second hearing on the issue next Tuesday. Hamburg is scheduled to testify, according to committee staffers.

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House Republicans fault FDA on meningitis outbreak

By Kimberly Kindy,

After reviewing 27,000 pages of documents from the Food and Drug Administration, Republicans and Democrats came to different conclusions about the agency's ability to prevent one of the worst public health crises in American history.

Republican members of the House Energy and Commerce Committee said Tuesday that its six-month investigation into the FDA's role in last fall's meningitis outbreak shows the agency knew for a decade about serious safety lapses at the specialized pharmacy that made the tainted drugs but failed to act.

Democrats said they believe the documents paint a different picture, one of an agency that made some efforts to rein in the Massachusetts-based New England Compounding Center (NECC), which made the contaminated steroids tied to the outbreak that has so far killed 53 people. However, they were thwarted by the Bush administration and by ambiguous federal laws and conflicting court rulings that do not give the FDA clear authority over compounders.

The documents show that, dating back to at least 2002, the FDA had received and largely ignored complaints from doctors, nurses and whistleblowers about safety problems at the NECC, according to the majority report from the Republicans. The complaints prompted two inspections, but, even as new complaints rolled in and after the agency issued a warning letter in 2006, the FDA did not return to the facility until after the outbreak.

"We know now that 53 Americans did not need to die," said the committee chairman, Rep. Fred Upton (R-Mich.). "It sickens me that this could have been avoided."

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FDA commissioner Margaret A. Hamburg, the only person scheduled to testify at the hearing, was sharply criticized about the agency's efforts with the NECC.

Members repeatedly asked why the agency has been able to conduct stepped-up inspections in recent months if they lack authority to do so. Earlier this month, the FDA released initial results of a targeted inspection of 30 compounding pharmacies, showing many of the firms had potentially dangerous safety violations.

"I wish we had been more aggressive," Hamburg told the committee.

"I bet the families who have lost loved ones wish you had acted as well," said Rep. Renee L. Ellmers (R-N.C.).

Hamburg told members that although the FDA is being more aggressive now, compounders are challenging their authority. In two recent instances, compounding pharmacies refused to give FDA inspectors access to the facility or records, so the agency had to secure warrants.

Hamburg asked for legislation that would require large, manufacturing-style compounding pharmacies to register with the agency and provide detailed information about the products they make. She said federal law must also make it clear that they have the right to conduct inspections, view pharmacy documents and order changes when they identify safety lapses.

The documents show that much of the delay was the result of internal agency debate about whether and how to proceed, in anticipation of having to defend an enforcement action.

"We are picking at gnats and straining at flies. We should be trying to figure out what are the problems," said Rep. John D. Dingell (D-Mich.). "We are dealing here with an agency that doesn't have the authority to do the things they need to do."

The committee's majority report from Republicans also criticized the agency for failing to take action against the NECC's sister company, Ameridose, which was inspected by the agency in 2007 and 2008 and had to recall a painkiller in 2008 because it was too strong. The report details numerous complaints the agency received about potential safety problems with Ameridose's products but delayed further action.

The majority report also faulted the FDA for failing to share information it had on the NECC and Ameridose with state regulators.

Democrats released their own report that cited internal e-mails and other documents to back their claims that the Bush administration stymied the FDA's efforts to send warning letters to the NECC and that this was partially to blame for the agency's inaction.

One August 2006 e-mail, written by a director in the FDA's complaint division to appointees in the agency's legal office, said: "I'm very frustrated that we still don't have a decision from your office about these warning letters. . . . For these letters to still be pending at this late date, especially given these extraordinary and unusual measures, is troubling."

Lena H. Sun contributed to this report.

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ATTACHMENT 9

Harkin Statement on HELP Committee Passage of the Pharmaceutical Compounding Quality and Accountability Act and the Drug Supply Chain Security Act

Wednesday, May 22, 2013

WASHINGTON—Today, Senator Tom Harkin (D-IA), Chairman of the Senate Health, Education, Labor and Pensions (HELP) Committee, issued the following statement on the Committee's passage of S. 959, the *Pharmaceutical Compounding Quality and Accountability Act*, and S. 957, the *Drug Supply Chain Security Act*.

"I am pleased that the HELP Committee has come together in a bipartisan effort to protect the public health from tainted and adulterated prescription drugs. These bills will enable Americans to be confident that the bottles in their medicine cabinet contain exactly what the doctor ordered.

"The *Pharmaceutical Compounding Quality and Accountability Act* will clarify oversight of pharmaceutical compounding, leaving traditional pharmacies under the supervision of states, while enabling the U.S. Food and Drug Administration to regulate compounding manufacturers, companies that make compounded sterile drugs without prescriptions, and ship them across state lines. This change will grant FDA the authority it needs to help protect Americans against future tragedies, like the meningitis outbreak—caused by tainted compound steroid injections—that claimed more than fifty lives in 2012.

"The *Drug Supply Chain Security Act* will strengthen the FDA's ability to track prescription drugs after they leave manufacturers, ensuring that they are accounted for at every step. That way, doctors, patients, and regulators can be sure that their medicines are safe."

"I plan to work with Senate leadership to bring this bipartisan legislation to the floor for a vote in a timely manner."

AMENDMENT NO._____ Calendar No._____

Purpose: In the nature of a substitute.

IN THE SENATE OF THE UNITED STATES—113th Cong., 1st Sess.

S. 959

A bill to amend the Federal Food, Drug, and Cosmetic Act with respect to compounding drugs.

Referred to the Committee on _____ and ordered to be printed

Ordered to lie on the table and to be printed

AMENDMENT IN THE NATURE OF A SUBSTITUTE intended to be proposed by _____

Viz:

1 Strike all after the enacting clause and insert the fol-
2 lowing:

3 **SECTION 1. SHORT TITLE; REFERENCES IN ACT.**

4 (a) SHORT TITLE.—This Act may be cited as the
5 "Pharmaceutical Compounding Quality and Account-
6 ability Act".

7 (b) REFERENCES IN ACT.—Except as otherwise spec-
8 ified, amendments made by this Act to a section or other
9 provision of law are amendments to such section or other
10 provision of the Federal Food, Drug, and Cosmetic Act
11 (21 U.S.C. 301 et seq.).

1 **SEC. 2. REGULATION OF HUMAN DRUG COMPOUNDING.**

2 (a) CLARIFICATION OF NEW DRUG STATUS.—For
3 purposes of the Federal Food, Drug and Cosmetic Act (21
4 U.S.C. 301 et seq.), the term "new drug" (as defined in
5 section 201(p) of such Act) shall include a compounded
6 human drug.

7 (b) REGULATION OF HUMAN DRUG
8 COMPOUNDING.—Section 503A (21 U.S.C. 353a) is
9 amended to read as follows:

10 **"SEC. 503A. HUMAN DRUG COMPOUNDING.**

11 "(a) SCOPE.—

12 "(1) COMPOUNDING.—In this section, the terms
13 'compounding' and 'compound'—

14 "(A) include—

15 "(i) the combining, admixing, mixing,
16 diluting, reconstituting, or otherwise alter-
17 ing of a marketed drug;

18 "(ii) compounding a drug from a bulk
19 drug substance; and

20 "(iii) repackaging; and

21 "(B) exclude mixing, reconstituting, or
22 other such acts with respect to a marketed drug
23 that are limited to and performed in accordance
24 with specific directions for such acts contained
25 in approved labeling provided by a drug's man-
26 ufacturer, when performed based upon a pre-

1 scription order for an identified individual pa-
2 tient.
3 "(2) ADMINISTRATION NOT A SALE.—In this
4 section, the terms 'sell' or 'resale' do not include cir-
5 cumstances in which a licensed practitioner admin-
6 isters a drug to a patient or provides a drug to a
7 patient who has been instructed to self-administer
8 the drug, including any fee associated with such ad-
9 ministration or provision of the drug.
10 "(3) INAPPLICABILITY TO CERTAIN DRUGS.—
11 "(A) IN GENERAL.—For purposes of this
12 section, the activities described in paragraph
13 (1) shall not be considered 'compounding' if
14 such activities are conducted in whole or in part
15 with respect to a drug described in subpara-
16 graph (B).
17 "(B) EXCLUDED DRUGS.—The drugs de-
18 scribed in this subparagraph are the following:
19 "(i) Blood and blood components for
20 transfusion.
21 "(ii) Medical gases, as defined in sec-
22 tion 575(2).
23 "(4) ANIMAL DRUGS FOR HUMAN USE.—Noth-
24 ing in this section shall be construed to permit the

1 use of animal drugs in compounding a drug for
2 human use.
3 "(b) DEFINITIONS.—In this section:
4 "(1) COMPOUNDING MANUFACTURER.—
5 "(A) IN GENERAL.—The term
6 'compounding manufacturer' means a facility at
7 one geographic location or address—
8 "(i) that compounds any sterile drug
9 without receiving a prescription order for
10 an identified individual patient for such
11 sterile drug prior to beginning
12 compounding, and distributes or offers to
13 sell such compounded sterile drug in inter-
14 state commerce; or
15 "(ii) that repackages any preservative-
16 free sterile drug or pools any sterile drugs,
17 except as provided in paragraph (9)(B).
18 "(B) EXCLUDED ACTIVITIES.—Notwith-
19 standing subparagraph (A)(ii), a facility shall
20 not be considered a compounding manufacturer
21 if such facility—
22 "(i) repackages drugs in accordance
23 with section 506F or the final guidance de-
24 scribed in section 506F(d) once the final
25 guidance is published; and

1 "(ii) does not otherwise meet the defi-
2 nition of compounding manufacturer under
3 subparagraph (A).
4 "(2) COMPOUNDING NUCLEAR PHARMACY.—
5 The term 'compounding nuclear pharmacy' means
6 an entity that—
7 "(A) is a State-licensed pharmacy or a
8 Federal facility;
9 "(B) holds a license currently in effect
10 from the Nuclear Regulatory Commission or
11 from a State pursuant to an agreement with
12 such commission under section 274 of the
13 Atomic Energy Act of 1954; and
14 "(C) does not compound other drugs that
15 would cause the entity to be a compounding
16 manufacturer described in paragraph (1)(A).
17 "(3) COPY.—The term 'copy' means an iden-
18 tical or nearly identical version of a drug.
19 "(4) POOLING; POOLS.—The terms 'pooling'
20 and 'pool'—
21 "(A) mean taking a single drug approved
22 under section 505 (other than a biological prod-
23 uct) from the container in which it is distrib-
24 uted by the original manufacturer and com-
25 bining it with the same drug from one or more

other containers without or before further manipulating the product (such as by diluting it or mixing it with another, different drug or drugs);

"(B) do not include combining the drug from two or more separate containers of the same drug when a single container of the drug is not sufficient to prepare a dose for administration to an individual patient; and

"(C) do not include combining a single drug from two or more separate containers of component products of a parenteral nutrition product, if such pooling, and labeling and use of the finished parenteral nutrition product, comply with State pharmacy law.

"(5) PRACTITIONER.—The term 'practitioner' includes a physician or any other person that is authorized to prescribe medication under State law.

"(6) RADIOACTIVE DRUG.—The term 'radioactive drug'—

"(A) means any substance defined as a drug in section 201(g)(1) that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide

1 regenerator which is intended to be used in the
2 preparation of any such substance but does not
3 include drugs such as carbon-containing com-
4 pounds or potassium-containing salts which
5 contain trace quantities of naturally occurring
6 radionuclides; and
7 "(B) includes a 'radioactive biological
8 product,' which means a biological product
9 which is labeled with a radionuclide or intended
10 solely to be labeled with a radionuclide.
11 "(7) REPACKAGE OR REPACKAGING.—The term
12 'repackage' or 'repackaging'—
13 "(A) means taking a drug approved under
14 section 505 or licensed under section 351 of the
15 Public Health Service Act from the container in
16 which it is distributed by the original manufac-
17 turer and placing it in a different container of
18 the same or smaller size without further manip-
19 ulating the drug (such as by diluting it or mix-
20 ing it with another, different drug or drugs);
21 and
22 "(B) does not include removing the drug
23 from its original container for immediate ad-
24 ministration to a patient, such as withdrawing
25 a drug into a syringe for immediate injection or

1 filling a cassette for immediate use within a
2 drug delivery device.
3 "(8) STERILE DRUG.—The term 'sterile drug'
4 means a drug that is—
5 "(A) intended for parenteral administra-
6 tion;
7 "(B) an ophthalmic or inhalation drug; or
8 "(C) required to be sterile under Federal
9 or State law.
10 "(9) TRADITIONAL COMPOUNDER.—
11 "(A) IN GENERAL.—The term 'traditional
12 compounder' means a facility operating pursu-
13 ant to State law—
14 "(i) wherein a drug is compounded
15 by—
16 "(I) a licensed pharmacist, in a
17 State-licensed pharmacy or a licensed
18 Federal facility; or
19 "(II) a licensed physician;
20 "(ii) that—
21 "(I) compounds a drug upon re-
22 ceipt of a prescription order for an
23 identified individual patient; or
24 "(II) compounds a drug in lim-
25 ited quantities before receipt of a pre-

1 scription order for an identified indi-
2 vidual patient, if such compounding is
3 based on a history of the licensed
4 pharmacist or licensed physician re-
5 ceiving prescription orders for the
6 compounding of the drug, which or-
7 ders have been generated solely within
8 an established relationship between
9 the licensed pharmacist or licensed
10 physician and—
11 "(aa) such individual patient
12 for whom the prescription order
13 will be provided; or
14 "(bb) the licensed physician
15 or other licensed practitioner who
16 will write such prescription order;
17 and
18 "(iii) that does not meet the definition
19 of a compounding manufacturer under
20 paragraph (1).
21 "(B) EXCEPTIONS.—
22 "(i) HOSPITALS AND HEALTH SYS-
23 TEMS.—A pharmacy within a hospital or
24 health system shall be considered a tradi-
25 tional compounder if such pharmacy other-

1 wise meets the definition under subpara-
2 graph (A) and if, with respect to a drug
3 compounded by such pharmacy, the only
4 activity conducted by the pharmacy is to
5 dispense or administer such drug (which
6 may include interstate shipment) solely to
7 a patient of such hospital or health system.
8 "(ii) HEALTH SYSTEM DEFINED.—
9 For purposes of this subparagraph, the
10 term 'health system' means one or more
11 hospitals that are owned and operated by
12 the same entity and that share access to
13 databases with drug order information for
14 patients. A health system includes the in-
15 patient, outpatient, and ambulatory facili-
16 ties wholly owned by the health system.
17 "(c) EXEMPTIONS FROM CERTAIN REQUIRE-
18 MENTS.—
19 "(1) IN GENERAL.—Except as otherwise pro-
20 vided in paragraphs (2), (3), and (4), a compounded
21 drug shall be subject to all the requirements of this
22 Act applicable to new drugs.
23 "(2) DRUGS COMPOUNDED BY TRADITIONAL
24 COMPOUNDERS.—Sections 501(a)(2)(B), 502(f)(1),
25 and 505 of this Act and section 351 of the Public

1 Health Service Act shall not apply to a compounded
2 drug if such drug—
3 "(A) is compounded by a traditional
4 compounder that is in compliance with this sec-
5 tion; and
6 "(B) meets the requirements of this sec-
7 tion applicable to drugs compounded by tradi-
8 tional compounders.
9 "(3) DRUGS COMPOUNDED BY COMPOUNDING
10 MANUFACTURERS.—Sections 502(f)(1) and 505 of
11 this Act and section 351 of the Public Health Serv-
12 ice Act shall not apply to a compounded prescription
13 drug, if such prescription drug—
14 "(A) is compounded by a compounding
15 manufacturer—
16 "(i) that is not licensed as a phar-
17 macy in any State; and
18 "(ii) that is in compliance with this
19 section; and
20 "(B) meets the requirements of this sec-
21 tion applicable to drugs compounded by
22 compounding manufacturers.
23 "(4) DRUGS COMPOUNDED BY COMPOUNDING
24 NUCLEAR PHARMACIES.—Sections 501(a)(2)(B),
25 502(f)(1), and 505 of this Act and section 351 of

1 the Public Health Service Act shall not apply to a
2 compounded radioactive drug if such drug is com-
3 pounded—
4 "(A) by a licensed pharmacist in a
5 compounding nuclear pharmacy;
6 "(B) solely using a radioactive drug ap-
7 proved under section 505 or licensed under sec-
8 tion 351 of the Public Health Service Act, and
9 one or more ingredients in compliance with sub-
10 section (e)(1)(B); and
11 "(C) in compliance with the United States
12 Pharmacopoeia chapters on pharmacy
13 compounding.
14 "(d) DRUGS THAT MAY NOT BE COMPOUNDED.—
15 "(1) IN GENERAL.—The following drugs may
16 not be compounded:
17 "(A) DRUGS THAT ARE DEMONSTRABLY
18 DIFFICULT TO COMPOUND.—A drug or category
19 of drugs that presents demonstrable difficulties
20 for compounding, which may include a complex
21 dosage form or biological product, as designated
22 by the Secretary pursuant to paragraph (2).
23 "(B) MARKETED DRUGS.—A drug (other
24 than a biological product) that is a copy of a
25 marketed drug approved under 505 or a vari-

1 ation of such drug compounded from bulk drug
2 substances, except as provided in paragraph
3 (3).
4 "(C) BIOLOGICAL PRODUCTS.—A drug
5 that is a biological product, except as provided
6 in paragraph (4).
7 "(D) DRUGS SUBJECT TO RISK EVALUA-
8 TION AND MITIGATION STRATEGY.—A copy or
9 variation of a drug approved under section 505
10 or licensed under section 351 of the Public
11 Health Service Act that is the subject of a risk
12 evaluation and mitigation strategy approved
13 with elements to assure safe use pursuant to
14 section 505–1, except provided in paragraph
15 (5).
16 "(E) DRUGS REMOVED FOR SAFETY AND
17 EFFICACY.—A drug that appears on a list pub-
18 lished by the Secretary in the Federal Register
19 of drugs that have been withdrawn or removed
20 from the market because such drug or compo-
21 nents of such drug have been found to be un-
22 safe or not effective.
23 "(2) DRUGS THAT ARE DEMONSTRABLY DIF-
24 FICULT TO COMPOUND.—

1 "(A) IN GENERAL.—The Secretary may
2 promulgate a regulation that designates drugs
3 or categories of drugs that are demonstrably
4 difficult to compound that may not be com-
5 pounded, or that may be compounded only
6 under conditions specified by the Secretary.
7 Such regulation may include the designation of
8 drugs or categories of drugs that are complex
9 dosage forms or biological products, such as ex-
10 tended release products, metered dose inhalers,
11 transdermal patches, and sterile liposomal prod-
12 ucts.
13 "(B) INTERIM LIST.—
14 "(i) IN GENERAL.—Before the effec-
15 tive date of the regulation promulgated
16 under subparagraph (A), the Secretary
17 may designate drugs or categories of drugs
18 that present demonstrable difficulties for
19 compounding, which may include complex
20 dosage forms or biological products that
21 cannot be compounded, except under con-
22 ditions specified by the Secretary, by—
23 "(I) publishing a notice of such
24 drugs or categories of drugs proposed
25 for designation, including the ration-

1 ale for such designation, in the Fed-
2 eral Register;
3 "(II) providing a period of not
4 less than 60 days for comment on the
5 notice; and
6 "(III) publishing a notice in the
7 Federal Register designating such
8 drugs or categories of drugs that can-
9 not be compounded, including the ra-
10 tionale for such designation.
11 "(ii) SUNSET.—Any notice provided
12 under clause (i) shall cease to have force or
13 effect on the date that is 5 years after the
14 date of enactment of the Pharmaceutical
15 Compounding Quality and Accountability
16 Act or on the effective date of the final
17 regulation under subparagraph (A), which-
18 ever is earlier.
19 "(C) CONSULTATION WITH STAKE-
20 HOLDERS.—Prior to establishing the lists de-
21 scribed in this paragraph, the Secretary shall
22 consult with relevant stakeholders including
23 pharmacists, professional associations, patient
24 advocacy groups, manufacturers and physicians

1 about the need for the compounded drugs to be
2 included or excluded from the lists.
3 "(D) UPDATES TO DIFFICULT TO COM-
4 POUND LIST.—Five years after the effective
5 date of the regulation described in subpara-
6 graph (A), and every 5 years thereafter, the
7 Secretary shall publish a Federal Register no-
8 tice seeking public input about the need for the
9 compounded drugs to be included or excluded
10 from the list described in subparagraph (A).
11 Nothing in the previous sentence prohibits noti-
12 fications or submissions before or during any 5-
13 year period described under such sentence re-
14 garding the need for the compounded drugs to
15 be included or excluded from the list.
16 "(3) EXCEPTIONS REGARDING MARKETED
17 DRUGS.—
18 "(A) IN GENERAL.—A drug (other than a
19 biological product) that is a copy of a marketed
20 drug approved under 505, including variations
21 of such drug compounded from bulk drug sub-
22 stances, may be compounded only if—
23 "(i) the compounded variation pro-
24 duces for the patient a clinical difference
25 between the compounded drug and such

1 marketed drug, as determined by the pre-
2 scribing practitioner, and, prior to begin-
3 ning compounding such variation, the tra-
4 ditional compounder compounding the vari-
5 ation receives a prescription order for an
6 identified individual patient specifying that
7 the variation may be compounded; or
8 "(ii)(I) such marketed drug, at the
9 time of compounding a copy of such drug
10 and at the time of distribution of the com-
11 pounded drug, is on the drug shortage list
12 under section 506E, or in the Secretary's
13 sole discretion, has otherwise been identi-
14 fied by the Secretary as in shortage such
15 as in a specific region or on a drug short-
16 age list maintained by a private party;
17 "(II) the facility compounding the
18 drug notifies the Secretary not later than
19 3 calendar days after beginning the
20 compounding; and
21 "(III) in the case of a compounding
22 manufacturer, the compounding manufac-
23 turer has registered under subsection
24 (g)(2) as an entity that intends to com-
25 pound pursuant to this paragraph and no-

1 tifies the Secretary at least 14 days prior
2 to beginning the compounding.
3 "(B) NOTICE WAIVER.—The Secretary
4 may waive a notice required under subpara-
5 graph (A)(ii)(II).
6 "(C) EXCLUSION.—For purposes of this
7 paragraph, repackaging a marketed drug ap-
8 proved under section 505 does not make the re-
9 packaged drug a copy of such marketed drug,
10 unless the repackaged drug is also a marketed
11 drug approved under section 505.
12 "(4) EXCEPTIONS REGARDING BIOLOGICAL
13 PRODUCTS.—
14 "(A) IN GENERAL.—A drug that is a vari-
15 ation of a licensed biological product may be
16 compounded only if—
17 "(i)(I) such compounded variation is
18 compounded solely using a licensed biologi-
19 cal product, or solely using a licensed bio-
20 logical product and one or more ingredi-
21 ents in compliance with subsection
22 (e)(1)(B); or
23 "(II) in the case of a licensed aller-
24 genic product, such variation is com-
25 pounded solely using one or more licensed

1 allergenic products, or solely using one or
2 more licensed allergenic products and one
3 or more ingredients in compliance with
4 subsection (e)(1)(B);
5 "(ii) such compounded variation pro-
6 duces for the patient a clinical difference
7 between such compounded variation and
8 the licensed biological product, as deter-
9 mined by—
10 "(I) the prescribing practitioner
11 (in the case of a variation com-
12 pounded by a traditional
13 compounder); or
14 "(II) a licensed practitioner re-
15 sponsible for the patient's care in a
16 health care entity that provides med-
17 ical services through licensed practi-
18 tioners directly to patients (in the
19 case of a variation compounded by a
20 compounding manufacturer);
21 "(iii) prior to beginning
22 compounding—
23 "(I) except as provided in sub-
24 paragraph (B), the traditional
25 compounder receives a prescription

1 order for an identified individual pa-
2 tient specifying that the biological
3 product may be compounded for an
4 identified individual patient; or
5 "(II) the compounding manufac-
6 turer receives a duly authorized med-
7 ical order from a health care entity
8 that provides medical services through
9 licensed practitioners directly to pa-
10 tients, specifying that the biological
11 product may be compounded for an
12 identified patient or patients; and
13 "(iv) in the case of a radioactive bio-
14 logical product, the compounded variation
15 is compounded by a compounding nuclear
16 pharmacy in accordance with subsection
17 (b)(2).
18 "(B) SPECIAL RULE FOR PEDIATRIC
19 USES.—A traditional compounder that is a hos-
20 pital or health system may begin compounding
21 a drug that is a variation of a licensed biologi-
22 cal product prior to receiving a prescription
23 order as required under subparagraph (A)(iii)
24 if—

"(i) such compounded variation is a diluted or repackaged variation of the licensed biological product for emergent use in pediatric patients; and

"(ii) such compounded variation produces for the patient a clinical difference between such compounded variation and the licensed biological product, as determined by a licensed practitioner responsible for the patient's care in the hospital or health system.

"(C) INAPPLICABILITY.—Clauses (ii) and (iii) of subparagraph (A) shall not apply to a compounded allergenic product.

"(5) REQUIREMENT FOR DRUGS THAT HAVE RISK EVALUATION AND MITIGATION STRATEGIES.—

"(A) IN GENERAL.—A copy or variation of a drug approved under section 505 or biological product licensed under section 351 of the Public Health Service Act that is the subject of a risk evaluation and mitigation strategy approved with elements to assure safe use pursuant to section 505–1, may be compounded only if—

1 "(i) the entity compounding the copy
2 or variation receives a prescription order
3 for an identified individual patient speci-
4 fying that the drug or biological product
5 may be compounded; and
6 "(ii) the entity compounding the copy
7 or variation demonstrates to the Secretary,
8 prior to beginning compounding, that the
9 entity will utilize controls that are com-
10 parable to the controls applicable under
11 the relevant risk evaluation and mitigation
12 strategy for the approved drug or licensed
13 biological product.
14 "(B) EFFECT.—Nothing in this paragraph
15 shall be construed to permit compounding a
16 copy or variation of a drug other than as per-
17 mitted in paragraphs (3) and (4).
18 "(e) QUALITY OF DRUG INGREDIENTS.—
19 "(1) HUMAN DRUGS.—A traditional
20 compounder or a compounding manufacturer shall—
21 "(A) if compounding a drug from bulk
22 drug substances (as defined in regulations of
23 the Secretary published at section 207.3(a)(4)
24 of title 21, Code of Federal Regulations (or any

1 successor regulations)), use only bulk sub-
2 stances—
3 "(i) that—
4 "(I) comply with the standards of
5 an applicable United States Pharma-
6 copoeia or National Formulary mono-
7 graph, if a monograph exists and has
8 not been identified under paragraph
9 (2);
10 "(II) if such a monograph does
11 not exist, are drug substances that
12 are components of drugs approved by
13 the Secretary; or
14 "(III) if such a monograph does
15 not exist and the drug substance is
16 not a component of a drug approved
17 by the Secretary, that appear on a list
18 developed by the Secretary through
19 regulations issued by the Secretary;
20 "(ii) that are manufactured by an es-
21 tablishment that is registered under sec-
22 tion 510 (including a foreign establishment
23 that is registered under section 510(i));
24 and

1 "(iii) that are accompanied by valid
2 certificates of analysis for each specific lot
3 of bulk drug substance;
4 "(B) use ingredients (other than bulk drug
5 substances) that comply with the standards of
6 an applicable United States Pharmacopoeia or
7 National Formulary monograph, if a mono-
8 graph exists and has not been identified under
9 paragraph (2); and
10 "(C) in the case of a traditional
11 compounder, comply with the standards of the
12 United States Pharmacopoeia chapters on phar-
13 macy compounding.
14 "(2) IDENTIFICATION BY SECRETARY.—
15 "(A) IN GENERAL.—Notwithstanding the
16 existence of an applicable monograph under
17 subparagraph (A)(i)(I) or (B) of paragraph (1),
18 the Secretary may identify bulk substances that
19 the Secretary determines, based on public
20 health concerns, may not be used in
21 compounding a drug.
22 "(B) PROCEDURE.—In identifying the bulk
23 substances that may not be used in
24 compounding, the Secretary shall—

1 "(i) publish a notice of such bulk sub-
2 stances proposed for identification in the
3 Federal Register;
4 "(ii) provide a period of not less than
5 60 days for comment on the notice; and
6 "(iii) publish a notice in the Federal
7 Register identifying the bulk substances
8 that may not be used in compounding a
9 drug.
10 "(f) REQUIREMENTS REGARDING WHOLESALING
11 AND LABELING APPLICABLE TO TRADITIONAL
12 COMPOUNDERS AND COMPOUNDING MANUFACTURERS.—
13 A compounded drug—
14 "(1) may not be sold by an entity other than
15 the compounding manufacturer or traditional
16 compounder that compounded the drug;
17 "(2) compounded by a compounding manufac-
18 turer may not be sold to an entity other than a
19 health care entity that provides medical services
20 through licensed practitioners directly to patients, or
21 a network of such providers, except that a
22 compounding manufacturer may transfer without
23 profit a compounded sterile drug to a licensed phar-
24 macy if—

1 "(A) the licensed pharmacy falls under the
2 same corporate ownership as the compounding
3 manufacturer;
4 "(B) the transfer of such compounded
5 sterile drug is solely for the purpose of dis-
6 pensing the compounded sterile drug to the end
7 user, who has been instructed by the pre-
8 scribing physician to self-administer such com-
9 pounded sterile drug;
10 "(C) as of the date of enactment of the
11 Pharmaceutical Compounding Quality and Ac-
12 countability Act, the compounding manufac-
13 turer is an entity that provides pharmacy bene-
14 fits management services on behalf of a health
15 benefits plan;
16 "(D) the compounding manufacturer iden-
17 tifies itself to the Secretary upon registering
18 under subsection (g)(2) as an entity that quali-
19 fies for the exception under this paragraph, and
20 provides documentation of the compounding of
21 such drugs as of the date of enactment of the
22 Pharmaceutical Compounding Quality and Ac-
23 countability Act, in a manner described by the
24 Secretary; and

1 "(E) the compounding manufacturer re-
2 ceives confirmation from the Secretary that the
3 compounding manufacturer qualifies for the ex-
4 ception under this paragraph and the sterile
5 drug or drugs for which the exemption applies;
6 and
7 "(3) in the case of a compounded drug offered
8 for sale, shall be labeled 'not for resale'.
9 "(g) OTHER REQUIREMENTS APPLICABLE TO
10 COMPOUNDING MANUFACTURERS.—
11 "(1) LICENSED PHARMACIST OVERSIGHT.—A
12 compounding manufacturer shall ensure that a phar-
13 macist licensed in the State where the compounding
14 manufacturer is located exercises direct supervision
15 over the operations of the compounding manufac-
16 turer.
17 "(2) REGISTRATION OF COMPOUNDING MANU-
18 FACTURERS AND REPORTING OF DRUGS.—
19 "(A) REGISTRATION OF COMPOUNDING
20 MANUFACTURERS.—
21 "(i) ANNUAL REGISTRATION.—During
22 the period beginning on October 1 and
23 ending on December 31 each year, each
24 compounding manufacturer shall register
25 with the Secretary its name, place of busi-

1 ness, and unique facility identifier (which
2 shall conform to the requirements for the
3 unique facility identifier established under
4 section 510), and a point of contact e-mail
5 address, and shall indicate whether the
6 compounding manufacturer intends to
7 compound drug in shortage pursuant to
8 subsection (d)(3)(A)(ii).
9 "(ii) NEW COMPOUNDING MANUFAC-
10 TURERS.—Each compounding manufac-
11 turer, upon first engaging in the oper-
12 ations described in subsection (b)(1), shall
13 immediately register with the Secretary
14 and provide the information described
15 under clause (i). The Secretary shall estab-
16 lish a timeline for registration for the first
17 year following the effective date of the
18 Pharmaceutical Compounding Quality and
19 Accountability Act. In no case may reg-
20 istration be required until at least 60 days
21 following publication of the timeline in the
22 Federal Register.
23 "(iii) AVAILABILITY OF REGISTRATION
24 FOR INSPECTION.—The Secretary shall
25 make available for inspection, to any per-

1 son so requesting, any registration filed
2 pursuant to this subparagraph.
3 "(B) DRUG REPORTING BY COMPOUNDING
4 MANUFACTURERS.—
5 "(i) IN GENERAL.—Each
6 compounding manufacturer who registers
7 with the Secretary under subparagraph (A)
8 shall submit to the Secretary, once during
9 the month of June of each year and once
10 during the month of December of each
11 year, a report—
12 "(I) identifying the drugs com-
13 pounded by such compounding manu-
14 facturer during the previous 6-month
15 period; and
16 "(II) with respect to each drug
17 identified under subclause (I), pro-
18 viding the active ingredient, the
19 source of such active ingredient, the
20 National Drug Code, if available,
21 number of the source drug or bulk ac-
22 tive ingredient, the strength of the ac-
23 tive ingredient per unit, the dosage
24 form and route of administration, the
25 package description, the number of in-

1 dividual units produced, the National
2 Drug Code number of the final prod-
3 uct, if assigned, and which conforms
4 to other applicable requirements iden-
5 tified by the Secretary in accordance
6 with clause (ii).
7 "(ii) FORM.—Each report under
8 clause (i) shall be prepared in such form
9 and manner as the Secretary may pre-
10 scribe by regulation or guidance.
11 "(iii) CONFIDENTIALITY.—Reports
12 submitted pursuant to this subparagraph
13 shall be exempt from inspection under sub-
14 paragraph (A)(iii), unless the Secretary
15 finds that such an exemption would be in-
16 consistent with the protection of the public
17 health.
18 "(C) ELECTRONIC REGISTRATION AND RE-
19 PORTING.—Registrations and drug reporting
20 under this paragraph (including the submission
21 of updated information) shall be submitted to
22 the Secretary by electronic means unless the
23 Secretary grants a request for waiver of such
24 requirement because use of electronic means is
25 not reasonable for the person requesting waiver.

1 "(D) RISK-BASED INSPECTION FRE-
2 QUENCY.—
3 "(i) IN GENERAL.—Compounding
4 manufacturers shall be subject to inspec-
5 tion pursuant to section 704.
6 "(ii) RISK-BASED SCHEDULE.—The
7 Secretary, acting through one or more offi-
8 cers or employees duly designated by the
9 Secretary, shall inspect compounding man-
10 ufacturers described in clause (i) in accord-
11 ance with a risk-based schedule established
12 by the Secretary.
13 "(iii) RISK FACTORS.—In establishing
14 the risk-based schedule under clause (ii),
15 the Secretary shall inspect compounding
16 manufacturers according to the known
17 safety risks of such compounding manufac-
18 turers, which shall be based on the fol-
19 lowing factors:
20 "(I) The compliance history of
21 the compounding manufacturer.
22 "(II) The record, history, and na-
23 ture of recalls linked to the
24 compounding manufacturer.

1 "(III) The inherent risk of the
2 drug compounded at the compounding
3 manufacturer.
4 "(IV) The inspection frequency
5 and history of the compounding man-
6 ufacturer, including whether the
7 compounding manufacturer has been
8 inspected pursuant to section 704
9 within the last 4 years.
10 "(V) Whether the compounding
11 manufacturer has registered under
12 subsection (g)(2) as an entity that in-
13 tends to compound pursuant to sub-
14 section (d)(3)(A)(ii).
15 "(VI) Any other criteria deemed
16 necessary and appropriate by the Sec-
17 retary for purposes of allocating in-
18 spection resources.
19 "(3) ADVERSE EVENT REPORTING.—
20 "(A) DEFINITIONS.—In this paragraph:
21 "(i) ADVERSE EVENT.—The term 'ad-
22 verse event' means any health-related event
23 associated with the use of a compounded
24 drug that is adverse, including—

1 "(I) an event occurring in the
2 course of the use of the drug in pro-
3 fessional practice;
4 "(II) an event occurring from an
5 overdose of the drug, whether acci-
6 dental or intentional;
7 "(III) an event occurring from
8 abuse of the drug;
9 "(IV) an event occurring from
10 withdrawal of the drug; and
11 "(V) any failure of expected
12 pharmacological action of the drug.
13 "(ii) SERIOUS ADVERSE EVENT.—The
14 term 'serious adverse event' means an ad-
15 verse event that—
16 "(I) results in—
17 "(aa) death;
18 "(bb) an adverse drug event
19 that places the patient at imme-
20 diate risk of death from the ad-
21 verse drug event as it occurred
22 (not including an adverse drug
23 event that might have caused
24 death had it occurred in a more
25 severe form);

1 "(cc) inpatient hospitaliza-
2 tion or prolongation of existing
3 hospitalization;
4 "(dd) a persistent or signifi-
5 cant incapacity or substantial
6 disruption of the ability to con-
7 duct normal life functions; or
8 "(ee) a congenital anomaly
9 or birth defect; or
10 "(II) based on appropriate med-
11 ical judgment, may jeopardize the pa-
12 tient and may require a medical or
13 surgical intervention to prevent an
14 outcome described in subclause (I).
15 "(B) REPORTS.—
16 "(i) ADVERSE EVENT REPORTING RE-
17 QUIREMENT.—
18 "(I) 15-DAY REPORT.—If a
19 compounding manufacturer becomes
20 aware of any serious adverse event,
21 such manufacturer shall submit re-
22 ports of each instance to the Sec-
23 retary as soon as practicable, but in
24 no case later than 15 calendar days
25 after the initial receipt of the applica-

1 ble information. Such manufacturer
2 shall investigate and submit to the
3 Secretary followup reports for each
4 such instance not later than 15 cal-
5 endar days after receipt of new infor-
6 mation or as requested by the Sec-
7 retary. Unless and until the Secretary
8 establishes the content and format of
9 adverse event reports by guidance or
10 regulation, reports shall be submitted
11 in accordance with the content and
12 format requirements under section
13 310.305 of title 21, Code of Federal
14 Regulations (or any successor regula-
15 tions) or section 600.80 of title 21,
16 Code of Federal Regulations (or any
17 successor regulations).
18 "(II) ANNUAL REPORT.—
19 Compounding manufacturers that re-
20 port serious adverse events shall sub-
21 mit in December of each year a nar-
22 rative summary of any analysis of
23 each report submitted under subclause
24 (I), including a history of actions
25 taken during the year because of each

1 report, using the content, format, and
2 manner established by the Secretary
3 by guidance or regulation. Until such
4 time as the Secretary publishes such
5 guidance or regulation, each
6 compounding manufacturer shall re-
7 tain such summaries as part of the
8 records to be maintained in accord-
9 ance with subparagraph (C).
10 "(ii) PRODUCT QUALITY REPORTING
11 REQUIREMENT.—Not later than 3 calendar
12 days after the compounding manufacturer
13 becomes aware of information pertaining
14 to sterility, stability, or other product qual-
15 ity concerns that could result in serious
16 adverse events, the compounding manufac-
17 turer shall submit to the Secretary a prod-
18 uct quality report, in a form and manner
19 established by the Secretary by guidance or
20 regulation.
21 "(C) MAINTENANCE OF RECORDS.—A
22 compounding manufacturer shall maintain for a
23 period of 10 years records of all serious adverse
24 drug events known to the compound manufac-
25 turer in accordance with section 314.80(i) of

1 title 21, Code of Federal Regulations (or any
2 successor regulation), or as otherwise directed
3 by the Secretary in regulations.
4 "(4) LABELING OF DRUGS.—
5 "(A) LABEL.—The label of a drug com-
6 pounded by a compounding manufacturer shall
7 include—
8 "(i) the statement 'This is a com-
9 pounded drug.' or a reasonable comparable
10 alternative statement (as specified by the
11 Secretary) that prominently identifies the
12 drug as a compounded drug;
13 "(ii) the name, address, and phone
14 number of the applicable compounding
15 manufacturer; and
16 "(iii) with respect to the compounded
17 drug—
18 "(I) the lot or batch number;
19 "(II) the established name of the
20 medication;
21 "(III) the dosage form and
22 strength;
23 "(IV) the statement of quantity
24 or volume, as appropriate;

1 "(V) the date that the drug was
2 compounded;
3 "(VI) the expiration date;
4 "(VII) storage and handling in-
5 structions;
6 "(VIII) the National Drug Code
7 number, if available;
8 "(IX) the 'not for resale' state-
9 ment as required by subsection (f)(3);
10 and
11 "(X) subject to subparagraph
12 (B)(i), a list of active and inactive in-
13 gredients, identified by established
14 name and the quantity or proportion
15 of each ingredient.
16 "(B) CONTAINER.—The container from
17 which the individual units of a drug com-
18 pounded by a compounding manufacturer are
19 removed for dispensing or for administration
20 (such as a plastic bag containing individual
21 product syringes) shall include—
22 "(i) the information described under
23 subparagraph (A)(iii)(X), if there is not
24 space on the label for such information;

1 "(ii) the following information to fa-
2 cilitate adverse event reporting:
3 www.fda.gov/medwatch and 1–800-FDA-
4 1088; and
5 "(iii) the directions for use, including,
6 as appropriate, dosage and administration.
7 "(C) ADDITIONAL INFORMATION.—The
8 label and labeling of a drug compounded by a
9 compounding manufacturer shall include any
10 other information as determined necessary and
11 specified in regulations promulgated by the Sec-
12 retary.
13 "(h) COMPOUNDING MANUFACTURER ESTABLISH-
14 MENT AND REINSPECTION FEES.—
15 "(1) DEFINITIONS.—In this subsection—
16 "(A) the term 'affiliate' has the meaning
17 given such term in section 735(11);
18 "(B) the term 'gross annual sales' means
19 the total worldwide gross annual sales, in
20 United States dollars, for a compounding man-
21 ufacturer, including the sales of all the affiliates
22 of the compounding manufacturer; and
23 "(C) the term 'reinspection' means, with
24 respect to a compounding manufacturer, 1 or
25 more inspections conducted under section 704

1 subsequent to an inspection conducted under
2 such provision which identified noncompliance
3 materially related to an applicable requirement
4 of this Act, specifically to determine whether
5 compliance has been achieved to the Secretary's
6 satisfaction.

7 "(2) ESTABLISHMENT AND REINSPECTION
8 FEES.—

9 "(A) IN GENERAL.—For fiscal year 2015
10 and each subsequent fiscal year, the Secretary
11 shall, in accordance with this subsection, assess
12 and collect—

13 "(i) an annual establishment fee from
14 each compounding manufacturer; and

15 "(ii) a reinspection fee from each
16 compounding manufacturer subject to a re-
17 inspection in such fiscal year.

18 "(B) MULTIPLE REINSPECTIONS.—A
19 compounding manufacturer subject to multiple
20 reinspections in a fiscal year shall be subject to
21 a reinspection fee for each reinspection.

22 "(3) ESTABLISHMENT AND REINSPECTION FEE
23 SETTING.—The Secretary shall establish the estab-
24 lishment and reinspection fee to be collected under
25 this subsection for each fiscal year, based on the

1 methodology described in paragraph (4) and shall
2 publish such fee in a Federal Register notice not
3 later than 60 days before the start of each such
4 year.
5 "(4) AMOUNT OF ESTABLISHMENT FEE AND
6 REINSPECTION FEE.—
7 "(A) IN GENERAL.—For each
8 compounding manufacturer in a fiscal year—
9 "(i) except as provided in subpara-
10 graph (D), the amount of the annual es-
11 tablishment fee under paragraph (2) shall
12 be equal to the sum of—
13 "(I) $15,000, multiplied by the
14 inflation adjustment factor described
15 in subparagraph (B); plus
16 "(II) the small business adjust-
17 ment factor described in subpara-
18 graph (C); and
19 "(ii) the amount of any reinspection
20 fee (if applicable) under paragraph (2)
21 shall be equal to $15,000, multiplied by
22 the inflation adjustment factor described in
23 subparagraph (B).
24 "(B) INFLATION ADJUSTMENT FACTOR.—

1 "(i) IN GENERAL.—For fiscal year
2 2015 and subsequent fiscal years, the fee
3 amounts established in subparagraph (A)
4 shall be adjusted by the Secretary by no-
5 tice, published in the Federal Register, for
6 a fiscal year by the amount equal to the
7 sum of—
8 "(I) one;
9 "(II) the average annual percent
10 change in the cost, per full-time equiv-
11 alent position of the Food and Drug
12 Administration, of all personnel com-
13 pensation and benefits paid with re-
14 spect to such positions for the first 3
15 years of the preceding 4 fiscal years,
16 multiplied by the proportion of per-
17 sonnel compensation and benefits
18 costs to total costs of an average full-
19 time equivalent position of the Food
20 and Drug Administration for the first
21 3 years of the preceding 4 fiscal
22 years; and
23 "(III) the average annual percent
24 change that occurred in the Consumer
25 Price Index for urban consumers

1 (U.S. City Average; Not Seasonally
2 Adjusted; All items; Annual Index) for
3 the first 3 years of the preceding 4
4 years of available data multiplied by
5 the proportion of all costs other than
6 personnel compensation and benefits
7 costs to total costs of an average full-
8 time equivalent position of the Food
9 and Drug Administration for the first
10 3 years of the preceding 4 fiscal
11 years.
12 "(ii) COMPOUNDED BASIS.—The ad-
13 justment made each fiscal year under
14 clause (i) shall be added on a compounded
15 basis to the sum of all adjustments made
16 each fiscal year after fiscal year 2014
17 under clause (i).
18 "(C) SMALL BUSINESS ADJUSTMENT FAC-
19 TOR.—The small business adjustment factor re-
20 ferred to subparagraph (A)(i)(II) shall be an
21 amount established by the Secretary for each
22 fiscal year based on the Secretary's estimate
23 of—

1 "(i) the number of small businesses
2 that will pay a reduced establishment fee
3 for such fiscal year; and
4 "(ii) the adjustment to the establish-
5 ment fee necessary to achieve total fees
6 equaling the total fees that the Secretary
7 would have collected if no entity qualified
8 for the small business exception in sub-
9 paragraph (D).
10 "(D) EXCEPTION FOR SMALL BUSI-
11 NESSES.—
12 "(i) IN GENERAL.—In the case of a
13 compounding manufacturer with gross an-
14 nual sales of $1,000,000 or less in the 12
15 months ending April 1 of the fiscal year
16 immediately preceding the fiscal year in
17 which the fees under this subsection are
18 assessed, the amount of the establishment
19 fee under paragraph (2) for a fiscal year
20 shall be equal to ⅓ of the amount cal-
21 culated under subparagraph (A)(i)(I) in
22 such fiscal year.
23 "(ii) APPLICATION.—To qualify for
24 the exception under this subparagraph, a
25 small business shall submit to the Sec-

1 retary a written request for such exception,
2 in a format specified by the Secretary in
3 guidance, certifying its gross annual sales
4 for the 12 months ending April 1 of the
5 fiscal year immediately preceding the fiscal
6 year in which fees under this subsection
7 are assessed. Any such application must be
8 submitted to the Secretary not later than
9 April 30 for the following fiscal year. Any
10 statement or representation made to the
11 Secretary shall be subject to section 1001
12 of title 18, United States Code.
13 "(E) CREDITING OF FEES.—In estab-
14 lishing the small business adjustment factor
15 under subparagraph (C) for a fiscal year, the
16 Secretary shall provide for the crediting of fees
17 from the previous year to the next year if the
18 Secretary overestimated the amount of the
19 small business adjustment factor for such pre-
20 vious fiscal year, and consider the need to ac-
21 count for any adjustment of fees and such other
22 factors as the Secretary determines appropriate.
23 "(5) USE OF FEES.—The Secretary shall make
24 all of the fees collected pursuant to clauses (i) and
25 (ii) of paragraph (2)(A) available solely to pay for

1 the costs of oversight of compounding manufactur-
2 ers.

3 "(6) SUPPLEMENT NOT SUPPLANT.—Funds re-
4 ceived by the Secretary pursuant to this subsection
5 shall be used to supplement and not supplant any
6 other Federal funds available to carry out the activi-
7 ties described in this section.

8 "(7) CREDITING AND AVAILABILITY OF FEES.—
9 Fees authorized under this subsection shall be col-
10 lected and available for obligation only to the extent
11 and in the amount provided in advance in appropria-
12 tions Acts. Such fees are authorized to remain avail-
13 able until expended. Such sums as may be necessary
14 may be transferred from the Food and Drug Admin-
15 istration salaries and expenses appropriation account
16 without fiscal year limitation to such appropriation
17 account for salaries and expenses with such fiscal
18 year limitation. The sums transferred shall be avail-
19 able solely for the purpose of paying the costs of
20 oversight of compounding manufacturers.

21 "(8) COLLECTION OF FEES.—

22 "(A) ESTABLISHMENT FEE.—A
23 compounding manufacturer shall remit the es-
24 tablishment fee due under this subsection in a

1 fiscal year when submitting a registration pur-
2 suant to subsection (g) for such fiscal year.
3 "(B) REINSPECTION FEE.—The Secretary
4 shall specify in the Federal Register notice de-
5 scribed in paragraph (3) the manner in which
6 reinspection fees assessed under this subsection
7 shall be collected and the timeline for payment
8 of such fees. Such a fee shall be collected after
9 the Secretary has conducted a reinspection of
10 the compounding manufacturer involved.
11 "(C) EFFECT OF FAILURE TO PAY FEES.—
12 "(i) REGISTRATION.—A compounding
13 manufacturer shall not be considered reg-
14 istered under subsection (g) in a fiscal year
15 until the date that the compounding manu-
16 facturer remits the establishment fee under
17 this subsection for such fiscal year.
18 "(ii) MISBRANDING.—All drugs manu-
19 factured, prepared, propagated, com-
20 pounded, or processed by a compounding
21 manufacturer for which any establishment
22 fee or reinspection fee has not been paid as
23 required by this subsection shall be deemed
24 misbranded under section 502(cc) until the

1 fees owed for such compounding manufac-
2 turer under this subsection have been paid.
3 "(D) COLLECTION OF UNPAID FEES.—In
4 any case where the Secretary does not receive
5 payment of a fee assessed under this subsection
6 within 30 days after it is due, such fee shall be
7 treated as a claim of the United States Govern-
8 ment subject to provisions of subchapter II of
9 chapter 37 of title 31, United States Code.
10 "(9) ANNUAL REPORT TO CONGRESS.—Not
11 later than 120 days after each fiscal year in which
12 fees are assessed and collected under this subsection,
13 the Secretary shall submit a report to the Com-
14 mittee on Health Education Labor and Pensions of
15 the Senate and the Committee on Energy and Com-
16 merce of the House of Representatives, to include a
17 description of fees assessed and collected for each
18 year, a summary description of entities paying the
19 fees, and the number of inspections and reinspec-
20 tions of such entities performed each year.
21 "(10) AUTHORIZATION OF APPROPRIATIONS.—
22 For fiscal year 2015 and each subsequent fiscal
23 year, there is authorized to be appropriated for fees
24 under this subsection an amount equivalent to the

1 total amount of fees assessed for such fiscal year
2 under this subsection.
3 "(i) ACTION BY SECRETARY REGARDING COM-
4 PLAINTS FROM STATE BOARDS OF PHARMACY.—
5 "(1) IDENTIFICATION OF COMPOUNDING MANU-
6 FACTURERS.—The Secretary shall encourage States
7 to identify to the Secretary facilities that are li-
8 censed by a State as a pharmacy that appear to be
9 entities that are required to be registered with the
10 Secretary as a compounding manufacturer.
11 "(2) DESIGNATION.—The Secretary shall des-
12 ignate a point of contact and establish a format and
13 procedure for a State Board of Pharmacy to notify
14 the Secretary if it appears to a State Board of Phar-
15 macy that an entity licensed by a State as a phar-
16 macy is required to be registered with the Secretary
17 as a compounding manufacturer.
18 "(3) DETERMINATION.—If the Secretary deter-
19 mines that such an entity described in paragraph (2)
20 is required to be registered with the Secretary as a
21 compounding manufacturer, the Secretary shall
22 transmit such determination to the State Board of
23 Pharmacy in the State in which the entity is located,
24 and to the State Board of Pharmacy in the notifying
25 State, if different, within 15 days of such determina-

1 tion and shall make such determination publicly
2 available on the Internet Web site of the Food and
3 Drug Administration.
4 "(4) EFFECT.—The Secretary shall encourage
5 direct communications between States regarding tra-
6 ditional compounders. Nothing in this subsection
7 shall expand the Secretary's authority over or re-
8 sponsibility for traditional compounders.".
9 (c) PROHIBITED ACT.—Section 301 (21 U.S.C. 331)
10 is amended—
11 (1) in subsection (e), by striking "417, 416,
12 504" and inserting "417, 416, 503A(g), 504"; and
13 (2) by adding at the end the following:
14 "(ccc)(1) The resale of a compounded drug that is
15 labeled 'not for resale' as required by section 503A.
16 "(2) The failure to register in accordance with sub-
17 section (g) of section 503A or the failure to submit a re-
18 port as required by subsection (g)(2)(B) or (g)(3) of such
19 section.".
20 (d) REPORT BY GAO.—Not later than November 1,
21 2016, the Comptroller General of the United States shall
22 conduct a study and submit to Congress a report on the
23 safety of animal drug compounding and the availability
24 of safe and effective drugs for animals.

1 **SEC. 3. OTHER REQUIREMENTS RELATING TO**
2 **COMPOUNDING MANUFACTURERS.**

3 (a) LABELING.—Section 502 (21 U.S.C. 352) is
4 amended by adding at the end the following:

5 "(bb) If it is a compounded drug and (1) the labeling
6 does not include the information as required by sub-
7 sections (f)(3) and (g)(4) of section 503A, as applicable,
8 or (2) the labeling or advertising or promotion of such
9 drug is false or misleading in any particular.

10 "(cc) If it is a drug, and it was manufactured, pre-
11 pared, propagated, compounded, or processed by a
12 compounding manufacturer for which fees have not been
13 paid as required by section 503A(g).".

14 (b) APPLICATION OF INSPECTION REQUIREMENTS TO
15 COMPOUNDING MANUFACTURERS.—Section 704(a)(2)
16 (21 U.S.C. 374(a)(2)) is amended by adding at the end
17 the following flush text:

18 "The exemption in subparagraph (A) does not apply with
19 respect to compounding manufacturers (as such term is
20 defined in section 503A).".

21 **SEC. 4. IMPLEMENTATION.**

22 (a) CONSULTATION WITH STAKEHOLDERS.—In im-
23 plementing this section, the Secretary of Health and
24 Human Services shall consult with relevant stakeholders
25 including pharmacists, professional associations, patient
26 advocacy groups, manufacturers and physicians.

1 (b) REGULATIONS.—In promulgating any regulations
2 to implement this Act (and the amendments made by this
3 Act), the Secretary of Health and Human Services shall—
4 (1) issue a notice of proposed rulemaking that
5 includes the proposed regulation;
6 (2) provide a period of not less than 60 days
7 for comments on the proposed regulation; and
8 (3) publish the final regulation not more than
9 18 months following publication of the proposed rule
10 and not less than 30 days before the effective date
11 of such final regulation.

12 **SEC. 5. EFFECTIVE DATE.**

13 This Act (and the amendments made by this Act)
14 shall take effect on the date that is 1 year after the date
15 of enactment of this Act.

ATTACHMENT 10

Sterile Compounding Crosswalk: USP 797 vs. California State Law

USP 797 Information extracted from both USP Chapter 797 and Appendix 1: Principal Competencies, Conditions, Practices, and Quality Assurances that are Required (†"shall") and Recommended (‡"should") in USP Chapter <797>
California State Law extracted from 2013 California Law Book for Pharmacy

USP 797 Topic	USP 797 Description	California State Law
Compounding Personnel Responsibilities, Training, and Competencies		
Responsibility of Compounding Personnel	†Practices and quality assurances required to prepare, store, and transport CSPs that are sterile, and acceptably accurate, pure, and stable. Compounding personnel are responsible for ensuring that CSPs are accurately identified, measured, diluted, and mixed and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispensed, and distributed. These performance responsibilities include maintaining appropriate cleanliness, conditions and providing labeling and supplementary instructions for the proper clinical administration of CSPs. All personnel who prepare CSPs shall be responsible for understanding these fundamental practices and precautions, for developing and implementing appropriate procedures, and for continually evaluating these procedures and the quality of final CSPs to prevent harm.	**1751. Sterile Injectable Compounding; Compounding Area; Self-Assessment** (a) Any pharmacy engaged in compounding sterile injectable drug products shall conform to the parameters and requirements stated by Article 4.5 (Section 1735 et seq.), applicable to all compounding, and shall also conform to the parameters and requirements stated by this Article 7 (Section 1751 et seq.), applicable solely to sterile injectable compounding. (c) Any pharmacy compounding a sterile injectable product from one or more non-sterile ingredients shall comply with Business and Professions Code section 4127.7.
Personnel Training and Evaluation in Aseptic Manipulations Skills	†Pass didactic, practical skill assessment and media-fill testing initially, followed by an annual assessment for a low- and medium-risk level compounding and semi-annual assessment for high-risk level compounding.	**Risk Levels are Not Specifically Defined in California State Law** **1735.7. Training of Compounding Staff** (a) Any pharmacy engaged in compounding shall maintain written documentation sufficient to demonstrate that pharmacy personnel have the skills and training required to properly and accurately perform their assigned responsibilities relating to compounding. (b) The pharmacy shall develop and maintain an on-going competency evaluation process for pharmacy personnel involved in compounding, and shall maintain documentation of any and all training related to compounding undertaken by pharmacy personnel. (c) Pharmacy personnel assigned to compounding duties shall demonstrate knowledge about processes and procedures used in compounding any drug product. **1751.3. Sterile Injectable Policies and Procedures.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall

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		maintain a written policy and procedure manual for compounding that includes, in addition to the elements required by section 1735.5, written policies and procedures regarding the following: (4) Training of staff in the preparation of sterile injectable products. (d) Pharmacies compounding sterile injectable products from one or more non-sterile ingredients must have written policies and procedures that comply with the following: (2) All personnel involved must read the policies and procedures before compounding sterile injectable products, and any additions, revisions, and deletions to the written policies and procedures must be communicated to all personnel involved in sterile compounding. **1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (a) Consultation shall be available to the patient and/or primary caregiver concerning proper use of sterile injectable products and related supplies furnished by the pharmacy. (b) The pharmacist-in-charge shall be responsible to ensure all pharmacy personnel engaging in compounding sterile injectable drug products shall have training and demonstrated competence in the safe handling and compounding of sterile injectable products, including cytotoxic agents if the pharmacy compounds products with cytotoxic agents. (d) The pharmacist-in-charge shall be responsible to ensure the continuing competence of pharmacy personnel engaged in compounding sterile injectable products. (e) Pharmacies that compound sterile products from one or more non-sterile ingredients must comply with the following training requirements: (1) The pharmacy must establish and follow a written program of training and performance evaluation designed to ensure that each person working in the designated area has the knowledge and skills necessary to perform their assigned tasks properly. This program of training and performance evaluation must address at least the following: (A) Aseptic technique. (B) Pharmaceutical calculations and terminology. (C) Sterile product compounding documentation. (D) Quality assurance procedures. (E) Aseptic preparation procedures. (F) Proper gowning and gloving technique. (G) General conduct in the controlled area. (H) Cleaning, sanitizing, and maintaining equipment used in the controlled area. (I) Sterilization techniques. (J) Container, equipment, and closure system selection. (2) Each person assigned to the controlled area must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures. Each person's

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		proficiency and continuing training needs must be reassessed every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (b) Each individual involved in the preparation of sterile injectable products must first successfully complete a validation process on technique before being allowed to prepare sterile injectable products. The validation process shall be carried out in the same manner as normal production, except that an appropriate microbiological growth medium is used in place of the actual product used during sterile preparation. The validation process shall be representative of all types of manipulations, products and batch sizes the individual is expected to prepare. The same personnel, procedures, equipment, and materials must be involved. Completed medium samples must be incubated. If microbial growth is detected, then the sterile preparation process must be evaluated, corrective action taken, and the validation process repeated. Personnel competency must be revalidated at least every twelve months, whenever the quality assurance program yields an unacceptable result, when the compounding process changes, equipment used in the compounding of sterile injectable drug products is repaired or replaced, the facility is modified in a manner that affects airflow or traffic patterns, or whenever improper aseptic techniques are observed. Revalidation must be documented.
	† Compounding personnel who fail written tests, or whose media-fill test vials result in gross microbial colonization, shall be immediately reinstructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic practice deficiencies.	**1735.8. (d)** The quality assurance plan shall include a written procedure for scheduled action in the event any compounded drug product is ever discovered to be below minimum standards for integrity, potency, quality, or labeled strength. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (b)...If microbial growth is detected, then the sterile preparation process must be evaluated, corrective action taken, and the validation process repeated.
PATIENT OR CAREGIVER TRAINING	† Multiple component formal training program to ensure patients and caregivers understand the proper storage, handling, use, and disposal of CSPs.	**State Law only addresses proper use. Storage, handling, and disposal are not addressed in California State Law.** **1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (a) Consultation shall be available to the patient and/or primary caregiver concerning proper use of sterile injectable products and related supplies furnished by the pharmacy.

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Personnel Cleansing And Garbing	†Personnel shall also be thoroughly competent and highly motivated to perform flawless aseptic manipulations with ingredients, devices, and components of CSPs.	**1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (b) The pharmacist-in-charge shall be responsible to ensure all pharmacy personnel engaging in compounding sterile injectable drug products shall have training and demonstrated competence in the safe handling and compounding of sterile injectable products, including cytotoxic agents if the pharmacy compounds products with cytotoxic agents. (d) The pharmacist-in-charge shall be responsible to ensure the continuing competence of pharmacy personnel engaged in compounding sterile injectable products. (e) Pharmacies that compound sterile products from one or more non-sterile ingredients must comply with the following training requirements: (1) The pharmacy must establish and follow a written program of training and performance evaluation designed to ensure that each person working in the designated area has the knowledge and skills necessary to perform their assigned tasks properly. This program of training and performance evaluation must address at least the following: (A) Aseptic technique. (E) Aseptic preparation procedures. (2) Each person assigned to the controlled area must successfully complete practical skills training in aseptic technique and aseptic area practices. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (b) Each individual involved in the preparation of sterile injectable products must first successfully complete a validation process on technique before being allowed to prepare sterile injectable products.
	†Personnel with rashes, sunburn, weeping sores, conjunctivitis, active respiratory infection, and cosmetics are prohibited from preparing CSPs.	**Not Specifically Addressed**
	†Compounding personnel remove personal outer garments; cosmetics; artificial nails; hand, wrist, and body jewelry that can interfere with the fit of gowns and gloves; and visible body piercing above the neck.	**State Law only addresses garbing requirements for sterile preparations made from one or more nonsterile ingredients and cytotoxic agents.**

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		1751.5. Sterile Injectable Compounding Attire. (a) When preparing cytotoxic agents, gowns and gloves shall be worn. (b) When compounding sterile products from one or more non-sterile ingredients the following standards must be met: 1. Cleanroom garb consisting of a low-shedding coverall, head cover, face mask, and shoe covers must be worn inside the designated area at all times. 2. Cleanroom garb must be donned and removed outside the designated area. 3. Hand, finger, and wrist jewelry must be eliminated. If jewelry cannot be removed then it must be thoroughly cleaned and covered with a sterile glove. 4. Head and facial hair must be kept out of the critical area or be covered. 5. Gloves made of low-shedding materials are required. (c) The requirements of subdivision (b) do not apply if a barrier isolator is used to compound sterile injectable products from one or more non-sterile ingredients.
	† Order of compounding garb and cleansing in ante-area: shoes or shoe covers, head and facial hair covers, face mask, fingernail cleansing, hand and forearm washing and drying; non-shedding gown.	**Not Specifically Addressed**
	† Order of cleansing and gloving in buffer room or area: hand cleansing with a persistently active alcohol-based product with persistent activity, allow hands to dry; don sterile gloves.	**Not Specifically Addressed**
	† Routinely disinfect gloves with sterile 70% IPA after contacting nonsterile objects.	**Not Specifically Addressed**
	† Inspect gloves for holes and replace when breaches are detected.	**Not Specifically Addressed**
	† Personnel repeat proper procedures after they are exposed to direct contact contamination or worse than ISO Class 8 air.	**Not Specifically Addressed**
	† These requirements are exempted only for immediate use CSPs and CAIs for which manufacturers provide written documentation based on validated testing that such personnel practices are not required to maintain sterility in CSPs.	**Not Specifically Addressed**
Personnel Training And Competency Evaluation Of Garbing, Aseptic Work Practices And Cleaning/Disinfection Procedures	† Personnel who prepare CSPs shall be trained conscientiously and skillfully by expert personnel, multi-media instructional sources, and professional publications in the theoretical principles and practical skills of garbing procedures, aseptic work practices, achieving and maintaining ISO Class 5 environmental conditions, and cleaning and disinfection procedures.	**1735.7. Training of Compounding Staff** (b) The pharmacy shall develop and maintain an on-going competency evaluation process for pharmacy personnel involved in compounding, and shall maintain documentation of any and all training related to compounding undertaken by pharmacy personnel. (c) Pharmacy personnel assigned to compounding duties shall demonstrate knowledge about processes and procedures used in compounding any drug product. **1751.3. Sterile Injectable Policies and Procedures.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall

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		maintain a written policy and procedure manual for compounding that includes, in addition to the elements required by section 1735.5, written policies and procedures regarding the following: (4) Training of staff in the preparation of sterile injectable products. (d) Pharmacies compounding sterile injectable products from one or more non-sterile ingredients must have written policies and procedures that comply with the following: (2) All personnel involved must read the policies and procedures before compounding sterile injectable products, and any additions, revisions, and deletions to the written policies and procedures must be communicated to all personnel involved in sterile compounding. **1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (b) The pharmacist-in-charge shall be responsible to ensure all pharmacy personnel engaging in compounding sterile injectable drug products shall have training and demonstrated competence in the safe handling and compounding of sterile injectable products, including cytotoxic agents if the pharmacy compounds products with cytotoxic agents. (d) The pharmacist-in-charge shall be responsible to ensure the continuing competence of pharmacy personnel engaged in compounding sterile injectable products. (e) Pharmacies that compound sterile products from one or more non-sterile ingredients must comply with the following training requirements: (1) The pharmacy must establish and follow a written program of training and performance evaluation designed to ensure that each person working in the designated area has the knowledge and skills necessary to perform their assigned tasks properly. This program of training and performance evaluation must address at least the following: (A) Aseptic technique. (B) Pharmaceutical calculations and terminology. (C) Sterile product compounding documentation. (D) Quality assurance procedures. (E) Aseptic preparation procedures. (F) Proper gowning and gloving technique. (G) General conduct in the controlled area. (H) Cleaning, sanitizing, and maintaining equipment used in the controlled area. (I) Sterilization techniques. (J) Container, equipment, and closure system selection. (2) Each person assigned to the controlled area must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures. Each person's proficiency and continuing training needs must be reassessed every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years.

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	† This training shall be completed and documented before any compounding personnel begin to prepare CSPs.	**1735.7. Training of Compounding Staff** (a) Any pharmacy engaged in compounding shall maintain written documentation sufficient to demonstrate that pharmacy personnel have the skills and training required to properly and accurately perform their assigned responsibilities relating to compounding. **1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (b) The pharmacist-in-charge shall be responsible to ensure all pharmacy personnel engaging in compounding sterile injectable drug products shall have training and demonstrated competence in the safe handling and compounding of sterile injectable products, including cytotoxic agents if the pharmacy compounds products with cytotoxic agents. (c) Records of training and demonstrated competence shall be available for each individual and shall be retained for three years beyond the period of employment. (e) Pharmacies that compound sterile products from one or more non-sterile ingredients must comply with the following training requirements: (2) Each person assigned to the controlled area must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures. Each person's proficiency and continuing training needs must be reassessed every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (b) Each individual involved in the preparation of sterile injectable products must first successfully complete a validation process on technique before being allowed to prepare sterile injectable products. The validation process shall be carried out in the same manner as normal production, except that an appropriate microbiological growth medium is used in place of the actual product used during sterile preparation. The validation process shall be representative of all types of manipulations, products and batch sizes the individual is expected to prepare. The same personnel, procedures, equipment, and materials must be involved. Completed medium samples must be incubated. If microbial growth is detected, then the sterile preparation process must be evaluated, corrective action taken, and the validation process repeated. Personnel competency must be revalidated at least every twelve months, whenever the quality assurance program yields an unacceptable result, when the compounding process changes, equipment used in the compounding of sterile injectable drug products is repaired or replaced, the facility is modified in a manner that affects airflow or traffic patterns, or whenever improper aseptic techniques are observed. Revalidation must be documented.
	† Compounding personnel shall complete didactic training, pass written competence assessments, undergo skill assessment using observational audit tools, and media-fill testing.	**1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (e) Pharmacies that compound sterile products from one or more non-sterile ingredients must comply with the following training requirements: (2) Each person assigned to the controlled area must successfully

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		complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures. Each person's proficiency and continuing training needs must be reassessed every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (b) Each individual involved in the preparation of sterile injectable products must first successfully complete a validation process on technique before being allowed to prepare sterile injectable products. The validation process shall be carried out in the same manner as normal production, except that an appropriate microbiological growth medium is used in place of the actual product used during sterile preparation. The validation process shall be representative of all types of manipulations, products and batch sizes the individual is expected to prepare. The same personnel, procedures, equipment, and materials must be involved. Completed medium samples must be incubated. If microbial growth is detected, then the sterile preparation process must be evaluated, corrective action taken, and the validation process repeated. Personnel competency must be revalidated at least every twelve months, whenever the quality assurance program yields an unacceptable result, when the compounding process changes, equipment used in the compounding of sterile injectable drug products is repaired or replaced, the facility is modified in a manner that affects airflow or traffic patterns, or whenever improper aseptic techniques are observed. Revalidation must be documented.
	†Media-fill testing of aseptic work skills shall be performed initially before beginning to prepare CSPs and at least annually thereafter for low- and medium-risk level compounding; and semiannually for high-risk level compounding.	**1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (e) Pharmacies that compound sterile products from one or more non-sterile ingredients must comply with the following training requirements: (2) Each person assigned to the controlled area must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures. Each person's proficiency and continuing training needs must be reassessed every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (b) Each individual involved in the preparation of sterile injectable products must first successfully complete a validation process on technique before being allowed to prepare sterile injectable products. The validation process shall be carried out in the same manner as normal production, except that an appropriate microbiological growth medium is used in place of the actual product used during sterile preparation. The validation process shall be representative of all types of manipulations, products and batch sizes the individual is expected to prepare. The same personnel, procedures, equipment, and materials must be involved. Completed medium samples must be incubated. If microbial growth is detected,

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		then the sterile preparation process must be evaluated, corrective action taken, and the validation process repeated. Personnel competency must be revalidated at least every twelve months, whenever the quality assurance program yields an unacceptable result, when the compounding process changes, equipment used in the compounding of sterile injectable drug products is repaired or replaced, the facility is modified in a manner that affects airflow or traffic patterns, or whenever improper aseptic techniques are observed. Revalidation must be documented.
	† Compounding personnel who fail written tests, observational audits, or whose media-fill test vials have one or more units showing visible microbial contamination, shall be reinstructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic work practice deficiencies.	**1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (b)...If microbial growth is detected, then the sterile preparation process must be evaluated, corrective action taken, and the validation process repeated.
	† Compounding personnel shall pass all evaluations prior to resuming compounding of sterile preparations.	**1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (b) The pharmacist-in-charge shall be responsible to ensure all pharmacy personnel engaging in compounding sterile injectable drug products shall have training and demonstrated competence in the safe handling and compounding of sterile injectable products, including cytotoxic agents if the pharmacy compounds products with cytotoxic agents. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (b)...If microbial growth is detected, then the sterile preparation process must be evaluated, corrective action taken, and the validation process repeated.
	† Compounding personnel must demonstrate proficiency of proper hand hygiene, garbing, and consistent cleaning procedures in addition to didactic evaluation and aseptic media fill.	**1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (e) Pharmacies that compound sterile products from one or more non-sterile ingredients must comply with the following training requirements: (1) The pharmacy must establish and follow a written program of training and performance evaluation designed to ensure that each person working in the designated area has the knowledge and skills necessary to perform their assigned tasks properly. This program of training and performance evaluation must address at least the following: (D) Quality assurance procedures. (F) Proper gowning and gloving technique. (G) General conduct in the controlled area. (H) Cleaning, sanitizing, and maintaining equipment used in the controlled area. (I) Sterilization techniques. (2) Each person assigned to the controlled area must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures. Each person's proficiency and continuing training needs must be reassessed every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years.

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	• Cleaning and disinfecting procedures performed by other support personnel shall be thoroughly trained in proper hand hygiene, and garbing, cleaning, and disinfection procedures by a qualified aseptic compounding expert. "In the event that cleaning and disinfecting procedures are also performed by other support personnel e.g. institutional environmental services, housekeeping), thorough training of proper hand hygiene, garbing, and cleaning and disinfection procedures shall be done by a qualified aseptic compounding expert. After completion of training, support personnel shall routinely undergo performance evaluation of proper hand hygiene, garbing, and all applicable cleaning and disinfecting procedures conducted by a qualified aseptic compounding expert."	**1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (e) Pharmacies that compound sterile products from one or more non-sterile ingredients must comply with the following training requirements: (1) The pharmacy must establish and follow a written program of training and performance evaluation designed to ensure that each person working in the designated area has the knowledge and skills necessary to perform their assigned tasks properly. This program of training and performance evaluation must address at least the following: (F) Proper gowning and gloving technique. (G) General conduct in the controlled area. (H) Cleaning, sanitizing, and maintaining equipment used in the controlled area. (I) Sterilization techniques.
	• Support personnel shall routinely undergo performance evaluation of proper hand hygiene, garbing, and all applicable cleaning and disinfecting procedures conducted by a qualified aseptic compounding expert.	**1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (2) Each person assigned to the controlled area must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures. Each person's proficiency and continuing training needs must be reassessed every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years.
Competency Evaluation of Garbing and Aseptic Work Practices	• Compounding personnel shall be evaluated initially prior to beginning compounding CSPs and whenever an aseptic media fill is performed using a Sample Form for Assessing Hand Hygiene and Garbing Related Practices of Compounding Personnel and the personnel glove fingertip sampling procedures.	**Not Specifically Addressed**
Aseptic Work Practice Assessment and Evaluation via Personnel Glove Fingertip Sampling	• Monitoring of compounding personnel glove fingertips shall be performed for all CSP risk level compounding.	**Not Specifically Addressed**
	• Glove fingertip sampling shall be used to evaluate the competency of personnel in performing hand hygiene and garbing procedures in addition to educating compounding personnel on proper work practices.	**Not Specifically Addressed**
	• All personnel shall demonstrate competency in proper hand hygiene and garbing procedures in addition to aseptic work practices.	**Not Specifically Addressed**
	• Sterile contact agar plates shall be used to sample the gloved fingertips of compounding personnel after garbing to assess garbing competency and after completing the media-fill preparation.	**Not Specifically Addressed**
	• Gloves shall not be disinfected with sterile 70% IPA immediately prior to sampling.	**Not Specifically Addressed**
Garbing and Gloving Competency Evaluation	• Compounding personnel shall be visually observed during the process of performing hand hygiene and garbing procedures.	**Not Specifically Addressed**

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	• The visual observation shall be documented on a Sample Form for Assessing Hand Hygiene and Garbing Related Practices of Compounding Personnel and maintained to provide a permanent record of and long-term assessment of personnel competency.	**Not Specifically Addressed**
Gloved Fingertip Sampling	• Immediately after the compounder completes the hand hygiene and garbing procedure, the evaluator shall collect a gloved fingertip and thumb sample from both hands of the compounder onto appropriate agar plates by lightly pressing each fingertip into the agar.	**Not Specifically Addressed**
	• The plates shall be incubated for the appropriate incubation period and at the appropriate temperature.	**Not Specifically Addressed**
	• All employees shall successfully complete an initial competency evaluation and gloved fingertip/thumb sampling procedure (0 cfu) no less than three times before initially being allowed to compound CSPs for human use.	**Not Specifically Addressed**
	• After completing the initial gowning and gloving competency evaluation, re-evaluation of all compounding personnel shall occur at least annually for low- and medium-risk level CSPs and semiannually for high-risk level CSPs before being allowed to continue compounding CSPs.	**1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (2) Each person assigned to the controlled area must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures. Each person's proficiency and continuing training needs must be reassessed every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years.
	• Gloves shall not be disinfected with sterile 70% IPA prior to testing.	**Not Specifically Addressed**
	• The sampled gloves shall be immediately discarded and proper hand hygiene performed after sampling. The nutrient agar plates shall be incubated as stated below.	**Not Specifically Addressed**
	• The cfu action level for gloved hands shall be based on the total number of cfu on both gloves and not per hand.	**Not Specifically Addressed**
	‡ Results should be reported separately as number of cfu per employee per hand (left hand, right hand).	**Not Specifically Addressed**
Incubation Period (For Gloved Fingertip Sampling)	• At the end of the designated sampling period, the agar plates are recovered, covers secured, inverted and incubated at a temperature and for a time period conducive to multiplication of microorganisms. Trypticase soy agar (TSA) with lecithin and polysorbate 80 shall be incubated at 35°±2° for 2–3 days.	**Not Specifically Addressed**
Aseptic Manipulation Competency Evaluation	• All compounding personnel shall have their aseptic technique and related practice competency evaluated initially during the media-fill test procedure and subsequent annual or semiannual media-fill test procedures on the Sample Form for Assessing Aseptic Technique and Related Practices of Compounding Personnel.	**1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (2) Each person assigned to the controlled area must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures.

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		Each person's proficiency and continuing training needs must be reassessed every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years.
Media-Fill Test Procedure	• The skill of personnel to aseptically prepare CSPs shall be evaluated using sterile fluid bacterial culture media-fill verification.	**1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (b) Each individual involved in the preparation of sterile injectable products must first successfully complete a validation process on technique before being allowed to prepare sterile injectable products. The validation process shall be carried out in the same manner as normal production, except that an appropriate microbiological growth medium is used in place of the actual product used during sterile preparation. The validation process shall be representative of all types of manipulations, products and batch sizes the individual is expected to prepare. The same personnel, procedures, equipment, and materials must be involved. Completed medium samples must be incubated. If microbial growth is detected, then the sterile preparation process must be evaluated, corrective action taken, and the validation process repeated. Personnel competency must be revalidated at least every twelve months, whenever the quality assurance program yields an unacceptable result, when the compounding process changes, equipment used in the compounding of sterile injectable drug products is repaired or replaced, the facility is modified in a manner that affects airflow or traffic patterns, or whenever improper aseptic techniques are observed. Revalidation must be documented.
	• Media-filled vials shall be incubated within a range of 35°C ±2° for 14 days.	**Not Specifically Addressed**
Surface Cleaning and Disinfection Sampling and Assessment	• Surface sampling shall be performed in all ISO classified areas on a periodic basis and can be accomplished using contact plates and/or swabs and shall be done at the conclusion of compounding.	**Not Specifically Addressed**
	• Locations to be sampled shall be defined in a sample plan or on a form.	**Not Specifically Addressed**
Cleaning and Disinfecting Competency Evaluation .	• Compounding personnel and other personnel responsible for cleaning shall be visually observed during the process of performing cleaning and disinfecting procedures during initial personnel training on cleaning procedures, changes in cleaning staff and at the completion of any Media-Fill Test Procedure.	**Not Specifically Addressed**
	• Visual observation shall be documented on a Sample Form for Assessing Cleaning and Disinfection Procedures and maintained to provide a permanent record of, and long-term assessment of, personnel competency.	**Not Specifically Addressed**
Surface Collection Methods	• Immediately after sampling a surface with the contact plate, the sampled area shall be thoroughly wiped with a non-shedding wipe soaked in sterile 70% IPA.	**Not Specifically Addressed**
	• Results should be reported as cfu per unit of surface area.	**Not Specifically Addressed**

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Action Levels, Documentation, and Data Evaluation	† Environmental sampling data shall be collected and reviewed on a routine basis as a means of evaluating the overall control of the compounding environment.	**Not Specifically Addressed**
	† If an activity consistently shows elevated levels of microbial growth, competent microbiology personnel shall be consulted.	**Not Specifically Addressed**
	† An investigation into the source of the contamination shall be conducted.	**Not Specifically Addressed**
	† When gloved fingertip sample results exceeds action levels after proper incubation, a review of hand hygiene and garbing procedures as well as glove and surface disinfection procedures and work practices shall be performed and documented.	**Not Specifically Addressed**
	‡ Any cfu count that exceeds its respective action level should prompt a re-evaluation of the adequacy of personnel work practices, cleaning procedures, operational procedures, and air filtration efficiency within the aseptic compounding location.	**Not Specifically Addressed**

Compounded Sterile Preparations

CSP Microbial Contamination Risk Levels	† Proper training and evaluation of personnel, proper cleansing and garbing of personnel, proper cleaning and disinfecting of compounding work environments, and proper maintenance and monitoring of controlled environmental locations (all of which are detailed in their respective sections).	**State law only addresses compounds made from one or more nonsterile ingredients and sterile compounds that do not meet these criteria.**
	Low-Risk Level CSPs † Aseptic manipulations within an ISO Class 5 environment using three or fewer sterile products and entries into any container. † In absence of passing sterility test, store not more than 48 hours at controlled room temperature, 14 days at cold temperature, and 45 days in solid frozen state at -25° to -10° or colder. † Media-fill test at least annually by compounding personnel.	**1735. Compounding in Licensed Pharmacies** (d) The parameters and requirements stated by this Article 4.5 (Section 1735 et seq.) apply to all compounding practices. Additional parameters and requirements applicable solely to sterile injectable compounding are stated by Article 7 (Section 1735 et seq.). **1735.2. Compounding Limitations and Requirements; Self-Assessment** (h) Every compounded drug product shall be given an expiration date representing the date beyond which, in the professional judgment of the pharmacist performing or supervising the compounding, it should not be used. This "beyond use date" of the compounded drug product shall not exceed 180 days from preparation or the shortest expiration date of any component in the compounded drug product, unless a longer date is supported by stability studies of finished drugs or compounded drug products using the same components and packaging. Shorter dating than set forth in this subsection may be used if it is deemed appropriate in the professional judgment of the responsible pharmacist. **1751. Sterile Injectable Compounding; Compounding Area; Self-Assessment**
	Low-Risk Level CSPs with 12-Hour or Less BUD † Fully comply with all four specific criteria. ‡ Sinks should not be located adjacent to the ISO Class 5 primary engineering control. ‡ Sinks should be separated from the immediate area of the ISO Class 5 primary engineering control device.	
	Medium-Risk Level CSPs † Aseptic manipulations within an ISO Class 5 environment using prolonged and complex mixing and transfer, more than three sterile products and entries into any container, and pooling ingredients from multiple sterile products to prepare multiple CSPs.	

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	†In absence of passing sterility test, store not more than 30 hours at controlled room temperature, 9 days at cold temperature, and 45 days in solid frozen state at -25°to -10°or colder. †Media-fill test at least annually by compounding personnel. **High-Risk Level CSPs** †Confirmed presence of nonsterile ingredients and devices, or confirmed or suspected exposure of sterile ingredients for more than one hour to air quality inferior to ISO Class 5 before final sterilization. †Sterilization method verified to achieve sterility for the quantity and type of containers. †Meet allowable limits for bacterial endotoxins. †Maintain acceptable strength and purity of ingredients and integrity of containers after sterilization. †In absence of passing sterility test, store not more than 24 hours at controlled room temperature, 3 days at cold temperature, and 45 days in solid frozen state at -25°to -10°or colder. Media-fill test at least semiannually by compounding personnel.	(a) Any pharmacy engaged in compounding sterile injectable drug products shall conform to the parameters and requirements stated by Article 4.5 (Section 1735 et seq.), applicable to all compounding, and shall also conform to the parameters and requirements stated by this Article 7 (Section 1751 et seq.), applicable solely to sterile injectable compounding. **1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (e) Pharmacies that compound sterile products from one or more non-sterile ingredients must comply with the following training requirements: (1) The pharmacy must establish and follow a written program of training and performance evaluation designed to ensure that each person working in the designated area has the knowledge and skills necessary to perform their assigned tasks properly. This program of training and performance evaluation must address at least the following: (A) Aseptic technique. (B) Pharmaceutical calculations and terminology. (C) Sterile product compounding documentation. (D) Quality assurance procedures. (E) Aseptic preparation procedures. (F) Proper gowning and gloving technique. (G) General conduct in the controlled area. (H) Cleaning, sanitizing, and maintaining equipment used in the controlled area. (I) Sterilization techniques. (J) Container, equipment, and closure system selection. (2) Each person assigned to the controlled area must successfully complete practical skills training in aseptic technique and aseptic area practices. Evaluation must include written testing and a written protocol of periodic routine performance checks involving adherence to aseptic area policies and procedures. Each person's proficiency and continuing training needs must be reassessed every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain, as part of its written policies and procedures, a written quality assurance plan including, in addition to the elements required by section 1735.8, a documented, ongoing quality assurance program that monitors personnel performance, equipment, and facilities. The end product shall be examined on a periodic sampling basis as determined by the pharmacist-in-charge to assure that it meets required specifications. The Quality Assurance Program shall include at least the following: (4) Written justification of the chosen expiration dates for compounded sterile injectable products.

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Determining Beyond-Use Dates	†Use the general criteria in USP <795> in the absence of direct stability-indicating assays or authoritative literature that supports longer durations.	**1735.2. Compounding Limitations and Requirements; Self-Assessment** (d) A drug product shall not be compounded until the pharmacy has first prepared a written master formula record that includes at least the following elements: (6) Expiration dating requirements. (h) Every compounded drug product shall be given an expiration date representing the date beyond which, in the professional judgment of the pharmacist performing or supervising the compounding, it should not be used. This "beyond use date" of the compounded drug product shall not exceed 180 days from preparation or the shortest expiration date of any component in the compounded drug product, unless a longer date is supported by stability studies of finished drugs or compounded drug products using the same components and packaging. Shorter dating than set forth in this subsection may be used if it is deemed appropriate in the professional judgment of the responsible pharmacist. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (4) Written justification of the chosen expiration dates for compounded sterile injectable products.
Maintaining Sterility, Purity, and Stability of Dispensed and Distributed CSPs	†Written procedures for proper packaging, storage, and transportation conditions to maintain sterility, quality, purity, and strength of CSPs.	**1751.3. Sterile Injectable Policies and Procedures.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain a written policy and procedure manual for compounding that includes, in addition to the elements required by section 1735.5, written policies and procedures regarding the following: (1) Compounding, filling, and labeling of sterile injectable compounds. (6) Quality assurance program. (d) Pharmacies compounding sterile injectable products from one or more non-sterile ingredients must have written policies and procedures that comply with the following: (3) Policies and procedures must address at least the following: (B) Storage and handling of products and supplies. (C) Storage and delivery of final products. (D) Process validation. (I) For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets and for appropriate documentation. (J) Sterilization. (K) End-product evaluation and testing. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain, as part of its written policies and procedures, a written quality assurance plan including, in addition to the elements required by section 1735.8, a documented, ongoing quality assurance program that monitors personnel performance, equipment, and facilities. The end product shall be examined on a periodic sampling basis as determined by the pharmacist-in-charge to assure that it meets required specifications. The Quality Assurance Program shall include at least the following:

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		(2) The storage of compounded sterile injectable products in the pharmacy and periodic documentation of refrigerator temperature.
Redispensed CSPs	† When sterility, and acceptable purity, strength, and quality can be ensured.	**Not Specifically Addressed**
	† Assignment of sterility storage times and stability beyond-use dates that occur later than those of originally dispensed CSPs must be based on results of sterility testing and quantitative assay of ingredients.	**Not Specifically Addressed**
Packaging And Transporting CSPs	† Packaging maintains physical integrity, sterility, stability, and purity of CSPs.	**Not Specifically Addressed**
	† Modes of transport that maintain appropriate temperatures and prevent damage to CSPs.	**Not Specifically Addressed**
Immediate Use CSPs	† Fully comply with all six specified criteria. The immediate use provision is intended only for those situations where there is a need for emergency or immediate patient administration of a CSP. Such situations may include cardiopulmonary resuscitation, emergency room treatment, preparation of diagnostic agents, or critical therapy where the preparation of the CSP under conditions described for Low-Risk Level CSPs subjects the patient to additional risk due to delays in therapy. Immediate-use CSPs are not intended for storage for anticipated needs or batch compounding. Preparations that are medium-risk level and high-risk level shall not be prepared as immediate-use CSPs. Immediate-use CSPs are exempt from the requirements described for Low-Risk Level CSPs only when all of the following criteria are met:	**Not Specifically Addressed**
	1. The compounding process involves simple transfer of not more than three commercially manufactured packages of sterile nonhazardous products or diagnostic radiopharmaceutical products from the manufacturers' original containers and not more than two entries into any one container or package (e.g., bag, vial) of sterile infusion solution or administration container/device. For example, anti-neoplastics shall not be prepared as immediate-use CSPs because they are hazardous drugs.	**1735.2. Compounding Limitations and Requirements; Self-Assessment** (d) A drug product shall not be compounded until the pharmacy has first prepared a written master formula record that includes at least the following elements: (3) Process and/or procedure used to prepare the drug. (6) Expiration dating requirements. **1751.4. Facility and Equipment Standards for Sterile Injectable Compounding** (e) Pharmacies preparing parenteral cytotoxic agents shall do so in accordance with Section 41106(b) of Title 24 of the California Administrative Code, requiring a laminar airflow hood. The hood must be certified annually by a qualified technician who is familiar with the methods and procedures for certifying laminar airflow hoods and cleanroom requirements, in accordance with National Sanitation Foundation Standard 49 for Class II (Laminar Flow) Biohazard Cabinetry, as revised May, 1983. Certification records must be retained for at least three years.
	2. Unless required for the preparation, the compounding procedure is a continuous process not to exceed 1 hour.	**Not Specifically Addressed**
	3. During preparation, aseptic technique is followed and, if not immediately administered, the finished CSP is under continuous supervision to minimize the potential for contact with non-sterile surfaces, introduction of particulate matter or biological fluids, mix-ups with other CSPs, and direct contact of	**1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver** (1) The pharmacy must establish and follow a written program of training and performance evaluation designed to ensure that each person working in the designated area has the knowledge and skills necessary to perform their assigned tasks properly. This program of training and performance evaluation must address

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	outside surfaces.	at least the following: (A) Aseptic technique. (B) Pharmaceutical calculations and terminology. (C) Sterile product compounding documentation. (D) Quality assurance procedures. (E) Aseptic preparation procedures. (F) Proper gowning and gloving technique. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (b) Each individual involved in the preparation of sterile injectable products must first successfully complete a validation process on technique before being allowed to prepare sterile injectable products. The validation process shall be carried out in the same manner as normal production, except that an appropriate microbiological growth medium is used in place of the actual product used during sterile preparation. The validation process shall be representative of all types of manipulations, products and batch sizes the individual is expected to prepare. The same personnel, procedures, equipment, and materials must be involved. Completed medium samples must be incubated. If microbial growth is detected, then the sterile preparation process must be evaluated, corrective action taken, and the validation process repeated. Personnel competency must be revalidated at least every twelve months, whenever the quality assurance program yields an unacceptable result, when the compounding process changes, equipment used in the compounding of sterile injectable drug products is repaired or replaced, the facility is modified in a manner that affects airflow or traffic patterns, or whenever improper aseptic techniques are observed. Revalidation must be documented.
	4. Administration begins not later than 1 hour following the start of the preparation of the CSP.	**Not Specifically Addressed**
	5. Unless immediately and completely administered by the person who prepared it or immediate and complete administration is witnessed by the preparer, the CSP shall bear a label listing patient identification information, the names and amounts of all ingredients, the name or initials of the person who prepared the CSP, and the exact 1-hour BUD and time.	**Not Specifically Addressed**

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	6. If administration has not begun within 1 hour following the start of preparing the CSP, the CSP shall be promptly, properly, and safely discarded.	**<u>**Time Constraints are Not Specifically Addressed</u>** **1735.2. Compounding Limitations and Requirements; Self-Assessment** (d) A drug product shall not be compounded until the pharmacy has first prepared a written master formula record that includes at least the following elements: (5) Post-compounding process or procedures required, if any. (6) Expiration dating requirements. (h) Every compounded drug product shall be given an expiration date representing the date beyond which, in the professional judgment of the pharmacist performing or supervising the compounding, it should not be used. This "beyond use date" of the compounded drug product shall not exceed 180 days from preparation or the shortest expiration date of any component in the compounded drug product, unless a longer date is supported by stability studies of finished drugs or compounded drug products using the same components and packaging. Shorter dating than set forth in this subsection may be used if it is deemed appropriate in the professional judgment of the responsible pharmacist. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** The Quality Assurance Program shall include at least the following: (4) Written justification of the chosen expiration dates for compounded sterile injectable products.
Single-Dose and Multiple-Dose Containers	† Beyond-use date 28 days, unless specified otherwise by the manufacturer, for closure sealed multiple-dose containers after initial opening or entry. † Beyond-use time of 6 hours, unless specified otherwise by the manufacturer, for closure sealed single-dose containers in ISO Class 5 or cleaner air after initial opening or entry. † Beyond-use time of 1 hour for closure sealed single-dose containers after being opened or entered in worse than ISO Class 5 air. † Storage of opened single-dose ampuls is not permitted.	**Not Specifically Addressed**
Hazardous Drugs as CSPs	† Appropriate personnel protective equipment. Appropriate personnel protective equipment (PPE) shall be worn when compounding in a BSC or CACI and when using CSTD devices. PPE should include gowns, face masks, eye protection, hair covers, shoe covers or dedicated shoes, double gloving with sterile chemo-type gloves, and compliance with manufacturers' recommendations when using a CACI	**<u>**State Law only addresses with respect to High Risk CSPs</u>** **1751.5. Sterile Injectable Compounding Attire.** (a) When preparing cytotoxic agents, gowns and gloves shall be worn. (b) When compounding sterile products from one or more non-sterile ingredients the following standards must be met: (1) Cleanroom garb consisting of a low-shedding coverall, head cover, face mask, and shoe covers must be worn inside the designated area at all times. (2) Cleanroom garb must be donned and removed outside the designated area. (3) Hand, finger, and wrist jewelry must be eliminated. If jewelry cannot be removed then it must be thoroughly cleaned and covered with a sterile glove. (4) Head and facial hair must be kept out of the critical area or be covered.

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		(5) Gloves made of low-shedding materials are required. (c) The requirements of subdivision (b) do not apply if a barrier isolator is used to compound sterile injectable products from one or more non-sterile ingredients.
	† Appropriate primary engineering controls (BSCs and CACIs) are used for concurrent personnel protection and exposure of critical sites.	**4127.7. Compounding Sterile Injectables from Nonsterile Ingredients; Requirements** On and after July 1, 2005, a pharmacy shall compound sterile injectable products from one or more nonsterile ingredients in one of the following environments: (a) An ISO class 5 laminar airflow hood within an ISO class cleanroom. The cleanroom must have a positive air pressure differential relative to adjacent areas. (b) An ISO class 5 cleanroom. (c) A barrier isolator that provides an ISO class 5 environment for compounding. **1751.3. Sterile Injectable Policies and Procedures.** (3) Policies and procedures must address at least the following: (F) Use and maintenance of environmental control devices used to create the critical area for manipulation of sterile products (e.g., laminar-airflow workstations, biological safety cabinets, class 100 clean rooms, and barrier isolator workstations). **1751.4. Facility and Equipment Standards for Sterile Injectable Compounding** (e) Pharmacies preparing parenteral cytotoxic agents shall do so in accordance with Section 41106(b) of Title 24 of the California Administrative Code, requiring a laminar airflow hood. The hood must be certified annually by a qualified technician who is familiar with the methods and procedures for certifying laminar airflow hoods and cleanroom requirements, in accordance with National Sanitation Foundation Standard 49 for Class II (Laminar Flow) Biohazard Cabinetry, as revised May, 1983. Certification records must be retained for at least three years. **505.5.1 Pharmacies: Laminar Flow Biological Safety Cabinet.** In all pharmacies preparing parenteral cytotoxic agents, all compounding shall be conducted within a certified Class II Type A or Class II Type B vertical laminar airflow hood with bag-in-bag-out design. The pharmacy must ensure that contaminated air plenums that are under positive air pressure are leak tight.
	† Hazardous drugs shall be stored separately from other inventory in a manner to prevent contamination and personnel exposure.	**Not Specifically Addressed** **1751.3. Sterile Injectable Policies and Procedures.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain a written policy and procedure manual for compounding that includes, in addition to the elements required by section 1735.5, written policies and procedures regarding the following: (5) Procedures for handling cytotoxic agents.
	† At least 0.01 inch water column negative pressure and 12 air changes per hour in non-cleanrooms in which CACIs are located.	**Not Specifically Addressed**

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	† Hazardous drugs shall be handled with caution at all times using appropriate chemotherapy gloves during receiving, distribution, stocking, inventorying, preparing for administration, and disposal.	**Not Specifically Addressed** **1751.2. Sterile Injectable Labeling Requirements.** (d) All cytotoxic agents shall bear a special label which states "Chemotherapy_ Dispose of Properly." **1751.3. Sterile Injectable Policies and Procedures.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain a written policy and procedure manual for compounding that includes, in addition to the elements required by section 1735.5, written policies and procedures regarding the following: (5) Procedures for handling cytotoxic agents. (c) Pharmacies compounding sterile injectable products shall have written policies and procedures for the disposal of infectious materials and/or materials containing cytotoxic residues. The written policies and procedures shall describe the pharmacy protocols for cleanups and spills in conformity with local health jurisdiction standards.
	† Hazardous drugs shall be prepared in an ISO Class 5 environment with protective engineering controls in place, and following aseptic practices specified for the appropriate contamination risk levels.	**No Specific Equivalent addressing risk levels** **4127.7. Compounding Sterile Injectables from Nonsterile Ingredients; Requirements** On and after July 1, 2005, a pharmacy shall compound sterile injectable products from one or more nonsterile ingredients in one of the following environments: (a) An ISO class 5 laminar airflow hood within an ISO class cleanroom. The cleanroom must have a positive air pressure differential relative to adjacent areas. (b) An ISO class 5 cleanroom. (c) A barrier isolator that provides an ISO class 5 environment for compounding. **1751.4. Facility and Equipment Standards for Sterile Injectable Compounding** (e) Pharmacies preparing parenteral cytotoxic agents shall do so in accordance with Section 41106(b) of Title 24 of the California Administrative Code, requiring a laminar airflow hood. The hood must be certified annually by a qualified technician who is familiar with the methods and procedures for certifying laminar airflow hoods and cleanroom requirements, in accordance with National Sanitation Foundation Standard 49 for Class II (Laminar Flow) Biohazard Cabinetry, as revised May, 1983. Certification records must be retained for at least three years. **1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: Any pharmacy that compounds sterile injectable products from one or more nonsterile ingredients must compound the medication in one of the following environments: • 5.1 An ISO class laminar airflow hood within an ISO class 7 cleanroom. The

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		cleanroom must have a positive air pressure differential relative to adjacent areas. • 5.2 An ISO class 5 cleanroom. • 5.3 A barrier isolator that provides an ISO class 5 environment for compounding. **Note**: For additional pharmacy mechanical standard requirements, see Chapter 5, California Mechanical Code. **505.5.1 Pharmacies: Laminar Flow Biological Safety Cabinet.** In all pharmacies preparing parenteral cytotoxic agents, all compounding shall be conducted within a certified Class II Type A or Class II Type B vertical laminar airflow hood with bag-in-bag-out design. The pharmacy must ensure that contaminated air plenums that are under positive air pressure are leak tight.
	† Access to drug preparation areas shall be limited to authorized personnel.	**Not Specifically Addressed**
		1751.3. Sterile Injectable Policies and Procedures. (d) Pharmacies compounding sterile injectable products from one or more non-sterile ingredients must have written policies and procedures that comply with the following: (3) Policies and procedures must address at least the following: (E) Personnel access and movement of materials into and near the controlled area.
	† A pressure indicator shall be installed that can readily monitor room pressurization, which is documented daily.	**Not Specifically Addressed**
	† Annual documentation of full training of personnel regarding storage, handling, and disposal of hazardous drugs.	**Storage and disposal not specifically addressed**
		1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver (b) The pharmacist-in-charge shall be responsible to ensure all pharmacy personnel engaging in compounding sterile injectable drug products shall have training and demonstrated competence in the safe handling and compounding of sterile injectable products, including cytotoxic agents if the pharmacy compounds products with cytotoxic agents. (c) Records of training and demonstrated competence shall be available for each individual and shall be retained for three years beyond the period of employment.
	† When used, a CSTD shall be used in an ISO Class 5 primary engineering control device.	**Not Specifically Addressed**
	† At least 0.01 inch water column negative pressure is required for compounding of hazardous drugs.	**Not Specifically Addressed**
	‡ Negative-pressure buffer area is not required for low-volume compounding operations when CSTD is used in BSC or CACI.	**Not Specifically Addressed**
	† Compounding personnel of reproductive capability shall confirm in writing that they understand the risks of handling hazardous drugs.	**Not Specifically Addressed**
	† Disposal of all hazardous drug wastes shall comply with all applicable federal and state regulations.	**1751.2.(d)** All cytotoxic agents shall bear a special label which states "Chemotherapy - Dispose of Properly." **1751.3. Sterile Injectable Policies and Procedures.** (c) Pharmacies compounding sterile injectable products shall have written policies and procedures for the disposal of infectious materials and/or materials

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		containing cytotoxic residues. The written policies and procedures shall describe the pharmacy protocols for cleanups and spills in conformity with local health jurisdiction standards.
	‡ Total external exhaust of primary engineering controls.	**Not Specifically Addressed**
	‡ Assay of surface wipe samples every 6 months.	**Not Specifically Addressed**
Radiopharmaceuticals as CSPs	† Positron Emission Tomography is according to USP chapter <823>.	**Radiopharmaceuticals as CSPs are Not Specifically Addressed in Sterile Compounding State Regulations.**
	† Appropriate primary engineering controls and radioactivity containment and shielding.	
	† Radiopharmaceuticals compounded from sterile components, in closed sterile containers, with volume of 100 mL or less for a single dose injection or not more than 30 mL taken from a multiple-dose container shall be designated as and conform to the standards for low-risk level CSPs.	
	† Radiopharmaceutical vials, designed for multi-use, compounded with technetium-99m, exposed to ISO Class 5 environment and punctured by needles with no direct contact contamination may be used up to the time indicated by manufacturers recommendations.	
	† Location of primary engineering controls permitted in ISO Class 8 controlled environment.	
	† Technetium-99m/Molybdenum-99 generators used according to manufacturer, state, and federal requirements.	
	† Radiopharmaceuticals prepared as low-risk level CSPs with 12-hour or less BUD shall be prepared in a segregated compounding area.	
	† Materials and garb exposed in patient-care and treatment area shall not cross a line of demarcation into the segregated compounding area.	
	† Technetium-99m/Molybdenum-99 generators must be eluted in ISO Class 8 conditions.	
	† Segregated compounding area will be designated with a line of demarcation	
	‡ Storage and transport of properly shielded vials of radiopharmaceutical CSPs may occur in a limited access ambient environment without a specific ISO class designation.	
Allergen Extracts as CSPs	† Allergen extracts as CSPs are not subject to the personnel, environmental, and storage requirements for all CSP Microbial Contamination Risk Levels when certain criteria are met.	**Not Specifically Addressed**
Patient Monitoring and Adverse Events Reporting	† Written standard procedures describe means for patients to ask questions and report concerns and adverse events with CSPs, and for compounding supervisors to correct and prevent future problems.	**Not Specifically Addressed**

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	‡ Adverse events and defects with CSPs reported to FDA's MedWatch and USP's MEDMARX programs.	**Not Specifically Addressed**
		1735.5. Compounding Policies and Procedures (c) The policy and procedure manual shall include the following: (2) Documentation of a plan for recall of a dispensed compounded drug product where subsequent verification demonstrates the potential for adverse effects with continued use of a compounded drug product. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain, as part of its written policies and procedures, a written quality assurance plan including, in addition to the elements required by section 1735.8, a documented, ongoing quality assurance program that monitors personnel performance, equipment, and facilities. The end product shall be examined on a periodic sampling basis as determined by the pharmacist-in-charge to assure that it meets required specifications. The Quality Assurance Program shall include at least the following: (3) Actions to be taken in the event of a drug recall.

Quality Assurance

Verification of Compounding Accuracy and Sterility	† Review labels and document correct measurements, aseptic manipulations, and sterilization procedures to confirm correct identity, purity, and strength of ingredients in, and sterility of, CSPs.	**1735.2. Compounding Limitations and Requirements; Self-Assessment** (f) The pharmacist performing or supervising compounding is responsible for the integrity, potency, quality, and labeled strength of a compounded drug product until it is dispensed. (i) The pharmacist performing or supervising compounding is responsible for the proper preparation, labeling, storage, and delivery of the compounded drug product.
	‡ Assay finished CSPs to confirm correct identity and, or, strength of ingredients.	1735.8. Compounding Quality Assurance (a) Any pharmacy engaged in compounding shall maintain, as part of its written policies and procedures, a written quality assurance plan designed to monitor and ensure the integrity, potency, quality, and labeled strength of compounded drug products. (b) The quality assurance plan shall include written procedures for verification, monitoring, and review of the adequacy of the compounding processes and shall also include written documentation of review of those processes by qualified pharmacy personnel. (c) The quality assurance plan shall include written standards for qualitative and quantitative integrity, potency, quality, and labeled strength analysis of compounded drug products. All qualitative and quantitative analysis reports for compounded drug products shall be retained by the pharmacy and collated with the compounding record and master formula.
	‡ Sterility test finished CSPs.	**1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain, as part of its written policies and procedures, a written quality assurance plan including, in addition to the elements required by section 1735.8, a

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		documented, ongoing quality assurance program that monitors personnel performance, equipment, and facilities. The end product shall be examined on a periodic sampling basis as determined by the pharmacist-in-charge to assure that it meets required specifications. (c) Batch-produced sterile injectable drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing for sterility and pyrogens and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens. (d) Batch-produced sterile to sterile transfers shall be subject to periodic testing through process validation for sterility as determined by the pharmacist-in-charge and described in the written policies and procedures. **1751.3. Sterile Injectable Policies and Procedures.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain a written policy and procedure manual for compounding that includes, in addition to the elements required by section 1735.5, written policies and procedures regarding the following: (6) Quality assurance program. (d) Pharmacies compounding sterile injectable products from one or more non-sterile ingredients must have written policies and procedures that comply with the following: (3) Policies and procedures must address at least the following: (J) Sterilization. (K) End-product evaluation and testing.
Sterilization Methods	**Sterilization Methods** † Verify that methods achieve sterility while maintaining appropriate strength, purity, quality, and packaging integrity.	**Not Specifically Addressed**
	‡ Prove effectiveness by USP chapter 71, equivalent, or superior sterility testing.	**Not Specifically Addressed**
Sterilization of High-Risk Level CSPs by Filtration	† Nominal 0.2-µm pore size sterile membranes that are chemically and physically compatible with the CSP.	**Not Specifically Addressed**
	† Complete rapidly without filter replacement.	**Not Specifically Addressed**
	† Subject filter to manufacturers recommended integrity test (e.g., bubble point test) after filtering CSPs.	**Not Specifically Addressed**
Sterilization of High-Risk Level CSPs by Steam	† Test to verify the mass of containers to be sterilized will be sterile after the selected exposure duration in the particular autoclave.	**Not Specifically Addressed**
	† Ensure live steam contacts all ingredients and surfaces to be sterilized.	**Not Specifically Addressed**
	† Pass solutions through a 1.2-µm or smaller nominal pore size filter into final containers to remove particulates before sterilization.	**Not Specifically Addressed**
	† Heated filtered air shall be evenly distributed throughout the chamber by a blower device.	**Not Specifically Addressed**
	† Dry heat shall only be used for those materials that cannot be sterilized by steam, when the moisture would either damage or be impermeable to the materials.	**Not Specifically Addressed**

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	• Sufficient space shall be left between materials to allow for good circulation of the hot air.	**Not Specifically Addressed**
	• The description of dry heat sterilization conditions and duration for specific CSPs shall be included in written documentation in the compounding facility. The effectiveness of dry heat sterilization shall be verified using appropriate biological indicators and other confirmation.	**Not Specifically Addressed**
	• The oven should be equipped with a system for controlling temperature and exposure period.	**Not Specifically Addressed**
Depyrogenation by Dry Heat	• Dry heat depyrogenation shall be used to render glassware or containers, such as vials free from pyrogens as well as viable microbes.	**Not Specifically Addressed**
	• The description of the dry heat depyrogenation cycle and duration for specific load items shall be included in written documentation in the compounding facility.	**Not Specifically Addressed**
	• The effectiveness of the dry heat depyrogenation cycle shall be verified using endotoxin challenge vials (ECVs).	**Not Specifically Addressed**
	• The bacterial endotoxin test should be performed on the ECVs to verify the cycle is capable of achieving a 3 log reduction in endotoxin.	**Not Specifically Addressed**
FINISHED PREPARATION RELEASE CHECKS AND TESTS		
Inspection of Solution Dosage Forms and Review of Compounding Procedures	• Review procedures and documents to ensure sterility, purity, correct identities and amounts of ingredients, and stability.	**1735.2. Compounding Limitations and Requirements; Self-Assessment** (d) A drug product shall not be compounded until the pharmacy has first prepared a written master formula record that includes at least the following elements: (1) Active ingredients to be used. (2) Inactive ingredients to be used. (3) Process and/or procedure used to prepare the drug. (4) Quality reviews required at each step in preparation of the drug. (5) Post-compounding process or procedures required, if any. (6) Expiration dating requirements. (f) The pharmacist performing or supervising compounding is responsible for the integrity, potency, quality, and labeled strength of a compounded drug product until it is dispensed. (g) All chemicals, bulk drug substances, drug products, and other components used for drug compounding shall be stored and used according to compendial and other applicable requirements to maintain their integrity, potency, quality, and labeled strength. (i) The pharmacist performing or supervising compounding is responsible for the proper preparation, labeling, storage, and delivery of the compounded drug product. **1735.8. Compounding Quality Assurance** (a) Any pharmacy engaged in compounding shall maintain, as part of its written policies and procedures, a written quality assurance plan designed to monitor and ensure the integrity, potency, quality, and labeled strength of compounded drug products. (b) The quality assurance plan shall include written procedures for

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		verification, monitoring, and review of the adequacy of the compounding processes and shall also include written documentation of review of those processes by qualified pharmacy personnel. (c) The quality assurance plan shall include written standards for qualitative and quantitative integrity, potency, quality, and labeled strength analysis of compounded drug products. All qualitative and quantitative analysis reports for compounded drug products shall be retained by the pharmacy and collated with the compounding record and master formula. (d) The quality assurance plan shall include a written procedure for scheduled action in the event any compounded drug product is ever discovered to be below minimum standards for integrity, potency, quality, or labeled strength. **1751.1. Sterile Injectable Recordkeeping Requirements.** (b) In addition to the records required by section 1735.3 and subdivision (a), for sterile products compounded from one or more non-sterile ingredients, the following records must be made and kept by the pharmacy: (6) Preparation records including the master work sheet, the preparation work sheet, and records of end-product evaluation results. (c) Pharmacies shall maintain and retain all records required by this article in the pharmacy in a readily retrievable form for at least three years from the date the record was created. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain, as part of its written policies and procedures, a written quality assurance plan including, in addition to the elements required by section 1735.8, a documented, ongoing quality assurance program that monitors personnel performance, equipment, and facilities. The end product shall be examined on a periodic sampling basis as determined by the pharmacist-in-charge to assure that it meets required specifications.
	† Visually inspect for abnormal particulate matter and color, and intact containers and seals.	**1735.8. Compounding Quality Assurance** (c) The quality assurance plan shall include written standards for qualitative and quantitative integrity, potency, quality, and labeled strength analysis of compounded drug products. All qualitative and quantitative analysis reports for compounded drug products shall be retained by the pharmacy and collated with the compounding record and master formula.
Sterility Testing	† High-risk level CSPs prepared in batches of more than 25 identical containers, or exposed longer than 12 hours at 2º to 8º and 6 hours at warmer than 8º before being sterilized.	**Not Specifically Addressed**
Bacterial Endotoxin (Pyrogen) Testing	† High-risk level CSPs, excluding those for inhalation and ophthalmic administration, prepared in batches of more than 25 identical containers, or exposed longer than 12 hours at 2º to 8º and 6 hours at warmer than 8º before being sterilized.	**Not Specifically Addressed**
Identity and Strength	† Written procedures to verify correct identity, quality, amounts, and	**1735.8. Compounding Quality Assurance**

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Verification of Ingredients	purities of ingredients used in CSPs.	(a) Any pharmacy engaged in compounding shall maintain, as part of its written policies and procedures, a written quality assurance plan designed to monitor and ensure the integrity, potency, quality, and labeled strength of compounded drug products. (b) The quality assurance plan shall include written procedures for verification, monitoring, and review of the adequacy of the compounding processes and shall also include written documentation of review of those processes by qualified pharmacy personnel. (c) The quality assurance plan shall include written standards for qualitative and quantitative integrity, potency, quality, and labeled strength analysis of compounded drug products. All qualitative and quantitative analysis reports for compounded drug products shall be retained by the pharmacy and collated with the compounding record and master formula. (d) The quality assurance plan shall include a written procedure for scheduled action in the event any compounded drug product is ever discovered to be below minimum standards for integrity, potency, quality, or labeled strength. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain, as part of its written policies and procedures, a written quality assurance plan including, in addition to the elements required by section 1735.8, a documented, ongoing quality assurance program that monitors personnel performance, equipment, and facilities. The end product shall be examined on a periodic sampling basis as determined by the pharmacist-in-charge to assure that it meets required specifications.
	†Written procedures to ensure labels of CSPs contain correct names and amounts or concentrations of ingredients, total volumes, beyond-use dates, storage conditions, and route(s) of administration.	**1735.8. Compounding Quality Assurance** (a) Any pharmacy engaged in compounding shall maintain, as part of its written policies and procedures, a written quality assurance plan designed to monitor and ensure the integrity, potency, quality, and labeled strength of compounded drug products. (c) The quality assurance plan shall include written standards for qualitative and quantitative integrity, potency, quality, and labeled strength analysis of compounded drug products. All qualitative and quantitative analysis reports for compounded drug products shall be retained by the pharmacy and collated with the compounding record and master formula. **1735.4. Labeling of Compounded Drug Products** (a) In addition to the labeling information required under Business and Professions Code section 4076, the label of a compounded drug product shall contain the generic name(s) of the principal active ingredient(s). (b) A statement that the drug has been compounded by the pharmacy shall be included on the container or on the receipt provided to the patient. (c) Drug products compounded into unit-dose containers that are too small or otherwise impractical for full compliance

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		with subdivisions (a) and (b) shall be labeled with at least the name(s) of the active ingredient(s), concentration of strength, volume or weight, pharmacy reference or lot number, and expiration date. **1735.5. Compounding Policies and Procedures** (c) The policy and procedure manual shall include the following: (4) Documentation of the methodology used to test integrity, potency, quality, and labeled strength of compounded drug products. **1735.8. Compounding Quality Assurance** (a) Any pharmacy engaged in compounding shall maintain, as part of its written policies and procedures, a written quality assurance plan designed to monitor and ensure the integrity, potency, quality, and labeled strength of compounded drug products. **1751.2. Sterile Injectable Labeling Requirements.** In addition to the labeling information required under Business and Professions Code section 4076 and section 1735.4, a pharmacy which compounds sterile products shall include the following information on the labels for those products: (b) Name and concentrations of ingredients contained in the sterile injectable product. (c) Instructions for storage and handling. (d) All cytotoxic agents shall bear a special label which states "Chemotherapy - Dispose of Properly." **1751.3. Sterile Injectable Policies and Procedures.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain a written policy and procedure manual for compounding that includes, in addition to the elements required by section 1735.5, written policies and procedures regarding the following: (1) Compounding, filling, and labeling of sterile injectable compounds. (2) Labeling of the sterile injectable product based on the intended route of administration and recommended rate of administration.
Environmental Quality and Control		
Exposure of Critical Sites	† ISO Class 5 or better air.	**State Law only addresses ISO Class 5 air for parenteral cytotoxic agents and sterile compounds made from one or more non-sterile ingredients.** **4127.7. Compounding Sterile Injectables from Nonsterile Ingredients; Requirements** On and after July 1, 2005, a pharmacy shall compound sterile injectable products from one or more nonsterile ingredients in one of the following environments: (a) An ISO class 5 laminar airflow hood within an ISO class cleanroom. The

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		cleanroom must have a positive air pressure differential relative to adjacent areas. (b) An ISO class 5 cleanroom. (c) A barrier isolator that provides an ISO class 5 environment for compounding. **1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 1. In accordance with Federal Standard 209(b), Clean Room and Work Station Requirements, Controlled Environment, as approved by the Commission, Federal Supply Service, General Services Administration meet standards for class 100 HEPA (high efficiency particulate air) filtered air such as laminar airflow hood or clean room. *Class 100 HEPA filtered air is equivalent to ISO 5 5. Any pharmacy that compounds sterile injectable products from one or more nonsterile ingredients must compound the medication in one of the following environments: • 5.1 An ISO class 1 laminar airflow hood within an ISO class 7 cleanroom. The cleanroom must have a positive air pressure differential relative to adjacent areas. • 5.2 An ISO class 5 cleanroom. • 5.3 A barrier isolator that provides an ISO class 5 environment for compounding. **Note**: For additional pharmacy mechanical standard requirements, see Chapter 5, California Mechanical Code. **505.5.1 Pharmacies: Laminar Flow Biological Safety Cabinet.** In all pharmacies preparing parenteral cytotoxic agents, all compounding shall be conducted within a certified Class II Type A or Class II Type B vertical laminar airflow hood with bag in-bag out design. The pharmacy must ensure that contaminated air plenums that are under positive air pressure are leak tight.
	†Preclude direct contact (e.g., touch and secretions) contamination.	**Not Specifically Addressed**

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ISO Class 5 Air Sources, Buffer Areas, and Ante-Areas	† A buffer area is an area that provides at least ISO Class 7 air quality.	**1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 2. In accordance with Federal Standard 209(b), Clean Room and Work Station Requirements, Controlled Environment, as approved by the Commission, Federal Supply Service, General Services Administration meet standards for class 100 HEPA (high efficiency particulate air) filtered air such as laminar air flow hood or clean room. *Class 100 HEPA filtered air is equivalent to ISO 5 6. Any pharmacy that compounds sterile injectable products from one or more nonsterile ingredients must compound the medication in one of the following environments: • 5.1 An ISO class 1 laminar airflow hood within an ISO class 7 cleanroom. The cleanroom must have a positive air pressure differential relative to adjacent areas. • 5.2 An ISO class 5 cleanroom. • 5.3 A barrier isolator that provides an ISO class 5 environment for compounding. **Note**: For additional pharmacy mechanical standard requirements, see Chapter 5, California Mechanical Code. **4127.7. Compounding Sterile Injectables from Nonsterile Ingredients; Requirements** On and after July 1, 2005, a pharmacy shall compound sterile injectable products from one or more nonsterile ingredients in one of the following environments: (a) An ISO class 5 laminar airflow hood within an ISO class cleanroom. The cleanroom must have a positive air pressure differential relative to adjacent areas. (b) An ISO class 5 cleanroom. (c) A barrier isolator that provides an ISO class 5 environment for compounding.
	† New representations of facility layouts.	**Not Specifically Addressed**
	† Each compounding facility shall ensure that each source of ISO Class 5 environment for exposure of critical sites and sterilization by filtration is properly located, operated, maintained, monitored, and verified.	**1735.6. Compounding Facilities and Equipment** (a) Any pharmacy engaged in compounding shall maintain written documentation regarding the facilities and equipment necessary for safe and accurate compounded drug products. Where applicable, this shall include records of certification(s) of facilities or equipment. (b) Any equipment used to compound drug products shall be stored, used, and maintained in accordance with manufacturers' specifications. (c) Any equipment used to compound drug products for which calibration or adjustment is appropriate shall be calibrated prior to use to ensure accuracy. Documentation of each such calibration shall be recorded in writing and these records of calibration shall be maintained and retained in the pharmacy. **1751. Sterile Injectable Compounding; Compounding Area; Self-Assessment**

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		(a) Any pharmacy engaged in compounding sterile injectable drug products shall conform to the parameters and requirements stated by Article 4.5 (Section 1735 et seq.), applicable to all compounding, and shall also conform to the parameters and requirements stated by this Article 7 (Section 1751 et seq.), applicable solely to sterile injectable compounding. (b) Any pharmacy compounding sterile injectable drug products shall have a designated area for the preparation of sterile injectable products which shall meet the following standards: (1) Clean Room and Work Station Requirements, shall be in accordance with Section 490A.3.1 of Title 24, Part 2, Chapter 4A of the California Code of Regulations. (3) Be ventilated in a manner in accordance with Section 505.12 Title 24, Part 4, Chapter 5 of the California Code of Regulations. (4) Be certified annually by a qualified technician who is familiar with the methods and procedures for certifying laminar airflow hoods and clean room requirements, in accordance with standards adopted by the United States General Services Administration. Certification records must be retained for at least 3 years. (5) The pharmacy shall be arranged in accordance with Section 490A.3 of Title 24, Part 2, Chapter 4A of the California Code of Regulations. Items related to the compounding of sterile injectable products within the compounding area shall be stored in such a way as to maintain the integrity of an aseptic environment. (c) Any pharmacy compounding a sterile injectable product from one or more non-sterile ingredients shall comply with Business and Professions Code section 4127.7. **1751.1. Sterile Injectable Recordkeeping Requirements.** (b) In addition to the records required by Section 1735.3 and subdivision (a), for sterile products compounded from one or more non-sterile ingredients, the following records must be made and kept by the pharmacy: (3) Certification of the sterile compounding environment. (4) Other facility quality control logs specific to the pharmacy's policies and procedures (e.g., cleaning logs for facilities and equipment). (c) Pharmacies shall maintain and retain all records required by this article in the pharmacy in a readily retrievable form for at least three years from the date the record was created. **1751.3. Sterile Injectable Policies and Procedures.** (d) Pharmacies compounding sterile injectable products from one or more non-sterile ingredients must have written policies and procedures that comply with the following: (3) Policies and procedures must address at least the following: (F) Use and maintenance of environmental control devices used to create the critical area for manipulation of sterile products (e.g., laminar-airflow workstations, biological safety cabinets, class 100 cleanrooms, and barrier isolator workstations). (G) Regular cleaning schedule for the controlled area and any equipment in the controlled area and the alternation of disinfectants. Pharmacies subject to an

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		institutional infection control policy may follow that policy as it relates to cleaning schedules and the alternation of disinfectants in lieu of complying with this subdivision. **1751.4. Facility and Equipment Standards for Sterile Injectable Compounding** (c) All equipment used in the designated area or cleanroom must be made of a material that can be easily cleaned and disinfected. (d) Exterior workbench surfaces and other hard surfaces in the designated area, such as walls, floors, ceilings, shelves, tables, and stools, must be disinfected weekly and after any unanticipated event that could increase the risk of contamination. (e) Pharmacies preparing parenteral cytotoxic agents shall do so in accordance with Section 41106(b) of Title 24 of the California Administrative Code, requiring a laminar airflow hood. The hood must be certified annually by a qualified technician who is familiar with the methods and procedures for certifying laminar airflow hoods and cleanroom requirements, in accordance with National Sanitation Foundation Standard 49 for Class II (Laminar Flow) Biohazard Cabinetry, as revised May, 1983. Certification records must be retained for at least three years. **505.5 Pharmacies: Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 1. Be ventilated in a manner not interfering with laminar airflow.
	† Placement of devices (e.g., computers and printers) and objects (e.g., carts and cabinets) can be placed in buffer areas and shall be verified by testing or monitoring.	**Placement of Devices are Not Specifically Addressed** **1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 3. The pharmacy shall be arranged in such a manner that the laminar-flow hood is located in an area which is exposed to minimal traffic flow, and is separate from any area used for bulk storage of items not related to the compounding of parenteral solution. There shall be sufficient space, well separated from the laminar-flow hood area, for the storage of bulk materials, equipment and waste materials.
Viable and Nonviable Environmental Sampling (ES) Testing	† Environmental sampling shall occur as part a comprehensive quality management program and shall occur minimally when several conditions exist.	**Not Specifically Addressed**
	‡ The ES program should provide information to staff and leadership to demonstrate that the engineering controls are maintaining an environment within the compounding area that consistently maintains acceptably low viable and nonviable particle levels.	**Not Specifically Addressed**
Environmental Nonviable Particle Testing Program	† Certification and testing of primary (LAFWs, BSCs, CAIs and CACIs) and secondary engineering controls (buffer and ante areas) shall be performed by a qualified individual no less than every six months and whenever the device or room is relocated, altered, or major service to the facility is performed. Certification procedures such as those outlined in the CETA Certification Guide for Sterile	**Not Specifically Addressed**

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	Compounding Facilities (CAG-003-2006) shall be used.	
Total Particle Counts	† Certification that each ISO classified area (e.g., ISO Class 5, 7 and 8) is within established guidelines shall be performed no less than every 6 months and whenever the LAFW, BSC, CAI, or CACI is relocated or the physical structure of the buffer room or ante-area has been altered.	**Not Specifically Addressed**
	† Testing shall be performed by qualified operators using current, state-of-the-art electronic equipment with results meeting ISO Class 5, 7, or 8 depending on the requirements of the area.	**Not Specifically Addressed**
	† All certification records shall be maintained and reviewed by supervising personnel or other designated employee to ensure that the controlled environments comply with the proper air cleanliness, room pressures, and air changes per hour.	**Not Specifically Addressed**
Environmental Viable Airborne Particle Testing Program—Sampling Plan	† An appropriate environmental sampling plan shall be developed for airborne viable particles based on a risk assessment of compounding activities performed.	**Not Specifically Addressed**
	† Selected sampling sites shall include locations within each ISO Class 5 environment and in the ISO Class 7 and 8 areas, and the segregated compounding areas at greatest risk of contamination (e.g., work areas near the ISO Class 5 environment, counters near doors, pass-through boxes).	**Not Specifically Addressed**
	† The plan shall include sample location, method of collection, frequency of sampling, volume of air sampled, and time of day as related to activity in the compounding area and action levels.	**Not Specifically Addressed**
	‡ It is recommended that compounding personnel refer to USP Chapter *Microbiological Evaluation of Clean Rooms and Other Controlled Environments* 1116 and the CDC Guidelines for Environmental Infection Control in Healthcare Facilities-2003 for more information.	**Not Specifically Addressed**
Viable Air Sampling	† Evaluation of airborne microorganisms using volumetric collection methods in the controlled air environments shall be performed by properly trained individuals for all compounding risk levels.	**Not Specifically Addressed**
	† Impaction shall be the preferred method of volumetric air sampling.	**Not Specifically Addressed**
	† For low-, medium-, and high-risk level compounding, air sampling shall be performed at locations that are prone to contamination during compounding activities and during other activities like staging, labeling, gowning, and cleaning.	**Not Specifically Addressed**
	† Locations shall include zones of air backwash turbulence within laminar airflow workbench and other areas where air backwash turbulence may enter the compounding area.	**Not Specifically Addressed**
	† For low-risk level CSPs with 12-hour or less BUD, air sampling shall be performed at locations inside the ISO Class 5 environment and other areas that are in close proximity to the ISO class 5 environment, during the certification of the primary engineering control.	**Not Specifically Addressed**
	‡ Consideration should be given to the overall effect the chosen sampling method will have on the unidirectional airflow within a	**Not Specifically Addressed**

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	compounding environment.	
Air Sampling Devices	† The instructions in the manufacturer's user manual for verification and use of electric air samplers that actively collect volumes of air for evaluation shall be followed.	**Not Specifically Addressed**
	† A sufficient volume of air (400–1000 liters) shall be tested at each location in order to maximize sensitivity.	**Not Specifically Addressed**
	‡ It is recommended that compounding personnel also refer to USP Chapter <1116> that can provide more information on the use of volumetric air samplers and volume of air that should be sampled to detect environmental bioburden excursions.	**Not Specifically Addressed**
Air Sampling Frequency and Process	† Air sampling shall be performed at least semiannually (i.e. every 6 months), as part of the re-certification of facilities and equipment for area where primary engineering controls are located.	**Not Specifically Addressed**
	† A sufficient volume of air shall be sampled and the manufacturer's guidelines for use of the electronic air sampling equipment followed.	**Not Specifically Addressed**
	‡ Any facility construction or equipment servicing may require the need to perform air sampling during these events.	**Not Specifically Addressed**
	† The microbial growth media plates used to collect environmental sampling are recovered, covers secured (e.g., taped), inverted, and incubated at a temperature and for a time period conducive to multiplication of microorganisms.	**Not Specifically Addressed**
	† The number of discrete colonies of microorganisms shall be counted and reported as colony-forming units (cfu) and documented on an environmental monitoring form. Counts from air monitoring need to be transformed into cfu/cubic meter of air and evaluated for adverse trends.	**Not Specifically Addressed**
	‡ TSA should be incubated at 35°±2° for 2–3 days.	**Not Specifically Addressed**
	‡ MEA or other suitable fungal media should be incubated at 28°±2° for 5–7	**Not Specifically Addressed**
Pressure Differential Monitoring	† A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the buffer area and ante area and the ante-area and the general environment outside the compounding area.	**Not Specifically Addressed**
	† The results shall be reviewed and documented on a log at least every work shift (minimum frequency shall be at least daily) or by a continuous recording device.	**Not Specifically Addressed**
	† The pressure between the ISO Class 7 and general pharmacy area shall not be less than 5 Pa (0.02 inch water column (w.c.).	**Not Specifically Addressed**
	† In facilities where low- and medium-risk level CSPs are prepared, differential airflow shall maintain a minimum velocity of 0.2 meter/second (40 fpm) between buffer area and ante-area.	**Not Specifically Addressed**
Growth Media	† A general microbiological growth medium such as Soybean–Casein Digest Medium (also known as trypticase soy broth (TSB) or agar (TSA)) shall be used to support the growth of bacteria.	**Not Specifically Addressed**

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	† Malt extract agar (MEA) or some other media that supports the growth of fungi shall be used in high-risk level compounding environments.	**Not Specifically Addressed**
	† Media used for surface sampling shall be supplemented with additives to neutralize the effects of disinfecting agents (e.g., TSA with lecithin and polysorbate 80).	**Not Specifically Addressed**
Incubation Period (For Environmental Sampling)	**Incubation Period** † The microbial growth media plates used to collect environmental sampling are recovered, covers secured (e.g., taped), inverted, and incubated at a temperature and for a time period conducive to multiplication of microorganisms.	**Not Specifically Addressed**
	† The number of discrete colonies of microorganisms shall be counted and reported as colony-forming units (cfu) and documented on an environmental monitoring form. Counts from air monitoring need to be transformed into cfu/cubic meter of air and evaluated for adverse trends.	**Not Specifically Addressed**
	‡ TSA should be incubated at 35°±2° for 2–3 days.	**Not Specifically Addressed**
	‡ MEA or other suitable fungal media should be incubated at 28°±2° for 5–7 days.	**Not Specifically Addressed**
Action Levels, Documentation and Data Evaluation	† Sampling data shall be collected and reviewed on a periodic basis as a means of evaluating the overall control of the compounding environment.	**Not Specifically Addressed**
	† Competent microbiology personnel shall be consulted if an environmental sampling consistently shows elevated levels of microbial growth.	**Not Specifically Addressed**
	† An investigation into the source of the environmental contamination shall be conducted.	**Not Specifically Addressed**
	‡ Any cfu count that exceeds its respective action level should prompt a re-evaluation of the adequacy of personnel work practices, cleaning procedures, operational procedures, and air filtration efficiency within the aseptic compounding location.	**Not Specifically Addressed**
	‡ Table titled, Recommended Action Levels for Microbial Contamination should only be used as a guideline	**Not Specifically Addressed**
Facility Design and Environmental Controls	† Compounding facilities are physically designed and environmentally controlled to minimize airborne contamination from contacting critical sites.	**1735.6. Compounding Facilities and Equipment** (a) Any pharmacy engaged in compounding shall maintain written documentation regarding the facilities and equipment necessary for safe and accurate compounded drug products. Where applicable, this shall include records of certification(s) of facilities or equipment. (b) Any equipment used to compound drug products shall be stored, used, and maintained in accordance with manufacturers' specifications. (c) Any equipment used to compound drug products for which calibration or adjustment is appropriate shall be calibrated prior to use to ensure accuracy. Documentation of each such calibration shall be recorded in writing and these records of calibration shall be maintained and retained in the pharmacy.

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		1751. Sterile Injectable Compounding; Compounding Area; Self-Assessment (a) Any pharmacy engaged in compounding sterile injectable drug products shall conform to the parameters and requirements stated by Article 4.5 (Section 1735 et seq.), applicable to all compounding, and shall also conform to the parameters and requirements stated by this Article 7 (Section 1751 et seq.), applicable solely to sterile injectable compounding. (b) Any pharmacy compounding sterile injectable drug products shall have a designated area for the preparation of sterile injectable products which shall meet the following standards: (1) Clean Room and Work Station Requirements, shall be in accordance with Section 490A.3.1 of Title 24, Part 2, Chapter 4A of the California Code of Regulations. (3) Be ventilated in a manner in accordance with Section 505.12 Title 24, Part 4, Chapter 5 of the California Code of Regulations. (4) Be certified annually by a qualified technician who is familiar with the methods and procedures for certifying laminar airflow hoods and clean room requirements, in accordance with standards adopted by the United States General Services Administration. Certification records must be retained for at least 3 years. (5) The pharmacy shall be arranged in accordance with Section 490A.3 of Title 24, Part 2, Chapter 4A of the California Code of Regulations. Items related to the compounding of sterile injectable products within the compounding area shall be stored in such a way as to maintain the integrity of an aseptic environment. (c) Any pharmacy compounding a sterile injectable product from one or more non-sterile ingredients shall comply with Business and Professions Code Section 4127.7. **1751.1. Sterile Injectable Recordkeeping Requirements.** (b) In addition to the records required by Section 1735.3 and subdivision (a), for sterile products compounded from one or more non-sterile ingredients, the following records must be made and kept by the pharmacy: (3) Certification of the sterile compounding environment. (4) Other facility quality control logs specific to the pharmacy's policies and procedures (e.g., cleaning logs for facilities and equipment). (c) Pharmacies shall maintain and retain all records required by this article in the pharmacy in a readily retrievable form for at least three years from the date the record was created. **1751.3. Sterile Injectable Policies and Procedures.** (3) Policies and procedures must address at least the following: (F) Use and maintenance of environmental control devices used to create the critical area for manipulation of sterile products (e.g., laminar-airflow workstations, biological safety cabinets, class 100 cleanrooms, and barrier isolator workstations). **1751.4. Facility and Equipment Standards for Sterile Injectable Compounding** (c) All equipment used in the designated area or cleanroom must be made of a material that can be easily cleaned and disinfected.

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		(d) Exterior workbench surfaces and other hard surfaces in the designated area, such as walls, floors, ceilings, shelves, tables, and stools, must be disinfected weekly and after any unanticipated event that could increase the risk of contamination. **1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 1 In accordance with Federal Standard 209(b), Clean Room and Work Station Requirements, Controlled Environment, as approved by the Commission, Federal Supply Service, General Services Administration meet standards for class 100 HEPA (high efficiency particulate air) filtered air such as laminar airflow hood or clean room. 2 Have non-porous and cleanable surfaces, walls, floors and floor coverings. 3 The pharmacy shall be arranged in such a manner that the laminar-flow hood is located in an area which is exposed to minimal traffic flow, and is separate from any area used for bulk storage of items not related to the compounding of parenteral solution. There shall be sufficient space, well separated from the laminar-flow hood area, for the storage of bulk materials, equipment and waste materials. 5 Any pharmacy that compounds sterile injectable products from one or more nonsterile ingredients must compound the medication in one of the following environments: • An ISO class laminar airflow hood within an ISO class 7 cleanroom. The cleanroom must have a positive air pressure differential relative to adjacent areas. • 5.2 An ISO class 5 cleanroom. • 5.3 A barrier isolator that provides an ISO class 5 environment for compounding. **Note**: For additional pharmacy mechanical standard requirements, see Chapter 5, California Mechanical Code. **505.5 Pharmacies: Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 1. Be ventilated in a manner not interfering with laminar airflow.
	† Compounding facilities shall provide a comfortable and well-lighted working environment, which typically includes a temperature of 20° or cooler to maintain comfortable conditions for compounding personnel when attired in the required aseptic compounding garb.	**Not Specifically Addressed**
	† Primary engineering controls provide unidirectional (i.e., laminar) HEPA air at a velocity sufficient to prevent airborne particles from contacting critical sites.	**1751.3. Sterile Injectable Policies and Procedures.** (d) Pharmacies compounding sterile injectable products from one or more non-sterile ingredients must have written policies and procedures that comply with the following: (3) Policies and procedures must address at least the following: (F) Use and maintenance of environmental control devices used to create the critical area for manipulation of sterile products (e.g., laminar-airflow

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		workstations, biological safety cabinets, class 100 cleanrooms, and barrier isolator workstations). **1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 1 In accordance with Federal Standard 209(b), Clean Room and Work Station Requirements, Controlled Environment, as approved by the Commission, Federal Supply Service, General Services Administration meet standards for class 100 HEPA (high efficiency particulate air) filtered air such as laminar air flow hood or clean room. 5 Any pharmacy that compounds sterile injectable products from one or more nonsterile ingredients must compound the medication in one of the following environments: • 5.1 An ISO class laminar airflow hood within an ISO class 7 cleanroom. The cleanroom must have a positive air pressure differential relative to adjacent areas. • 5.2 An ISO class 5 cleanroom. • 5.3 A barrier isolator that provides an ISO class 5 environment for compounding. **Note**: For additional pharmacy mechanical standard requirements, see Chapter 5, California Mechanical Code.
	† In situ air pattern analysis via smoke studies shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions.	**Not Specifically Addressed**
	† Policies and procedures for maintaining and working within the primary engineering control area shall be written and followed. The policies and procedures will be determined by the scope and risk levels of the aseptic compounding activities used during the preparation of the CSPs.	**State Law only addresses sterile compounds made from one or more non-sterile ingredients. Other risk levels are not specifically addressed.** **1751.3. Sterile Injectable Policies and Procedures.** (d) Pharmacies compounding sterile injectable products from one or more non-sterile ingredients must have written policies and procedures that comply with the following: (3) Policies and procedures must address at least the following: (F) Use and maintenance of environmental control devices used to create the critical area for manipulation of sterile products (e.g., laminar-airflow workstations, biological safety cabinets, class 100 cleanrooms, and barrier isolator workstations). **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain, as part of its written policies and procedures, a written quality assurance plan including, in addition to the elements required by section 1735.8, a documented, ongoing quality assurance program that monitors personnel performance, equipment, and facilities. The end product shall be examined on a periodic sampling basis as determined by the pharmacist-in-charge to assure that it meets required

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		specifications. The Quality Assurance Program shall include at least the following: (1) Cleaning and sanitization of the parenteral medication preparation area
	† The principles of HEPA-filtered unidirectional airflow in the work environment shall be understood and practiced in the compounding process in order to achieve the desired environmental conditions.	**1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 1 In accordance with Federal Standard 209(b), Clean Room and Work Station Requirements, Controlled Environment, as approved by the Commission, Federal Supply Service, General Services Administration meet standards for class 100 HEPA (high efficiency particulate air) filtered air such as laminar air flow hood or clean room. 3 The pharmacy shall be arranged in such a manner that the laminar-flow hood is located in an area which is exposed to minimal traffic flow, and is separate from any area used for bulk storage of items not related to the compounding of parenteral solution. There shall be sufficient space, well separated from the laminar-flow hood area, for the storage of bulk materials, equipment and waste materials.
	† Clean rooms for nonhazardous and nonradioactive CSPs are supplied with HEPA that enters from ceilings with return vents low on walls, and provide not less than 30 air changes per hour.	**Not Specifically Addressed**
	† Buffer areas maintain 0.02- to 0.05-inch water column positive pressure, and do not contain sinks or drains.	**Not Specifically Addressed**
	† Air velocity from buffer rooms or zones to ante-areas is at least 40 feet/minute.	**Not Specifically Addressed**
	† The primary engineering controls shall be placed within a buffer area in such a manner as to avoid conditions that could adversely affect their operation.	**1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 1 In accordance with Federal Standard 209(b), Clean Room and Work Station Requirements, Controlled Environment, as approved by the Commission, Federal Supply Service, General Services Administration meet standards for class 100 HEPA (high efficiency particulate air) filtered air such as laminar air flow hood or clean room. 3 The pharmacy shall be arranged in such a manner that the laminar-flow hood is located in an area which is exposed to minimal traffic flow, and is separate from any area used for bulk storage of items not related to the compounding of parenteral solution. There shall be sufficient space, well separated from the laminar-flow hood area, for the storage of bulk materials, equipment and waste materials.
	† The primary engineering controls shall be placed out of the traffic flow and in a manner to avoid disruption from the HVAC system and room cross-drafts.	**State law does not address HVAC system and room cross-drafts** **1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 1. In accordance with Federal Standard 209(b), Clean Room and Work Station Requirements, Controlled Environment, as approved by the Commission, Federal Supply Service, General Services Administration meet standards for class 100 HEPA (high efficiency particulate air) filtered air such as laminar air flow hood or clean room.

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		3. The pharmacy shall be arranged in such a manner that the laminar-flow hood is located in an area which is exposed to minimal traffic flow, and is separate from any area used for bulk storage of items not related to the compounding of parenteral solution. There shall be sufficient space, well separated from the laminar-flow hood area, for the storage of bulk materials, equipment and waste materials.
	† HEPA-filtered supply air shall be introduced at the ceiling.	**Not Specifically Addressed**
	† All HEPA filters shall be efficiency tested using the most penetrating particle size and shall be leak tested at the factory and then leak tested again in situ after installation.	**Not Specifically Addressed**
	† Activities and tasks carried out within the buffer area shall be limited to only those necessary when working within a controlled environment.	**1751.3. Sterile Injectable Policies and Procedures.** (3) Policies and procedures must address at least the following: (E) Personnel access and movement of materials into and near the controlled area.
	† Only the furniture, equipment, supplies, and other material required for the compounding activities to be performed shall be brought into the room.	**1751.3. Sterile Injectable Policies and Procedures.** (3) Policies and procedures must address at least the following: (E) Personnel access and movement of materials into and near the controlled area.
	† Surfaces and essential furniture in buffer rooms or zones and clean rooms shall be nonporous, smooth, nonshedding, impermeable, cleanable, and resistant to disinfectants.	**1751.4. Facility and Equipment Standards for Sterile Injectable Compounding** (c) All equipment used in the designated area or cleanroom must be made of a material that can be easily cleaned and disinfected. **1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 2. Have non-porous and cleanable surfaces, walls, floors and floor coverings.
	† The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the buffer area shall be smooth, impervious, free from cracks and crevices, and nonshedding, thereby promoting cleanability and minimizing spaces in which microorganisms and other contaminants may accumulate.	**1751.4. Facility and Equipment Standards for Sterile Injectable Compounding** (c) All equipment used in the designated area or cleanroom must be made of a material that can be easily cleaned and disinfected. **1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 2. Have non-porous and cleanable surfaces, walls, floors and floor coverings.
	† The surfaces shall be resistant to damage by disinfectant agents.	**1751.4. Facility and Equipment Standards for Sterile Injectable Compounding** (c) All equipment used in the designated area or cleanroom must be made of a material that can be easily cleaned and disinfected. **1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 2. Have non-porous and cleanable surfaces, walls, floors and floor coverings.
	† Junctures of ceilings to walls shall be coved or caulked to avoid cracks and crevices where dirt can accumulate.	**Not Specifically Addressed**
	† Ceiling tiles shall be caulked around each perimeter to seal them to the support frame.	**Not Specifically Addressed**
	† The exterior lens surface of ceiling lighting fixtures shall be smooth, mounted flush, and sealed.	**Not Specifically Addressed**

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	† Any other penetrations through the ceiling or walls shall be sealed.	**Not Specifically Addressed**
	† The buffer area shall not contain sources of water (sinks) or floor drains. Work surfaces shall be constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are easily cleaned and disinfected.	**Not Specifically Addressed**
	† Carts shall be of stainless steel wire, nonporous plastic, or sheet metal construction with good quality, cleanable casters to promote mobility.	**Not Specifically Addressed**
	† Storage shelving, counters, and cabinets shall be smooth, impervious, free from cracks and crevices, nonshedding, cleanable, and disinfectable.	**1751.4. Facility and Equipment Standards for Sterile Injectable Compounding** (c) All equipment used in the designated area or cleanroom must be made of a material that can be easily cleaned and disinfected. **1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 2 Have non-porous and cleanable surfaces, walls, floors and floor coverings.
	† Their number, design, and manner of installation the items above shall promote effective cleaning and disinfection.	**Not Specifically Addressed**
	‡ If ceilings consist of inlaid panels, the panels should be impregnated with a polymer to render them impervious and hydrophobic.	**Not Specifically Addressed**
	‡ Dust-collecting overhangs, such as ceiling utility pipes, or ledges, such as windowsills, should be avoided.	**Not Specifically Addressed**
	‡ Air returns should be mounted low on the wall creating a general top-down dilution of room air with HEPA-filtered make-up air.	**Not Specifically Addressed**
Placement Of Primary Engineering Controls Within ISO Class 7 Buffer Areas	† Primary engineering controls for nonhazardous and nonradioactive CSPs are located in buffer areas, except for CAIs that are proven to maintain ISO Class 5 air when particle counts are sampled 6 to 12 inches upstream of critical site exposure areas during performance of normal inward and outward transfer of materials, and compounding manipulations when such CAIs are located in air quality worse than ISO Class 7.	**Not Specifically Addressed**
	† Presterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in no worse than an ISO Class 8 environment.	**Not Specifically Addressed**
	† Primary engineering controls shall be located out of traffic patterns and away from room air currents that could disrupt the intended airflow patterns.	**1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 1 In accordance with Federal Standard 209(b), Clean Room and Work Station Requirements, Controlled Environment, as approved by the Commission, Federal Supply Service, General Services Administration meet standards for class 100 HEPA (high efficiency particulate air) filtered air such as laminar air flow hood or clean room. 3 The pharmacy shall be arranged in such a manner that the laminar-flow hood is located in an area which is exposed to minimal traffic flow, and is separate

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		from any area used for bulk storage of items not related to the compounding of parenteral solution. There shall be sufficient space, well separated from the laminar-flow hood area, for the storage of bulk materials, equipment and waste materials.
	† When isolators are used for sterile compounding, the recovery time to achieve ISO Class 5 air quality shall be documented and internal procedures developed to ensure that adequate recovery time is allowed after material transfer before and during compounding operations.	**Not Specifically Addressed**
	† When compounding activities require the manipulation of a patient's blood-derived or other biological material (e.g., radiolabeling a patients or a donors white blood cells), the manipulations shall be clearly separated from routine material-handling procedures and equipment used in CSP preparation activities, and they shall be controlled by specific standard operating procedures in order to avoid any cross-contamination.	**Not Specifically Addressed**
	† Food, drinks, and items exposed in patient care areas, and unpacking of bulk supplies and personnel cleansing and garbing are prohibited from buffer areas or rooms.	**Not Specifically Addressed**
	† Demarcation designation between buffer areas or rooms and ante-areas.	**Not Specifically Addressed**
	† Antiseptic hand cleansing and sterile gloves in buffer areas or rooms.	**Not Specifically Addressed**
	‡ Packaged compounding supplies and components, such as needles, syringes, tubing sets, and small- and large-volume parenterals, should be uncartoned and wiped down with a disinfectant that does not leave a residue (e.g., sterile 70% IPA) when possible in an ante-area, of ISO Class 8 air quality, before being passed into the buffer areas.	**Not Specifically Addressed**
Cleaning and Disinfecting the Sterile Compounding Areas	† Trained personnel write detailed procedures including cleansers, disinfectants, and non-shedding wipe and mop materials.	**1735.5. Compounding Policies and Procedures** (a) Any pharmacy engaged in compounding shall maintain a written policy and procedure manual for compounding that establishes procurement procedures, methodologies for the formulation and compounding of drugs, facilities and equipment cleaning, maintenance, operation, and other standard operating procedures related to compounding. (c) The policy and procedure manual shall include the following: (3) The procedures for maintaining, storing, calibrating, cleaning, and disinfecting equipment used in compounding, and for training on these procedures as part of the staff training and competency evaluation process. **1751.3. Sterile Injectable Policies and Procedures.** (3) Policies and procedures must address at least the following: (G) Regular cleaning schedule for the controlled area and any equipment in the controlled area and the alternation of disinfectants. Pharmacies subject to an institutional infection control policy may follow that policy as it relates to cleaning schedules and the alternation of disinfectants in lieu of complying with this subdivision.
	† Cleaning and disinfecting surfaces in the LAFWs, BSCs, CAIs, and CACIs shall be cleaned and disinfected frequently including at the beginning of	**Not Specifically Addressed**

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	each work shift, before each batch preparation is started, every 30 minutes during continuous compounding periods of individual CSPs, when there are spills, and when surface contamination is known or suspected from procedural breaches.	
	Trained compounding personnel are responsible for developing, implementing, and practicing the procedures for cleaning and disinfecting the DCAs written in the SOPs.	**1735.5. Compounding Policies and Procedures** (3) The procedures for maintaining, storing, calibrating, cleaning, and disinfecting equipment used in compounding, and for training on these procedures as part of the staff training and competency evaluation process.
	Cleaning and disinfecting shall occur before compounding is performed. Items shall be removed from all areas to be cleaned and surfaces shall be cleaned by removing loose material and residue from spills, e.g., water-soluble solid residues are removed with Sterile Water (for Injection or Irrigation) and low-shedding wipes. This shall be followed by wiping with a residue-free disinfecting agent, such as sterile 70% IPA, which is allowed to dry before compounding begins.	**Not Specifically Addressed**
	Work surfaces in ISO Class 7 and 8 areas and segregated compounding areas are cleaned at least daily.	**Not Specifically Addressed**
	Dust and debris shall be removed when necessary from storage sites for compounding ingredients and supplies, using a method that does not degrade the ISO Class 7 or 8 air quality.	**Not Specifically Addressed**
	Floors in ISO Class 7 and 8 areas are cleaned daily when no compounding occurs.	**State law requires weekly disinfection of floors, while USP 797 requires daily.** **1751.4. Facility and Equipment Standards for Sterile Injectable Compounding** (d) Exterior workbench surfaces and other hard surfaces in the designated area, such as walls, floors, ceilings, shelves, tables, and stools, must be disinfected weekly and after any unanticipated event that could increase the risk of contamination.
	IPA (70% isopropyl alcohol) remains on surfaces to be disinfected for at least 30 seconds before such are used to prepare CSPs.	**Not Specifically Addressed**
	Emptied shelving, walls, and ceilings in ante-areas are cleaned and disinfected at least monthly.	**Difference in disinfecting schedules between USP797 and State Law** **1751.4. Facility and Equipment Standards for Sterile Injectable Compounding** (d) Exterior workbench surfaces and other hard surfaces in the designated area, such as walls, floors, ceilings, shelves, tables, and stools, must be disinfected weekly and after any unanticipated event that could increase the risk of contamination.
	Mopping shall be performed by trained personnel using approved agents and procedures described in the written SOPs.	**Not Specifically Addressed**
	Cleaning and disinfecting agents, their schedules of use and methods of application shall be in accordance with written SOPs and followed by custodial and/or compounding personnel.	**1735.5. Compounding Policies and Procedures** (a) Any pharmacy engaged in compounding shall maintain a written policy and procedure manual for compounding that establishes procurement procedures, methodologies for the formulation and compounding of drugs, facilities and equipment cleaning, maintenance, operation, and other standard operating procedures related to compounding. (c) The policy and procedure manual shall include the following: (3) The procedures for maintaining, storing, calibrating, cleaning, and disinfecting equipment used in compounding, and for training on these procedures

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		as part of the staff training and competency evaluation process. **1751.3. Sterile Injectable Policies and Procedures.** (3) Policies and procedures must address at least the following: (G) Regular cleaning schedule for the controlled area and any equipment in the controlled area and the alternation of disinfectants. Pharmacies subject to an institutional infection control policy may follow that policy as it relates to cleaning schedules and the alternation of disinfectants in lieu of complying with this subdivision. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain, as part of its written policies and procedures, a written quality assurance plan including, in addition to the elements required by section 1735.8, a documented, ongoing quality assurance program that monitors personnel performance, equipment, and facilities. The end product shall be examined on a periodic sampling basis as determined by the pharmacist-in-charge to assure that it meets required specifications. The Quality Assurance Program shall include at least the following: (1) Cleaning and sanitization of the parenteral medication preparation area.
	† All cleaning materials, such as wipers, sponges, and mops, shall be nonshedding, preferably composed of synthetic microfibers, and dedicated to use in the buffer area, or ante-area, and segregated compounding areas and shall not be removed from these areas except for disposal.	**Not Specifically Addressed**
	† If cleaning materials are reused (e.g., mops), procedures shall be developed (based on manufacturer recommendations) that ensure that the effectiveness of the cleaning device is maintained and repeated use does not add to the bioburden of the area being cleaned.	**Not Specifically Addressed**
	† Supplies and equipment removed from shipping cartons shall be wiped with a suitable disinfecting agent (e.g., sterile 70% IPA) delivered from a spray bottle or other suitable delivery method.	**Not Specifically Addressed**
	† After the disinfectant is sprayed or wiped on a surface to be disinfected, the disinfectant shall be allowed to dry, and during this time the item shall not be used for compounding purposes.	**Not Specifically Addressed**
	† Sterile 70% IPA wetted gauze pads or other particle-generating material shall not be used to disinfect the sterile entry points of packages and devices.	**Not Specifically Addressed**

Standard Operating Procedures

Suggested Standard Operating Procedures	† All facilities are required to have these, and they must include at least the items enumerated in this section. The Compounding Facility shall have written, properly approved SOPs designed to ensure the quality of the environment in which a CSP is prepared. The following procedures are recommended:	**1735.5. Compounding Policies and Procedures** (a) Any pharmacy engaged in compounding shall maintain a written policy and procedure manual for compounding that establishes procurement procedures, methodologies for the formulation and compounding of drugs, facilities and equipment cleaning, maintenance, operation, and other standard operating

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		procedures related to compounding. (b) The policy and procedure manual shall be reviewed on an annual basis by the pharmacist-in-charge and shall be updated whenever changes in processes are implemented. (c) The policy and procedure manual shall include the following: (1) Procedures for notifying staff assigned to compounding duties of any changes in processes or to the policy and procedure manual. (2) Documentation of a plan for recall of a dispensed compounded drug product where subsequent verification demonstrates the potential for adverse effects with continued use of a compounded drug product. (3) The procedures for maintaining, storing, calibrating, cleaning, and disinfecting equipment used in compounding, and for training on these procedures as part of the staff training and competency evaluation process. (4) Documentation of the methodology used to test integrity, potency, quality, and labeled strength of compounded drug products. (5) Documentation of the methodology used to determine appropriate expiration dates for compounded drug products. **1735.8. Compounding Quality Assurance** (a) Any pharmacy engaged in compounding shall maintain, as part of its written policies and procedures, a written quality assurance plan designed to monitor and ensure the integrity, potency, quality, and labeled strength of compounded drug products. **1751.3. Sterile Injectable Policies and Procedures.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain a written policy and procedure manual for compounding that includes, in addition to the elements required by section 1735.5, written policies and procedures regarding the following: (1) Compounding, filling, and labeling of sterile injectable compounds. (2) Labeling of the sterile injectable product based on the intended route of administration and recommended rate of administration. (3) Equipment and supplies. (4) Training of staff in the preparation of sterile injectable products. (5) Procedures for handling cytotoxic agents. (6) Quality assurance program. (7) Record keeping requirements. (b) The ingredients and the compounding process for each preparation must be determined in writing before compounding begins and must be reviewed by a pharmacist. (c) Pharmacies compounding sterile injectable products shall have written policies and procedures for the disposal of infectious materials and/or materials containing cytotoxic residues. The written policies and procedures shall describe the pharmacy protocols for cleanups and spills in conformity with local health jurisdiction standards. (d) Pharmacies compounding sterile injectable products from one or more

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		non-sterile ingredients must have written policies and procedures that comply with the following: (1) All written policies and procedures shall be immediately available to all personnel involved in these activities and board inspectors. (2) All personnel involved must read the policies and procedures before compounding sterile injectable products, and any additions, revisions, and deletions to the written policies and procedures must be communicated to all personnel involved in sterile compounding. (3) Policies and procedures must address at least the following: (A) Competency evaluation. (B) Storage and handling of products and supplies. (C) Storage and delivery of final products. (D) Process validation. (E) Personnel access and movement of materials into and near the controlled area. (F) Use and maintenance of environmental control devices used to create the critical area for manipulation of sterile products (e.g., laminar-airflow workstations, biological safety cabinets, class 100 cleanrooms, and barrier isolator workstations). (G) Regular cleaning schedule for the controlled area and any equipment in the controlled area and the alternation of disinfectants. Pharmacies subject to an institutional infection control policy may follow that policy as it relates to cleaning schedules and the alternation of disinfectants in lieu of complying with this subdivision. (H) Disposal of packaging materials, used syringes, containers, and needles to enhance sanitation and avoid accumulation in the controlled area.. (I) For sterile batch compounding, written policies and procedures must be established for the use of master formulas and work sheets and for appropriate documentation. (J) Sterilization. (K) End-product evaluation and testing. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain, as part of its written policies and procedures, a written quality assurance plan including, in addition to the elements required by section 1735.8, a documented, ongoing quality assurance program that monitors personnel performance, equipment, and facilities. The end product shall be examined on a periodic sampling basis as determined by the pharmacist-in-charge to assure that it meets required specifications.
	1. Access to the buffer area is restricted to qualified personnel with specific responsibilities or assigned tasks in the compounding area.	**1751.3. Sterile Injectable Policies and Procedures.** (3) Policies and procedures must address at least the following: (E) Personnel access and movement of materials into and near the controlled area.
	2. All cartoned supplies are decontaminated in the area by removing them from shipping cartons and wiping or spraying them with a nonresidue-generating disinfecting agent while	**1751.3. Sterile Injectable Policies and Procedures.** (3) Policies and procedures must address at least the following: (H) Disposal of packaging materials, used syringes, containers, and needles

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	they are being transferred to a clean and properly disinfected cart or other conveyance for introduction into the buffer area. Manufacturer's directions or published data for minimum contact time will be followed/individual pouched sterile supplies need not be wiped because the pouches can be removed as these sterile supplies are introduced into the buffer area.	to enhance sanitation and avoid accumulation in the controlled area.
	3. Supplies that are required frequently or otherwise needed close at hand but not necessarily needed for the scheduled operations of the shift are decontaminated and stored on shelving in the ante-area.	**Not Specifically Addressed**
	4. Carts used to bring supplies from the storeroom cannot be rolled beyond the demarcation line in the ante-area, and carts used in the buffer area cannot be rolled outward beyond the demarcation line unless cleaned and disinfected before returning.	**Not Specifically Addressed**
	5. Generally, supplies required for the scheduled operations of the shift are wiped down with an appropriate disinfecting agent and brought in the buffer area, preferably on one or more movable carts. Supplies that are required for back-up for general support of operations may be stored on the designated shelving in the buffer area, but excessive amounts of supplies are to be avoided.	**1250.4 Compounding Area for Parenteral Solutions.** The pharmacy shall have a designated area for the preparation of sterile products for dispensing which shall: 3. The pharmacy shall be arranged in such a manner that the laminar-flow hood is located in an area which is exposed to minimal traffic flow, and is separate from any area used for bulk storage of items not related to the compounding of parenteral solution. There shall be sufficient space, well separated from the laminar-flow hood area, for the storage of bulk materials, equipment and waste materials.
	6. Nonessential objects that shed particles shall not be brought into the buffer area, including pencils, cardboard cartons, paper towels, and cotton items (e.g., gauze pads).	**Not Specifically Addressed**
	7. Essential paper-related products (e.g. paper syringe overwraps, work records contained in protective sleeve) shall be wiped down with an appropriate disinfecting agent prior to being brought into the buffer area.	**State Law Addresses Equipment but Makes No Specific Mention of Essential Paper-related Products.**
	8. Traffic flow in and out of the buffer area shall be minimized.	**1751.3. Sterile Injectable Policies and Procedures.** (3) Policies and procedures must address at least the following: (E) Personnel access and movement of materials into and near the controlled area.
	9. Personnel preparing to enter the buffer area shall remove all personal outer garments, cosmetics (because they shed flakes and particles), and all hand, wrist, and other visible jewelry or piercings that can interfere with the effectiveness of PPE.	**State Law Only Addresses Garbing Requirements for Sterile Preparations Made from One or More Non-sterile Ingredients and Cytotoxic agents.**
	10. Personnel entering the ante-area shall don attire described in *Personnel Cleansing and Garbing and Personnel Training and Competency Evaluation of Garbing, Aseptic Work Practices and Cleaning/Disinfection Procedures.*	**1751.4. Facility and Equipment Standards for Sterile Injectable Compounding** (b) During the preparation of sterile injectable products, access to the designated area or cleanroom must be limited to those individuals who are properly attired.
	11. Personnel shall then thoroughly wash hands and forearms to	**Not Specifically Addressed**

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	the elbow with soap and water for at least 30 seconds. An air dryer or disposable nonshedding towels are used to dry hands and forearms after washing.	
	12. Personnel entering the buffer area shall perform antiseptic hand cleansing prior to donning sterile gloves using waterless alcohol-based surgical hand scrub with persistent activity.	**Not Specifically Addressed**
	13. Chewing gum, drinks, candy, or food items shall not be brought into the buffer area or ante-area. Materials exposed in patient care and treatment areas shall never be introduced into areas where components and ingredients for CSPs are present.	**Not Specifically Addressed**
	14. At the beginning of each compounding activity session, and whenever liquids are spilled, the surfaces of the direct compounding environment are first cleaned with USP Purified Water to remove water-soluble residues. Immediately thereafter, the same surfaces are disinfected with a nonresidue-generating agent using a nonlinting wipe.	**Not Specifically Addressed**
	15. Primary engineering controls shall be operated continuously during compounding activity. When the blower is turned off and before other personnel enter to perform compounding activities, only one person shall enter the buffer area for the purposes of turning on the blower (for at least 20 minutes) and disinfecting the work surfaces.	**Not Specifically Addressed**
	16. Traffic in the area of the DCA is minimized and controlled.	**1751.3. Sterile Injectable Policies and Procedures.** (3) Policies and procedures must address at least the following: (E) Personnel access and movement of materials into and near the controlled area.
	17. Supplies used in the DCA for the planned procedures are accumulated and then decontaminated by wiping or spraying the outer surface with sterile 70% IPA or removing the outer wrap at the edge of the DCA as the item is introduced into the aseptic work area.	**Not Specifically Addressed**
	18. All supply items are arranged in the DCA so as to reduce clutter and provide maximum efficiency and order for the flow of work.	**Not Specifically Addressed**
	19. After proper introduction into the DCA of supply items required for and limited to the assigned operations, they are so arranged that a clear, uninterrupted path of HEPA-filtered air will bathe all critical sites at all times during the planned procedures. That is, no objects may be placed between the first air from HEPA filters and an exposed critical site.	**Not Specifically Addressed**
	20. All procedures are performed in a manner designed to minimize the risk of touch contamination. Gloves are disinfected with adequate frequency with an approved disinfectant such as sterile 70% IPA.	**Not Specifically Addressed**
	21. All rubber stoppers of vials and bottles and the necks of ampuls are disinfected by wiping with sterile 70% IPA and	**Not Specifically Addressed**

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	waiting for at least 10 seconds before they are used to prepare CSPs.	
	22. After the preparation of every CSP, the contents of the container are thoroughly mixed and then inspected for the presence of particulate matter, evidence of incompatibility, or other defects.	**1735.2. Compounding Limitations and Requirements; Self-Assessment** (d) A drug product shall not be compounded until the pharmacy has first prepared a written master formula record that includes at least the following elements: (4) Quality reviews required at each step in preparation of the drug. (5) Post-compounding process or procedures required, if any. (f) The pharmacist performing or supervising compounding is responsible for the integrity, potency, quality, and labeled strength of a compounded drug product until it is dispensed. **1735.8. Compounding Quality Assurance** (a) Any pharmacy engaged in compounding shall maintain, as part of its written policies and procedures, a written quality assurance plan designed to monitor and ensure the integrity, potency, quality, and labeled strength of compounded drug products. (b) The quality assurance plan shall include written procedures for verification, monitoring, and review of the adequacy of the compounding processes and shall also include written documentation of review of those processes by qualified pharmacy personnel. (c) The quality assurance plan shall include written standards for qualitative and quantitative integrity, potency, quality, and labeled strength analysis of compounded drug products. All qualitative and quantitative analysis reports for compounded drug products shall be retained by the pharmacy and collated with the compounding record and master formula. (d) The quality assurance plan shall include a written procedure for scheduled action in the event any compounded drug product is ever discovered to be below minimum standards for integrity, potency, quality, or labeled strength. **1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.** (a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain, as part of its written policies and procedures, a written quality assurance plan including, in addition to the elements required by section 1735.8, a documented, ongoing quality assurance program that monitors personnel performance, equipment, and facilities. The end product shall be examined on a periodic sampling basis as determined by the pharmacist-in-charge to assure that it meets required specifications.
	23. After procedures are completed, used syringes, bottles, vials and other supplies are removed, but with a minimum of exit and reentry into the DCA so as to minimize the risk of introducing contamination into the aseptic workspace.	**State law addresses disposal of equipment and materials but makes no mention of minimum of exit and reentry into the DCA**

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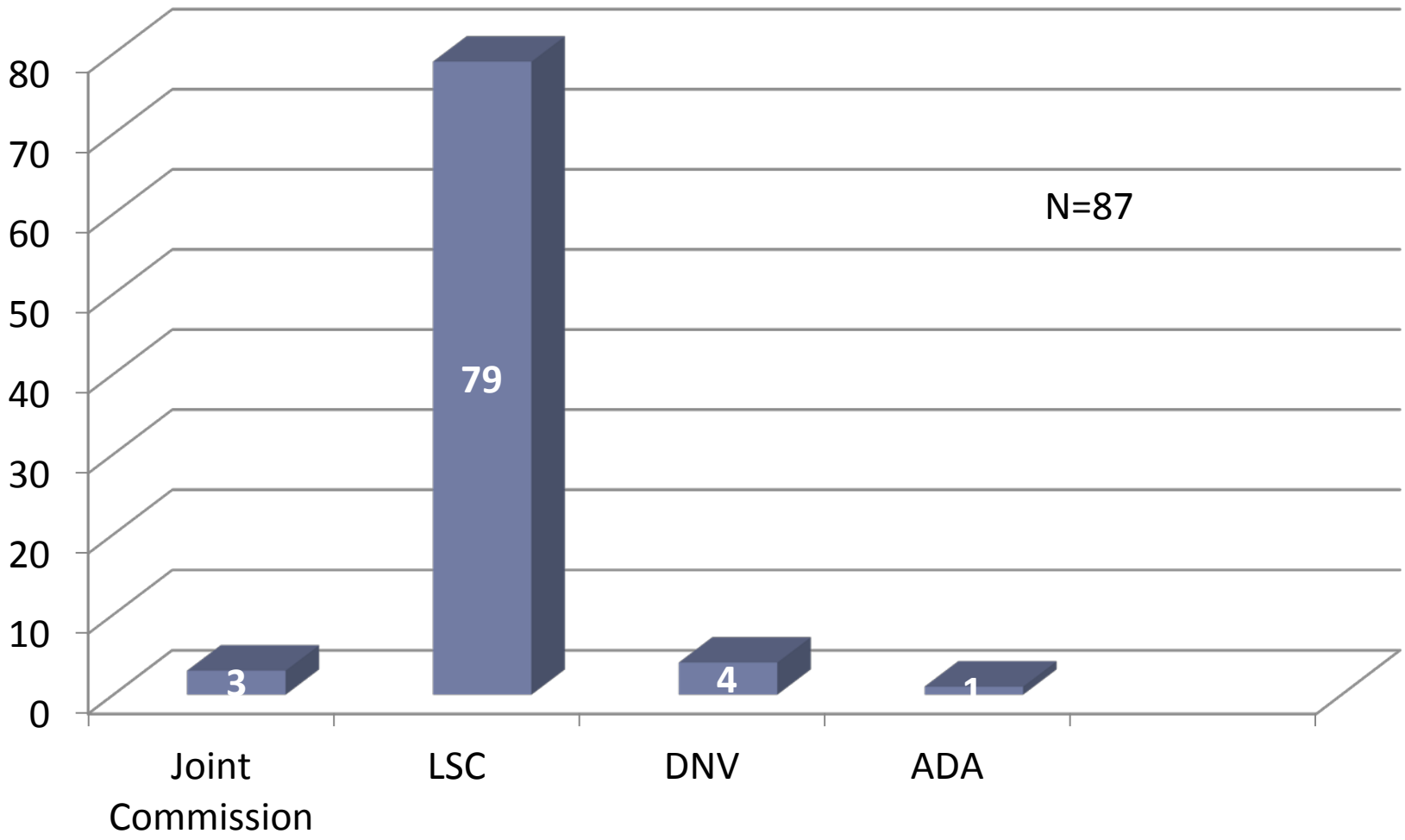
ATTACHMENT 11

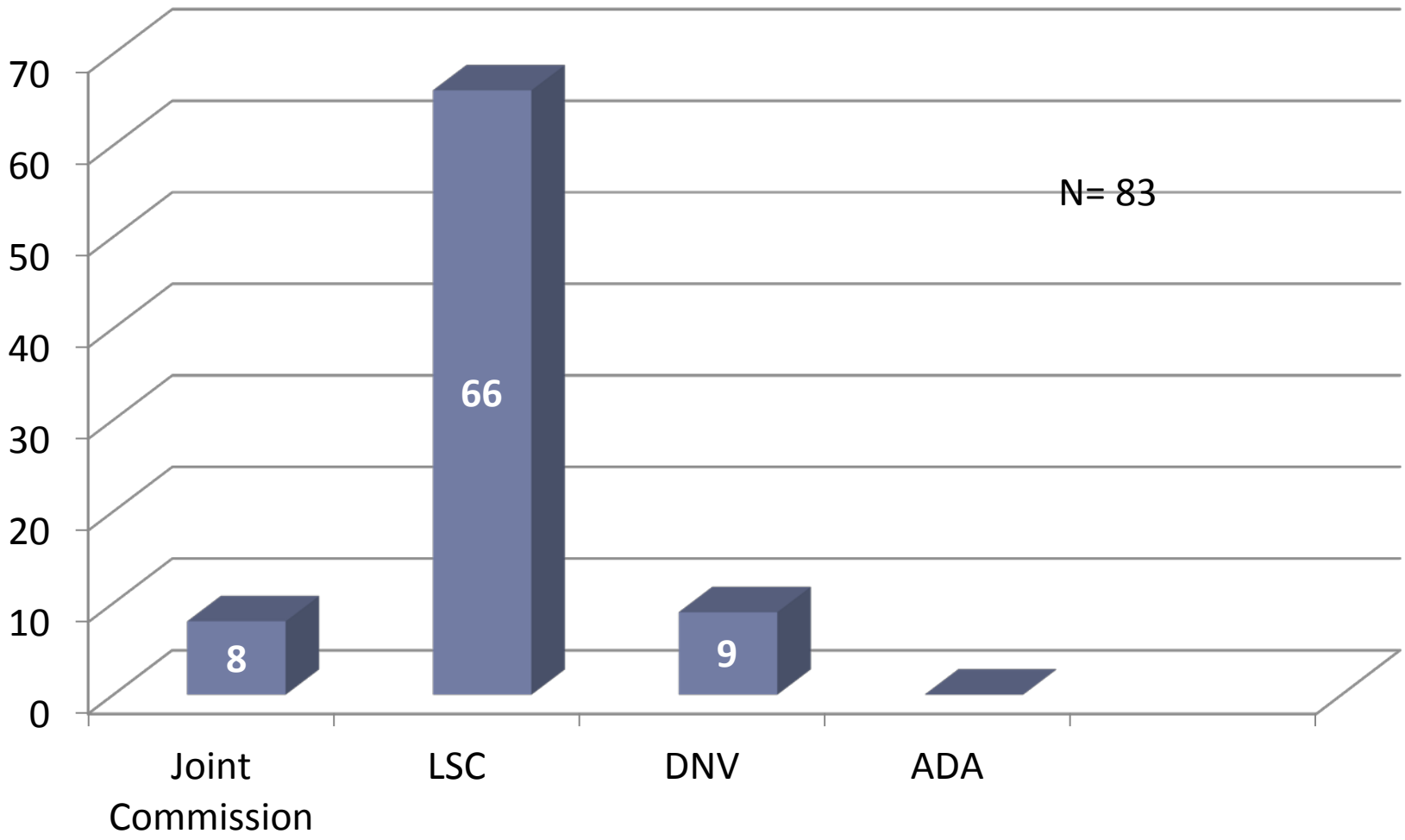
Recent BOP Sterile Compounding Inspection Results

87 pharmacies – all located within California

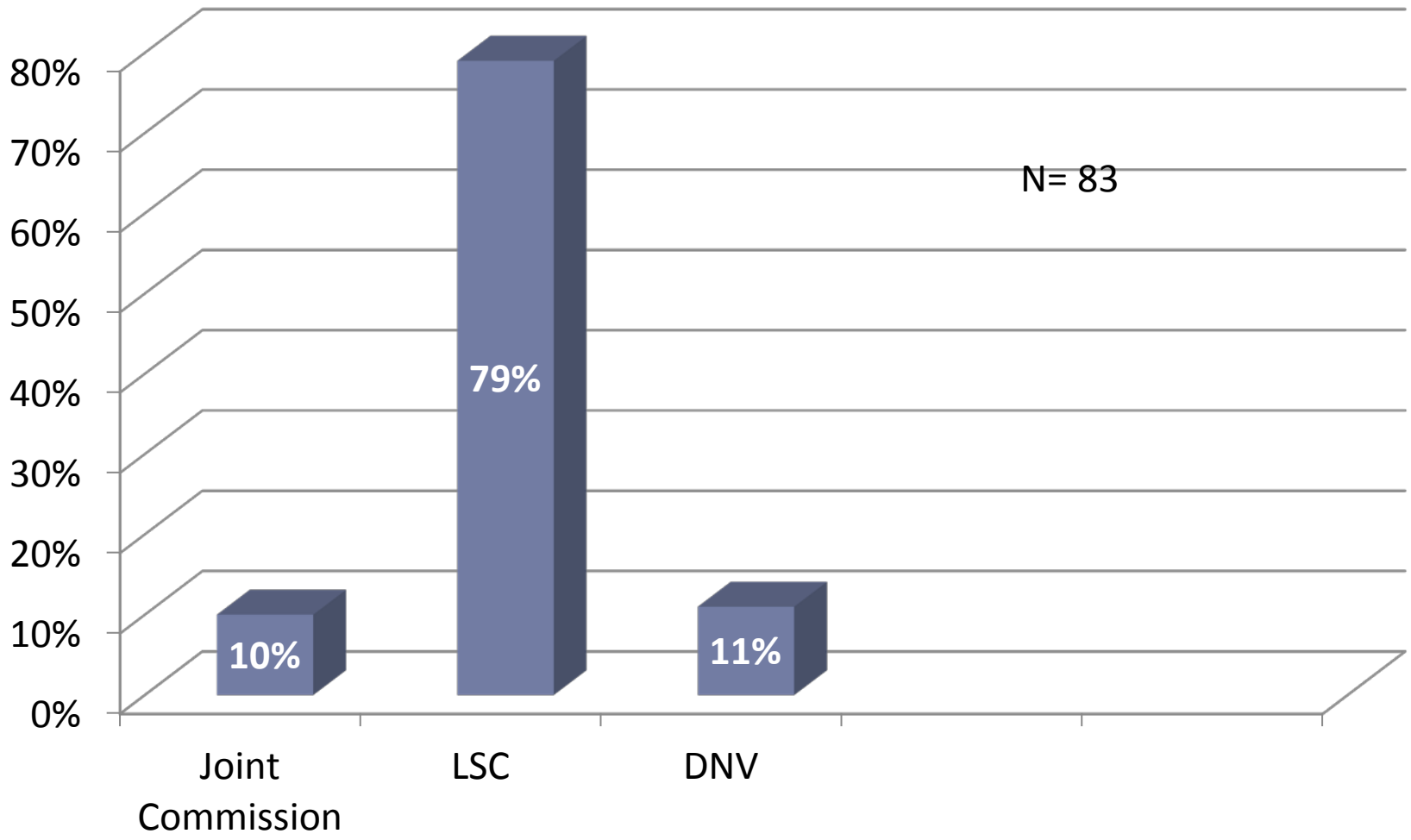
Recent Inspections- By Accreditation Type



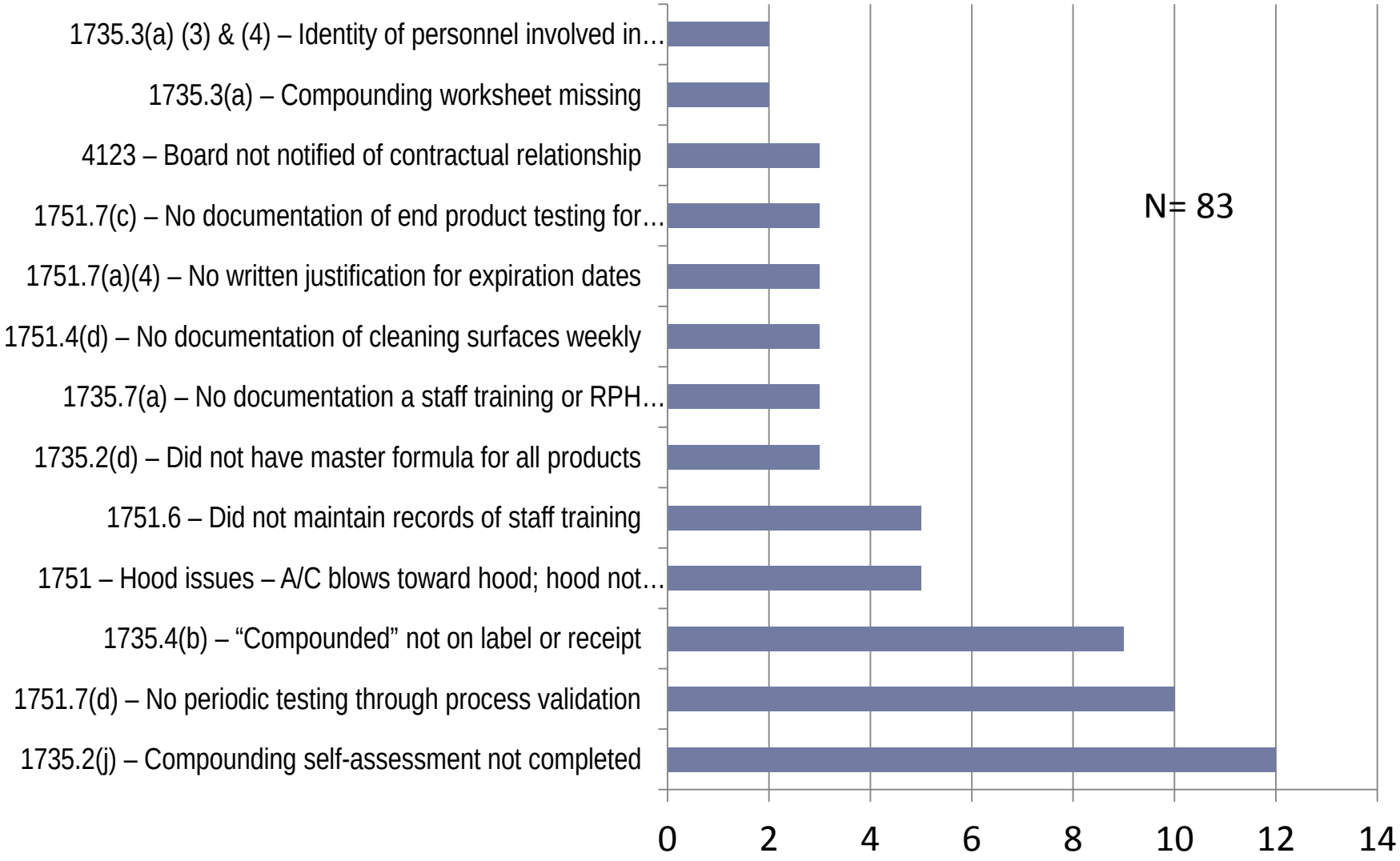
Corrections Issued for Recent Inspections By Accreditation Type



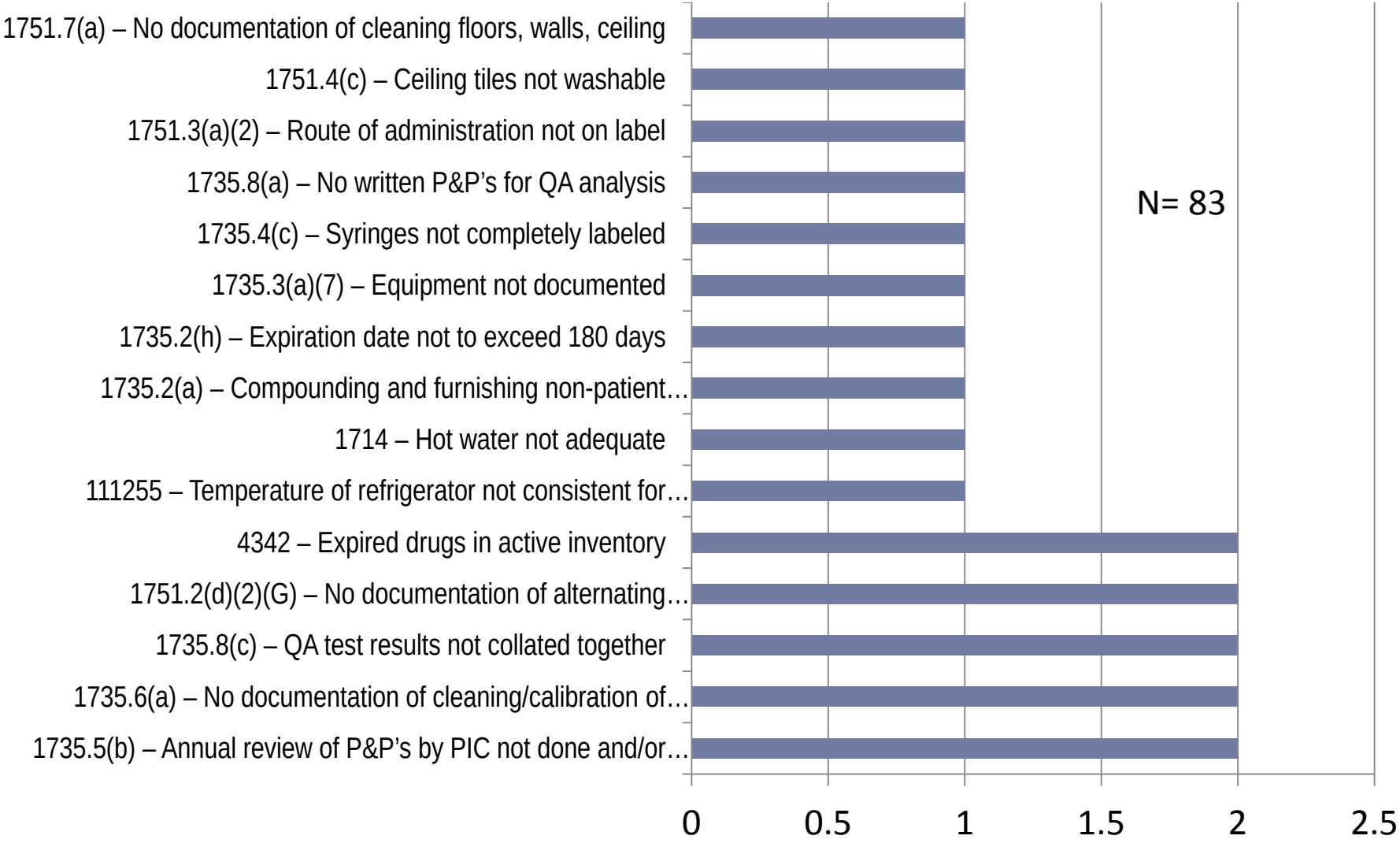
Total Corrections Issued
Percentage By Accreditation Type



Consolidated Inspection Report Citation Data



Consolidated Inspection Report Citation Data Continued



ATTACHMENT 12

California State Board of Pharmacy
1625 N. Market Blvd, N219, Sacramento, CA 95834
Phone: (916) 574-7900
Fax: (916) 574-8618
www.pharmacy.ca.gov

BUSINESS, CONSUMER SERVICES AND HOUSING AGENCY
DEPARTMENT OF CONSUMER AFFAIRS
GOVERNOR EDMUND G. BROWN JR.

STATE BOARD OF PHARMACY
DEPARTMENT OF CONSUMER AFFAIRS
ENFORCEMENT COMMITTEE MEETING
MINUTES

DATE: June 4, 2013

LOCATION: DCA Headquarters
1625 N Market Blvd – Hearing Room
Sacramento, CA 95834

COMMITTEE MEMBERS PRESENT:
Amy Gutierrez, PharmD, Chair
Rosalyn Hackworth, Public Member
Randy Kajioka, PharmD
Victor Law, RPh
Gregg Lippe, Public Member

COMMITTEE MEMBERS NOT PRESENT: Tappan Zee, Public Member

STAFF PRESENT:
Virginia Herold, Executive Officer
Robert Ratcliff, PharmD, Supervising Inspector
Rob Buckner, Manager, Criminal Investigations
Carolyn Klein, Manager, Legislation and Regulations
Kristy Shellans, DCA Senior Staff Counsel

The meeting was called to order at 9:30. Dr. Gutierrez, Chair, welcomed those in attendance. Roll call was taken and a quorum was established.

I. <u>Enforcement Matters</u>:

a. Enforcement and Compounding Committee Meeting Dates for the Remainder of 2013

Future Enforcement and Compounding Committee meetings are scheduled for September 10, 2013 and December 3, 2013. These dates are subject to change.

b. Discussion on Whether Emerging Technologies Necessitate Revisions to Title 16, Section 1713 of the California Code of Regulations

Background

Several years ago, the board promulgated regulations (16 California Code of Regulation section 1713) to allow for the use of automated delivery devices, which are markedly like vending machines, to permit the furnishing of refill medication in specified circumstances. These circumstances include, that the patient must opt in to use the machine, the medication to be refilled through the machine is appropriate. The conditions are listed below in the highlighted segment of section 1713.

1713. *Receipt and Delivery of Prescriptions and Prescription Medications Must be To or From Licensed Pharmacy*

(a) Except as otherwise provided in this Division, no licensee shall participate in any arrangement or agreement, whereby prescriptions, or prescription medications, may be left at, picked up from, accepted by, or delivered to any place not licensed as a retail pharmacy.

(b) A licensee may pick up prescriptions at the office or home of the prescriber or pick up or deliver prescriptions or prescription medications at the office of or a residence designated by the patient or at the hospital, institution, medical office or clinic at which the patient receives health care services. In addition, the Board may, in its sole discretion, waive application of subdivision (a) for good cause shown.

(c) A patient or the patient's agent may deposit a prescription in a secure container that is at the same address as the licensed pharmacy premises. The pharmacy shall be responsible for the security and confidentiality of the prescriptions deposited in the container.

(d) A pharmacy may use an automated delivery device to deliver previously dispensed prescription medications provided:

(1) Each patient using the device has chosen to use the device and signed a written consent form demonstrating his or her informed consent to do so.

(2) A pharmacist has determined that each patient using the device meets inclusion criteria for use of the device established by the pharmacy prior to delivery of prescription medication to that patient.

(3) The device has a means to identify each patient and only release that patient's prescription medications.

(4) The pharmacy does not use the device to deliver previously dispensed prescription medications to any patient if a pharmacist determines that such patient requires counseling as set forth in section 1707.2(a)(2).

(5) The pharmacy provides an immediate consultation with a pharmacist, either in-person or via telephone, upon the request of a patient.

(6) The device is located adjacent to the secure pharmacy area.

(7) The device is secure from access and removal by unauthorized individuals.

(8) The pharmacy is responsible for the prescription medications stored in the device.

(9) Any incident involving the device where a complaint, delivery error, or omission has occurred shall be reviewed as part of the pharmacy's quality assurance program mandated by Business and Professions Code section 4125.

(10) The pharmacy maintains written policies and procedures pertaining to the device as described in subdivision (e).

(e) Any pharmacy making use of an automated delivery device as permitted by subdivision (d) shall maintain, and on an annual basis review, written policies and procedures providing for:

(1) Maintaining the security of the automated delivery device and the dangerous drugs within the device.

(2) Determining and applying inclusion criteria regarding which medications are appropriate for placement in the device and for which patients, including when consultation is needed. 1

(3) Ensuring that patients are aware that consultation with a pharmacist is available for any prescription medication, including for those delivered via the automated delivery device.

(4) Describing the assignment of responsibilities to, and training of, pharmacy personnel regarding the maintenance and filing procedures for the automated delivery device.

(5) Orienting participating patients on use of the automated delivery device, notifying patients when expected prescription medications are not available in the device, and ensuring that patient use of the device does not interfere with delivery of prescription medications.

(6) Ensuring the delivery of medications to patients in the event the device is disabled or malfunctions.

(f) Written policies and procedures shall be maintained at least three years beyond the last use of an automated delivery device.

(g) For the purposes of this section only, "previously-dispensed prescription medications" are those prescription medications that do not trigger a non-discretionary duty to consult under section 1707.2(b)(1), because they have been previously dispensed to the patient by the pharmacy in the same dosage form, strength, and with the same written directions.

In 2009-10, Pharmacist Consultant Philip Burgess, on behalf of a manufacturer of one of these machines (Asteres), sought an exemption to permit the use of these machines in areas away from adjacent to the licensed pharmacy premises. The board did not approve the request, and requested more information about how and where the kiosks would be used. One concern was that the board considered that it lacked the ability to provide the exemption sought (which would have required a regulation change).

At the Committee's March 14, 2013 meeting, Mr. Carter, representing Walgreens, discussed a request that would allow for Walgreens to place kiosks in workplace clinics. Mr. Carter provided an overview of the types of services that are provided at the clinic and how Walgreens would provide medication. Mr. Carter highlighted that the kiosk would not be stored in the clinic, but would be housed across the street in a separate building. The Board did not approve the request, indicating there was insufficient evidence to act.

Presentation and Discussion:

Representatives from Asteres, Inc., and Sharp HealthCare discussed the need to revise section 1713 and presented a request to allow three separate pilot studies on the campuses of Sharp, UCSD Health System and USC Hospital to review the use of automated delivery devices. Mr. Burgess, representing Asteres, Inc. reminded the Board that section 1713(b) already allows the delivery of prescriptions to employees at their worksite.

Mr. Burgess proposed to revise section 1713(d)(6) to allow for the placement of automated devices in a secure building controlled by a Board licensee at an alternate location readily accessible for Board inspection, but not adjacent to a secure pharmacy area.

Mr. Lippe and Dr. Gutierrez asked whether the devices would be on the premises of the licensee. The answer was that the devices would not have to be on the premises of a licensee but could be at corporate offices, for example, a non-licensed facility.

Mr. Burgess also proposed to revise section 1713(d) to also allow the dispensing of new prescriptions delivered from automated devices, provided consultation has taken place and proper documentation has been reviewed and saved. He explained that the Asteres system allows the ability to load filled prescriptions in the device and lock them in the device. The prescriptions would not be released to the patients until the patients had been counseled by a pharmacist via telephone (adjacent to the device). Mr. Burgess indicated the devices could also be used for prescription refills.

Mr. Burgess then provided photos of automated devices already in operation at an Air Force Base in El Segundo (Installed 2009) and St Joseph's Hospital in Phoenix, Arizona (Installed 2011) where employee utilization of the device had grown from 13 percent to 44 percent.

Mr. Lippe asked if the devices were tamper proof. The Board heard comments that security measures include a camera in the device which takes a photo of every patient, required signatures and the fact that the device itself is bolted to the floor and weighs over 1,350 pounds. More than 700,000 prescriptions have been delivered without incident. Representatives from Sharp HealthCare indicated they have seven hospitals, seven retail pharmacies and 22 clinics in San Diego serving 200,000 patients. Sharp believes the automated devices align with their vision of providing patient/employee-centered care to

the 3000 employees who work in their corporate offices. Although their pharmacy is only two miles away, getting to the pharmacy can be difficult due to work schedules and heavy traffic. She believes the automated devices would easier and more convenient for employees to pick up their medications. Representatives from Sharp HealthCare provided photos of the proposed location for the automated device and indicated that the building in which the device would be placed has 24-hour security and requires a badge for entry.

Ms. Herold asked how a prescription gets to a pharmacy two miles away and was advised a prescription would get to the pharmacy as any other. Ms. Herold was also advised that a patient could drop off a paper prescription in a slot in the device. The paper prescription would be picked up and delivered to a pharmacy when the device is serviced during the day.

Ms. Shellans stated she did not think the Board could act on the request because current law does not allow for the storage of dangerous drugs at a location not licensed by the Board. Mr. Burgess argued that current law allows for the delivery of prescription medications to a patient at his or her office and that the Board should focus on delivery of medications as opposed to the storage of medications.

Dr. Gutierrez asked whether all seven Sharp pharmacies would be depositing prescriptions in the automated devices and was advised that it was Sharp's plan to have only one pharmacy responsible for filling and delivering prescriptions to an automated device. She also introduced another proposal in which Sharp would use the same pharmacy to deliver prescriptions an automated device located at Sharp Memorial Hospital Campus to dispense discharge medications. Sharp envisions a patient being counseled by a Pharmacist at the bedside or over the phone, obtaining an access code, then being discharged and obtaining their prescription from the automated device. The device allows for the use of a credit or debit card for payment.

Dr. Gutierrez asked if Sharp provided mail delivery and was advised that Sharp provides next-day home delivery via mail, but prefers delivery via an automated device because the device is secure in that it allows for the tracking of who picks up their medications and who does not.

Dr. Kajioka asked how long delivery transaction data are kept on file. Mr. Burgess answered that data is kept forever and there is no purge criteria. Data includes a full audit trail which includes a photo of the person picking up the prescription and the signature log. He believes the control and accuracy associated with prescription deliveries via automated device is much better than normal.

Mr. Burgess stated UC San Diego and USC couldn't appear at the meeting, but would like to appear at the full Board meeting in July to discuss proposed changes to section 1713.
Dr. Gutierrez advised the presenters to create a formal proposal for the Board to review.
Ms. Herold indicated Board would also need to see some parameters from the school explaining parts such as what measurements they would take and how long the pilot study

would last. Ms. Herold stated that the UC San Diego conducted the initial pilot and that contacting them might be helpful. Also, because the requirements and concerns raised varied due to whether a proposed location was licensed or not, Ms. Herold advised the presenters to break up their proposals so the Board could address each individually.

Ms. Herold stated that the Board has limited authority to waive a regulation based on an experimental program pursuant to the requirements listed in section California Code of Regulations Section 1706.5. The results of the experimental program would have to demonstrate to the Board that the automated device is safe and that a regulation revision would be advantageous.

Motion: Recommend to Board that it consider moving forward with an experimental program/research study once UC San Diego and USC can develop and submit a specific proposal.

M/S: Lippe/Hackworth
Support: 5 Oppose: 0 Abstain: 0

c. Request from California Society of Health-System Pharmacists to Discuss Drug Shortages

Background

At the March 13, 2013, Committee meeting, Jonathon Nelson, representing the California Society of Health-System Pharmacists (CSHP), addressed the Committee to discuss the drug shortages and requested the topic be discussed at a future meeting.

Presentation and Discussion

Jonathan Nelson, representing CSHP, thanked the Committee for giving him the opportunity to discuss the crisis of drug shortages. He shared an article from the Washingtonian Magazine which detailed rationing, hoarding and bartering of medications in Washington area hospitals.

Maria Serpa, a Pharmacist at Sutter Medical Center, Sacramento, addressed the Committee and shared her experiences with drug shortages and how they are impacting patients everyday. She and her team monitor and anticipate drug shortages, constantly look for alternative drug sources and medications, create back orders with wholesalers, and when necessary, begin rationing. She provided examples of times when her team has sent drugs to other healthcare centers that were completely out of specific drugs. The shortages have created an informal bartering system where healthcare centers share drugs with each other.

Dr. Serpa also shared a recent New England Journal article that outlined a study in which first line standard treatments for cancer became a drug shortage problem. Researchers

switched the patients to an equivalent treatment to deal with the shortage. When researchers reviewed the results of the alternative equivalent therapies, they found that patients had a significant increase in cancer recurrence.

Mr. Lippe asked why there are shortages now. Dr. Serpa answered that there are multiple reasons including financial decisions which result in a dropped product line; drugs dropped from the market due to regulatory issues; and short supplies of raw product used in drug production.

Dr. Gutierrez stated that President Obama issued an Executive Order in 2011 to have the FDA begin tackling the issue of drug shortages. Mr. Nelson indicated the Food and Drug Administration (FDA) is working with manufacturers to identify the reasons for drug shortages and address those issues.

Mr. Lippe asked whether a database could be created so healthcare centers would more easily locate other healthcare centers with a surplus of the specific drug. Ms. Herold stated brokering drugs between facilities on a large scale would require a license to prevent people from moving drugs through the gray market. A pharmacy, for instance, is only allowed to sell drugs back to the wholesaler with some limited exceptions, one of which being drug shortages.

Mr. Herold stated she was not sure what the Board could do to address the problem. Dr. Serpa suggested the Board, as well as other associations, could provide information regarding the seriousness of the problem and different methods of dealing with drug shortages before and after they arise.

Public Comment

The Board heard public comment regarding a pending law which will create a Compounded Manufacturing License issued by the FDA. The Board also heard public comment regarding the possibility of relying more on compounding pharmacies to fill the need during times of drug shortages as well as the need for state and federal government to oversee the safety of compounding manufacturing while also allowing flexibility in allowing compounding manufacturers to fill an important need.

d. Implementation of Penal Code section 11105 – Board Requirement to Provide Criminal Offender Record Information to an Applicant or Licensee When the Information is Used as the Basis for a Licensing Decision

Background

As part of its licensing process, the Board is required to conduct a criminal background check to determine whether an applicant has committed acts that would constitute grounds for denial of a license. Applicants must submit their fingerprints to the California

Department of Justice (DOJ) who then matches the fingerprints against state and federal criminal history databases. The DOJ provides the results of the background check to the Board who uses the information to help determine the suitability of the applicant for licensure. The Board also receives a notice from the DOJ when a licensee is arrested in California subsequent to initial licensure.

Penal Code section 11105 authorizes the DOJ to release criminal offender record information (CORI) to law enforcement and other authorized agencies such as the Board. The Board cannot share criminal offender record information (CORI), including responses that indicates no criminal history exists, with anyone unless expressly authorized. Individuals have the right to request a copy of their own criminal history record from the DOJ to review for accuracy and completeness, but CORI is not subject to disclosure under the Public Records Act. Release of information to unauthorized individuals can result in civil or criminal penalties pursuant to Penal Code sections 11142 and 11143.

Effective January 1, 2013, however, Penal Code section 11105 (Amended by Stats. 2012, c. 256, A.B. 2343) requires authorized agencies to expeditiously furnish a copy of CORI to the person to whom the information relates if the information is the basis for an adverse employment, licensing or certification decision.

The Board implemented procedures on January 1, 2013, to comply with this new requirement and since that time has provided a copy of the CORI to every applicant who has been denied and every licensee who has received a Letter of Admonishment, Citation or has been referred to the Attorney General's office for disciplinary action based, to some degree, on information contained in the CORI.

Discussion and Comment

Chair Gutierrez provided information on the new law and the board's implementation. There were no questions or comments from the Committee or public.

e. National Association of Boards of Pharmacy Report on Sales of Fake and Substandard Medications

Background

The National Association of Boards of Pharmacy (NABP) issued a report on April 26, 2013 which focused on the global distribution of counterfeit and substandard medications. The report found that the proliferation of these medications was primarily due to illegal distribution by internet pharmacies operating out of compliance with US pharmacy laws. A copy of the report was provided in the meeting materials, and can also be found on the NAB website at:
https://awarerx.s3.amazonaws.com/system/redactor_assets/documents/179/NABP_Internet_Drug_Outlet_Report_Apr2013.pdf

Discussion:

Ms. Herold stated the Board has a very limited role in regulating internet pharmacies short of disciplining people or businesses for unlicensed activity. Ms. Herold described the video on the Board's website that educates and warns the public about the appropriate way to deal with internet pharmacies. She stated the Board rarely gets complaints regarding internet pharmacies because the people using them are happy to get their drugs without a prescription or without having to see a prescriber. The Board generally receives complaints only when there's a problem regarding continuing shipping or billing and identity fraud. When the Board receives complaints, they are generally referred to the National Association of Boards of Pharmacy and the FDA.

Dr. Gutierrez mentioned consumers can look for **Verified Internet Pharmacy Practice Sites *(VIPPS)*** symbol on the website which indicates that the internet pharmacy has completed the NABP accreditation classes and is licensed in the state in which they're located.

Public Comment

There were no questions or comments from the public.

f. NABP Announces Development of Standards for the .pharmacy Generic Top Level Domain for Internet Pharmacy Web Sites

Background

According to the NABP, which monitors Web sites selling prescription drugs among its various programs, 97 percent of the 10,300 Internet drug outlets it has reviewed are out of compliance with pharmacy laws and practice standards in the US established to protect patients. Correspondingly, NABP has labeled as "Not Recommended" 10,082 Web sites; nearly half of these are offering foreign or non-FDA approved drugs, and many include counterfeits.

Generic top level domains are the suffix part of a Web site address (e.g., .com, .org, .edu). Late last year, the NABP sought the formal approval to be able to approve anyone using the general top level domain (gTLD) of .pharmacy. Earlier this year, an international group of experts were convened by the NABP to develop parameters for anyone that would be able to use the .pharmacy gTLD. The board's executive officer was one of the individuals who participated in this process, and the intent is to have the parameters for the .pharmacy gTLD in place by the end of 2013. A copy of the NABP press release issued May 21, 2013 was provided in the meeting materials.

Discussion

Ms. Herold stated the Board was one of two state Boards of Pharmacy invited was to participate in the development of the .pharmacy internet domain.

Public Comment

There were no questions or comments from the public.

Break for lunch 11:30 – 12:32

II. Compounding Matters

a. Discussion on Pending California Legislation on Sterile Compounding: Senate Bill 294 (Emmerson) and Assembly Bill 1045 (Quirk-Silva)

Background

Following two large-scale public health emergencies last year in which dangerous products compounded by two out-of-state pharmacies were shipped nationwide, staff suggested modifying existing sterile compounding requirements in California. As a result, Senator Emmerson has authored Senate Bill 294 (SB 294) to carry this Board-sponsored legislation.

Senate Bill 294 will strengthen the Board's ability to regulate and monitor pharmacies that compound sterile drug products. This legislation would prohibit a pharmacy from compounding or dispensing, and a nonresident pharmacy from compounding for shipment into this state, sterile drug products for injection, administration into the eye, or inhalation, unless the pharmacy has obtained a sterile compounding pharmacy license from the board.

Additionally, on April 22, 2013, Assembly Member Quirk-Silva amended Assembly Bill 1045 to carry provisions that would amend existing law to allow the Board to suspend or revoke a nonresident pharmacy's license if its license is suspended or revoked in the pharmacy's home state. It would also require resident and nonresident pharmacies that issue a recall notice regarding a sterile compounded drug to contact the recipient pharmacy, prescriber or patient of the recalled drug and the Board within 24 hours of the recall notice if use of or exposure to the recalled drug may cause serious adverse health consequences or death and if the recalled drug was dispensed or is intended for use in this state.

Discussion

There were no Committee comments.

Public Comment

The Committee heard public comment asking about current licensing requirements. With regard to AB 1045, Ms. Herold clarified that the qualifying method for someone to become licensed as a non-resident pharmacy in California is for the pharmacy to be licensed in the home state. If the license in the home state is revoked, suspended or cancelled for any reason, the California license will correspondingly be revoked, suspended or cancelled by operation of law. Ms. Herold also clarified that the California license could still be disciplined whether or not the license is disciplined in the home state.

b. Discussion of Recent Federal Reports and Articles Relating to Compounding Pharmacies

1. FDA's oversight of NECC and Ameridose: A history of missed opportunities
2. Office of the Inspector General Memorandum Report: High-Risk Sterile Preparations and Outsourcing by Hospitals That Use Them, OEI-01-013-00150
3. ASHP Guidelines on Outsourcing Sterile Compounding Services
4. FDA's Guidance for FDA Staff and Industry – Marketed Unapproved Drugs , Compliance Policy Guide
5. U.S. Senate Health, Education and Pensions Committee Report: The Case for Clarifying FDA Authority: Large-Scale Drug Compounding and the Ongoing Risk to Public Health
6. Miscellaneous Articles

Background

Full articles were provided in the meeting materials.

Discussion

Dr. Gutierrez provided some background and a brief overview of each report and article. There were no questions or comments from the Committee.

Public Comment

There were no questions or comments from the public.

c. Proposed Federal Legislation on Compounding Introduced by the U.S. Senate (S. 959)

Background

On May 22, 2013, the United States Senate Committee on Health Education Labor & Pensions passed S. 959, the *Pharmaceutical Compounding Quality and Accountability Act*. A copy of a statement from Senator Harkin made Wednesday, May 22, 2013, was provided in the meeting materials.

Discussion

Ms. Herold stated the pending Senate legislation is currently linked with the supply chain security provisions which would preempt California's e-pedigree law if enacted. There is competing legislation for the e-pedigree law which just passed the House.

Regarding compounding, non-patient specific drugs moving across state lines into a state would be regulated by the FDA and drugs within a state would be regulated by the state Board. For the most part, the federal legislation is on the same path as California's e-pedigree law.

Public Comment

The Committee heard a public question on whether out-of-state pharmacies are able to ship high-risk sterile injectable compounded drugs. Ms. Herold answered that an out-of-state pharmacy would have to hold a California specialty license or be accredited by one of the accrediting agencies. Further, Ms. Herold indicated that as she reads the Senate Bill, non-patient specific shipping across state lines would cease if the Bill passes.

d. Discussion Regarding USP's 797 Standards and Regulation Requirements of the Board of Pharmacy

Background

For a number of years, California has had its own statutory and regulation requirements for those pharmacies that compound medication or perform parenteral compounding. Since 2001, again through legislation as well as through regulations, the board has several times developed additional requirements to respond to emergent public health or regulatory concerns.

Many states rely upon USP 797 components to regulate compounding activities. California, instead, relies on its own standards for compounders and sterile compounding.

During this segment of the meeting, the Committee will review the components in a crosswalk comparing the two sets of requirements. This crosswalk has been prepared by the Los Angeles County Department of Health Services, and was provided in the meeting materials.

Discussion and Comment

Dr. Ratcliff and Dr. Smith presented the crosswalk and the Committee reviewed and compared the two sets of requirements. Ms. Herold advised that the Committee make sure all the requirements in USP 797 eventually be included in the Board's regulation and that the regulations be written as clearly and concisely as possible for the benefit of everyone.

The Committee and public made several comments regarding the best process for making sure the Board's regulations are inclusive of the requirements in USP 797. In addition the committee heard comments and suggestion regarding the best path forward in its review and recommendations as well as the need to keep in mind that there are instances, therapies, formulations, and practice settings that don't fit into the norm.

Motion: Form subcommittee to work with staff to create third column on crosswalk with proposed regulation changes for public comment.
M/S: Kajioka/Law
Support: 5 Oppose: 0 Abstain: 0

e. <u>Discussion Regarding "Batches"</u>

<u>Background</u>

Board regulations related to compounding are found in Title 16 of the California Code of Regulations, Article 4.5 (all compounding) and Article 7 (related to sterile injectable compounding). On April 1, 2013, regulation changes went into effect that apply to compounding definitions, expiration dating, recordkeeping requirements, and labeling of cytotoxic agents. During this rulemaking, the board was asked what the board's definition of "batch" is, and what requirements apply to batching – but these topics were not within the scope of the regulation change.

At this meeting, the Committee will initiate a new discussion of "batch." The following references are provided for the Committee's information.

Existing Board Regulation

§ 1751.7. Sterile Injectable Compounding Quality Assurance and Process Validation.
(c) Batch-produced sterile injectable drug products compounded from one or more non-sterile ingredients shall be subject to documented end product testing for sterility and pyrogens and shall be quarantined until the end product testing confirms sterility and acceptable levels of pyrogens.
(d) Batch-produced sterile to sterile transfers shall be subject to periodic testing through process validation for sterility as determined by the pharmacist-in-charge and described in the written policies and procedures.

United States Pharmacopeial Convention (USP)
"Batch" – More than 25 units

[1]**American Society of Health System Pharmacists** (ASHP)
Excerpt:
Risk Level 2.

Risk level 2 sterile products exhibit characteristic 1, 2, *or* 3, stated below. All risk level 2 products should be prepared with sterile equipment, sterile ingredients and solutions, and sterile contact surfaces for the final product and with closed-system transfer methods.
[1] American Society of Health-System Pharmacists. ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products. *Am J Health-Syst Pharm.* 2000; 57:1150-69. Available at http://www.ashp.org

Risk level 2 includes the following:
1. Products stored beyond 7 days under refrigeration, stored beyond 30 days frozen, or administered beyond 28 hours after preparation and storage at room temperature.

2. Batch-prepared products *without preservatives* (e.g., epidural products) that are intended for use by more than one patient. (Note: Batch-prepared products without preservatives that will be administered to multiple patients carry a greater risk to the patients than products prepared for a single patient because of the potential effect of inaccurate ingredients or product contamination on the health and well-being of a larger patient group.)

3. Products compounded by complex or numerous manipulations of sterile ingredients obtained from licensed manufacturers in a sterile container or reservoir obtained from a licensed manufacturer by using closed-system aseptic transfer; for example, TPN solutions prepared with an automated compounder. (Note: So many risks have been associated with automated compounding of TPN solutions that its complexity requires risk level 2 procedures.)

Discussion

Dr. Ratcliff stated that the term "batch" is defined as 25 more or by USP 797 and as 10 or more by ASHP. Dr. Ratcliff stated he believed the two numbers were arbitrary and there was no scientific evidence to support either. He has advised that, in the interest of public safety, the batch should be defined as affecting more than one patient.

Dr. Gutierrez stated the Board should adopt the definition of a batch from the CGMP (Current Good Manufacturing Practices from the federal register) which doesn't have a number associated with it. She also said she believed the reason USP came up with 25 was because that's the smallest amount you can sample and actually have any useful data.

Public Comment

The Committee heard another comment that if you're talking about batching, you need to talk about sampling, processes, and process validation.

f. Discussion on the Board of Pharmacy's Questions and Answers Document on Compounding

Background

To provide guidance to pharmacies and others, the board has various "Questions and Answers" on its website in response to questions from practitioners. To reflect recent changes in the board's compounding regulations which took effect April 1, 2013, the Board is in the process of amending some of its "Questions and Answers."

Discussion

There were no questions or comments from the Committee.

Public Comment

The Committee heard one comment in appreciation of the Board's efforts in this area.

g. Outcomes of Recent Sterile Compounding Inspections

Presentation and Discussion

Dr. Ratcliff provided the Committee with a summary of outcomes from recent board inspections of sterile compounding pharmacies. Between January 1, 2013 and mid-May 2013, staff completed 87 inspections. See attached graphs and charts for more specific information.

Public Comment

The Committee heard clarifying questions from the public.

h. Recalls of Compounded Drugs Throughout the United States

Background

Between April 11, 2013 and May 20, 2013, the Board posted seven subscriber alerts related to compounding drug recalls and two subscriber alerts related to cease and desist orders issued. A summary of the alerts are listed below.

- Green Valley Drugs in Henderson, Nevada, voluntarily recalled all lots of sterile products compounded, repackaged, and distributed by the pharmacy due to lack of sterility assurance and concerns associated with the quality control processes.

- ApotheCure, Inc. recalled all lots of sterile products compounded by the pharmacy that are not expired to the user. The recall was initiated due to lack of sterility assurance and concerns associated with the quality control processes.
- NuVision Pharmacy recalled all unexpired lots of lyophilized compounds of HcG 5000IU-5ml and Sermorelin/GHRH6-5ml to the user. The recall was initiated due to the lack of sterility assurance and concerns associated with the quality control processes identified during a FDA inspection.
- Balances Solutions Compounding Pharmacy, LLC recalled all lots of sterile products compounded by the pharmacy that were not expired. The recall was initiated due to concerns associated with quality control processes, which present a lack of sterility assurance.
- Nora Apothecary & alternative Therapies recalled a multi-state recall of all sterile drug products compounded by the pharmacy that have not reached the expiration date listed on the product. The compounded products that are subject to the recall were products within their expiration date that were compounded and dispensed by the pharmacy on or before Friday, April 19, 2013. The recall was initiated due to concerns associated with quality control processes that present a lack of sterility assurance and were observed during a recent FDA inspection.
- The U.S. Food and Drug Administration alerted health care providers, hospital supply managers, and pharmacists that the FDA's preliminary findings of practices at The Compounding Shop of St. Petersburg, Florida, raised concerns about a lack of sterility assurance for sterile drugs produced at and distributed from this site.
- Pentec Health, Inc. initiated a limited recall of in-date nutritional prescriptions for renal patients due to lack of sterility assurance associated with one of its laminar flow hoods used in compounding.
- Southern California Compounding Pharmacy, LLC was issued a cease and desist order on April 19, 2013, for any and all non-sterile compounding.
- Advance Outcome Management Pharmacy Services was issued a cease and desist order on April 29, 2013, from furnishing sterile injectable compounded products.

Discussion and Comment

Chair Gutierrez presented information on the recalls and Board actions. There were no questions or comments from the Committee or public.

Chair Gutierrez adjourned the meeting at 2:42 p.m.