



ENFORCEMENT AND COMPOUNDING COMMITTEE REPORT AUGUST 31, 2016

Amy Gutierrez, PharmD, Chair, Board President

Greg Lippe, Public Member, Vice Chair

Stan Weisser, Professional Member

Allan Schaad, Professional Member

Ricardo Sanchez, Public Member

Valerie Muñoz, Public Member

II. PUBLIC COMMENT FOR ITEMS NOT ON THE AGENDA/AGENDA ITEMS FOR FUTURE MEETINGS

Note: The committee may not discuss or take action on any matter raised during this public comment section that is not included on this agenda, except to recommend whether to place the matter on the agenda of a future meeting. [Government Code Sections 11125, 11125.7(a)]

III. ENFORCEMENT MATTERS

- a. University of California, San Diego's Pilot Program to Permit Patients to Access Medications From an Automated Storage Device Not Immediately Adjacent to the Pharmacy -- Update and Discussion and Consideration of Modifications to the Pilot Program, if Necessary.**

Attachment 1

At the Board of Pharmacy's April 2015 Board Meeting, the board approved an 18-month pilot study under the auspices of the University of California, San Diego (UCSD) School of Pharmacy involving use of an automated storage device for prescription medication from which staff of Sharp Hospital in San Diego and their families, who opted in, could pick up their outpatient medications. Consultation would be provided via telephone before medication could be dispensed to a patient.

At the June 2016 Enforcement and Compounding meeting, Dr. Hirsch delivered a presentation via telephone on the progress of the implementation and reported that the program launched on January 20, 2016.

The kiosk has about 200 users, which is approximately 4 percent of the 4,800 Sharp employees. Additionally, the kiosk has 24-hour video surveillance and on-site monitoring.

Dr. Hirsch's statistics indicated there had been 534 total pickups at the kiosk and 334 of those pickups had been during normal business hours. Additionally, 191 were identified as new prescriptions, 99 were refill prescriptions, and 234 were for OTC medications.

Dr. Hirsch stated they need to average 140 prescription pickups per month to reach the study target of 820; however, at the current rate of only 80 pickups per month, the project will fall short of that goal based on the current length of the study. Dr. Hirsch requested an

extension to continue collecting data through December 2016 and proposed reporting back to the board in March 2017.

After a discussion, the committee decided to recommend allowing more time for the collection of data and reporting of the study's findings. The committee recommended to the board to:

- 1) allow UCSD to collect data through the first quarter of 2017,
- 2) allow UCSD to report the findings of the study at the May 2017 board meeting, and
- 3) allow UCSD to continue operating the kiosk until a decision is made at the May 2017 board meeting

The board approved these modifications to the study at the July 2016 board meeting.

At this Meeting:

Dr. Hirsch will provide an update of the study via telephone and respond to questions from the committee. A copy of the planned presentation is provided in **Attachment 1**.

Reports on this study will continue to be provided at each quarterly Enforcement and Compounding Committee meeting while the study is underway.

b. CURES 2.0 Prescription Monitoring Program and Use of CURES by Pharmacists – Update and Discussion and Consideration of Next Steps, if Necessary.

Attachment 2

On July 1, California law required that all pharmacists with active licenses to apply with the California Department of Justice (DOJ) to access CURES. The board made considerable efforts to ensure pharmacists with active licenses were advised of this requirement. This included a postcard mailing to all pharmacists in February and a letter sent exclusively to pharmacists who did not have their names listed in CURES at the end of May. The letter triggered more than 2,000 inquiries to the board from pharmacists seeking to become registered or with questions on various issues. The board worked diligently with DOJ over the following weeks to resolve every issue.

On August 10, 2016, the DOJ reported that there were 30,096 pharmacists registered for CURES. This number excludes pharmacists who were approved under CURES 1.0 and have not yet logged in to CURES 2.0 to update their profiles and indicate their board and licensee type. Board staff believes that there are 2,280 active pharmacists who may not have registered to access CURES.

Later this fall, staff will make another attempt to identify pharmacists with active licenses who have not applied for access to CURES.

Statistics for CURES are reported as **Attachment 2**. There has been considerable growth since January in the number of pharmacist registrants and especially in the number of patient profile reports requested by pharmacists and physicians each month.

As approved by the board at the July board meeting, researchers from the University of California, Davis will be surveying pharmacists who renew their licenses in November to learn about their use, access to, likes, dislikes and concerns with CURES. Physicians will also participate in a related survey at the same time. Once available, these results will be shared with the board.

c. Discussion and Consideration of Consumer Enrollment in Automated Refill Programs for Prescription Medications.

Attachment 3

Traditionally, pharmacies have refilled prescriptions only upon the request of the patient or the patient's prescriber. However, in recent years computer programs have been developed which allow pharmacies to enroll patients in automatic refill programs ("auto-refill").

These programs automatically refill prescriptions before the patient runs out of medication. In most cases, these auto-refill programs are limited to drugs identified as maintenance medications.

The argued benefit of auto-refill programs is that they increase patient compliance with drug therapy by automatically refilling maintenance medications and sending reminders to patients to pick up their prescriptions.

In 2012, the *Los Angeles Times*, and other media outlets, reported that some of these programs actually had adverse consequences for the public in that they contributed to medication errors, waste and fraudulent billing practices. There were allegations pharmacy staff enrolled patients in auto-refill programs without their knowledge or consent because pharmacists were working under work quotas that directed or rewarded patient enrollment in these programs.

From late 2012 thru 2013, the board received over 100 complaints directly related to auto-refill programs due to the media attention. Many of the complaints were from patients who received prescriptions they did not request and who had difficulty returning the prescriptions for a refund. Other patients inadvertently ingested medication they had not requested or ingested medication that was previously discontinued by their prescriber. Some of these events resulted in patient harm.

In response to the large number of complaints, Executive Officer Herold and other staff worked with the various agencies to address these concerns and explore possible violations of pharmacy laws and regulations.

Meanwhile in 2013, the Federal Centers for Medicare & Medicaid Services proposed new regulations which resulted in additional rules for auto-refill programs for Medicare patients receiving prescriptions from mail order pharmacies. A copy of the proposed new regulations is provided in **Attachment 3**.

Since 2013, the number of auto-refill complaints received by the board has decreased, however the board continues to receive complaints related to these programs.

At this Meeting:

The committee may wish to consider developing requirements for pharmacies to retain signed documentation that patients have “opted in” to a pharmacy’s auto-refill program. Most pharmacies contend patients are asked whether or not they wish to enroll in the auto-refill program prior to enrollment. Enrollment is then documented in the computer; however, there is no written documentation or signed consent from the patient. Instead, enrollment in these programs is based on verbal consent. The board continues to receive complaints which allege patients are enrolled into auto-refill programs without consent. This committee may also wish to consider how often signed consent should be obtained (e.g., annually) and whether signed consent should be obtained separately for each prescription placed on auto-refill.

With regard to pharmacies in the community practice setting, the committee may wish to consider additional requirements for pharmacies to notify patients upon pick up, both verbally and in writing (on the receipt), if the prescription was refilled automatically. Many consumers, especially the elderly, assume that if the pharmacy refilled a prescription, then the prescriber must have authorized it and wanted them to continue taking the medication. This is not always the case and can cause confusion for consumers. Notifying the patient that the prescription was refilled because it was on auto-refill might help to eliminate some of the confusion, or at least open a dialogue with the pharmacist to prevent potential harm to the patient from unwanted refills.

The committee may also wish to consider whether the above requirement for notification should be documented in writing by the pharmacy.

With regard to mail order pharmacies, the committee may wish to consider adding requirements consistent with guidance from the Federal Centers for Medicare and Medicaid Services. See **Attachment 3**.

With respect to both community pharmacies and mail order pharmacies, the committee may wish to consider requirements for written policies and procedures related to auto-refill. One of the elements of the policies and procedures might include procedures to ensure discontinued medications are removed from the auto-refill program and drug therapy reviews are conducted by the pharmacist to prevent duplicate therapies.

d. Discussion and Consideration of Statistics for Board Issued Citations and Fines.

Attachment 4

The board has asked staff to provide information about board-issued citations and fines. During this meeting, Board Chief of Enforcement, Julie Ansel, will provide information regarding citations and fines issued by the board. A copy of the planned presentation is provided in **Attachment 4**.

e. Discussion and Consideration of Data Describing Medication Errors and Board Issued Citations and Fines.

The board has asked staff to provide a report on the medication errors reported to the board. At this meeting, Board Chief of Enforcement, Julie Ansel, will be discussing medication errors during the presentation for the prior agenda item (see **Attachment 4**).

IV. COMPOUNDING MATTERS

a. Discussion and Consideration of Statistics on Compounding Violations Identified by the Board (2014 – 2016).

Attachment 5

Board Supervising Inspector Christine Acosta will provide the committee with an overview of compounding violations identified by the board over the last several years. A copy of this presentation is provided as **Attachment 5**.

b. Pending Compounding Regulations, Title 16 California Code of Regulations, 1735 et seq., and 1751 et seq.; Status Update and Discussion and Consideration of Next Steps, if Necessary.

Attachment 6

On May 8, 2015, the board initiated a formal rulemaking to update California’s compounding regulations. The rulemaking is currently at the Office of Administrative Law undergoing final review. The chronological timeline for the regulation has been provided in the table below:

Action	Date
Board approves proposed the text for rulemaking	April 21, 2015
Regulation Hearing	June 25, 2015
45-Day Comment Period	May 8 - June 22, 2015
15-Day Comment Period	July 31 - August 15, 2015
Second 15-Day Comment Period	November 20 - December 5, 2015
Board Approves the final text	January 19, 2016
Rulemaking file submitted to DCA for review	March 10, 2016
Rulemaking file submitted to OAL for review	August 1, 2016
Deadline for OAL’s review	September 13, 2016

The board set the effective date of the regulation as January 1, 2017. **Attachment 6** contains the regulation language as approved by the board on January 19, 2016.

c. Discussion and Consideration of the Proposed Process for Pharmacies Seeking Waivers From Structural Requirements in Title 16 California Code of Regulations, 1735 et seq., and 1751 et seq.

The final version of the proposed compounding regulations contains a waiver provision for some of the structural requirements to provide the pharmacy time to secure the construction modifications needed. As proposed in the regulation (as subdivision 1735.6(f) and in 1751.4(l)), the waiver request shall:

1. be made in writing;
2. identify the provision(s) requiring physical construction, alteration, or improvement;
and
3. contain a timeline for any such change.

Since the last meeting, staff has met with the Office of Statewide Health Planning and Development in attempts to tap into their review and approval process as one route for the board's waiver process. Using the OSHPD review process would not be a feasible option for community compounding pharmacies which, in many instances, do not require OSHPD review. In such cases these pharmacies would be requested to provide similar information directly to the board.

Board staff will provide a presentation on a proposed process during this part of the meeting.

d. Discussion and Consideration of the Draft Compounding Self-Assessment Form to Implement the Pending Compounding Regulations

Attachment 7

During this part of the meeting, the committee will review the proposed draft of the compounding self-assessment that will be pursued if the board's compounding regulations are approved. A copy of the proposed compounding self-assessment is provided in **Attachment 7**.

Use of this form will address some questions compounding pharmacies may otherwise have in understanding the proposed requirements, and as such, will be an important tool in aiding licensees to comply with the requirements.

e. Discussion and Consideration of Frequently Asked Questions about Sterile Compounding.

Attachment 8

Supervising Inspector Acosta has developed *draft* FAQ's regarding compounding which are provided in **Attachment 8**.

f. Discussion and Consideration of Frequently Asked Questions about Venting in Compounding Pharmacies.

Included in the FAQ's above are three questions that deal with venting issues in compounding pharmacies. These are questions 37, 52 and 53. The board has been asked questions several times regarding this subject. Again, although the responses to these questions are in draft form and are not necessarily the final version of the board, the committee will have a chance to discuss them during this part of the meeting.

g. Federal Food and Drug Administration's Draft Guidance Documents – Discussion and Consideration, including Whether to Submit Board Comments, regarding:

In recent months, the FDA has released multiple guidance documents regarding compounding and outsourcing duties and regulation. During this meeting, the committee will have the opportunity to discuss several of the guidance documents which contain proposed elements for FDA regulation.

The FDA notes in each of these documents that the guidance documents “do not establish legally enforceable responsibilities. Instead, the guidance documents 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 guidance documents are instructional in that they reflect enforcement priorities the FDA pursues during inspections. They are described in some detail below. The board has an opportunity to provide written comments on a guidance document. Staff suggests that the first two documents be considered for possible comments.

1. Insanitary Conditions at Compounding Facilities: Released 8/3/16

Attachment 9

Below is a description and paraphrasing of information contained in this guidance. The document itself can be found in **Attachment 9**.

The FDA considers a drug to be adulterated “if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health.” Drug products prepared, packed, or held under insanitary conditions could become contaminated and cause serious adverse events, including death. This includes both drugs produced under facilities licensed under section 503A or section 503B.

Drugs prepared, packed, or held under insanitary conditions are deemed to be adulterated. This includes compounded human and animal drugs; repackaged drug products; compounded or repackaged radiopharmaceuticals; and mixed, diluted, or repackaged biological products. The FDA’s guidance on insterility specifically addresses pharmacies; federal facilities; physician offices (including veterinarian offices); and outsourcing facilities that compound or repackage human or animal drugs (including radiopharmaceuticals); or that mix, dilute, or repackage biological products.

FDA states that since 2012, it has identified insanitary conditions at many of the compounding facilities that it has inspected, and numerous compounding facilities have voluntarily recalled drug products intended to be sterile and temporarily or permanently ceased sterile operations as a result of those findings. However, FDA states that it does not inspect the vast majority of compounding facilities in the United States because they generally do not register with FDA unless they elect to become outsourcing facilities. The following are examples of insanitary conditions that are applicable to both sterile and non-sterile drug production:

- Vermin (e.g., insects, rodents) observed in production areas or areas immediately adjacent to production.

- Visible microbial contamination (e.g., bacteria, mold) in the production area.
- Non-microbial contamination in the production area (e.g., rust, glass shavings, hairs).
- Handling beta-lactam, hazardous, or highly potent drugs (e.g., hormones) without providing adequate containment, segregation, and cleaning of work surfaces, utensils, and personnel to prevent cross-contamination.
- Production of drugs while construction is underway in an adjacent area without adequate controls to prevent contamination of the production environment and product.

Aseptic Practices

- Putting on gowning apparel improperly, in a way that may cause the gowning apparel to become contaminated. This includes gowning in non-classified areas, gowning apparel touching the floor, or putting on sterile gloves improperly (e.g., touching the outside of a glove with bare hands).
- Failing to disinfect or change gloves frequently enough given the nature of the operations to prevent contamination.
- Engaging in aseptic processing wearing non-sterile gloves. This could contaminate the critical area.
- Engaging in aseptic manipulations with exposed hands, wrists, legs, hair, or mouth.
- Performing aseptic manipulations outside of ISO 5 area.
- Exposing unprotected sterile product, including stock solutions, to lower than ISO 5 quality air (e.g., removing it from the ISO 5 area without a robust and intact container closure system).
- Engaging in aseptic processing after leaving the cleanroom and re-entering from a non-classified area without first replacing gowning apparel (e.g., sterile gloves, gowns, mask, foot covers). Movement of personnel in and out of the cleanroom without re-gowning may bring contaminants from the non-classified areas into the cleanroom.
- Moving quickly in the vicinity of open containers or instruments (e.g., needles). While conducting aseptic manipulations, ISO 5 airflow must be unidirectional to protect the product from contaminating particles. Quick movement of personnel disrupts the airflow and increases the risk of bringing lesser quality air into the ISO 5 area.
- Conducting aseptic manipulations or placing equipment/supplies in an area that blocks the movement of first pass air around an open container, whether before or after it is filled with sterile product. If unidirectional air over the critical surface is blocked, the area is no longer protected. If it is blocked by personnel conducting aseptic manipulations, contamination on personnel, particularly on exposed skin, could be introduced to the critical area.
- Using a non-sterile tool or manually contacting the inner surface of the container or closure. For example, during manual stoppering (e.g., hand stoppering), personnel touching the top of open containers, or the lower side or bottom of closures. This could contaminate the drug in the vials.

- Touching equipment or other surfaces (e.g., walls, telephone, and floors) located outside of the ISO 5 area with gloved hands and then proceeding with aseptic manipulations without changing or sanitizing gloves.

Actionable microbial contamination of the ISO 5 area or in adjacent areas includes:

- Cleanroom with unsealed, loose ceiling tiles.
- ISO classified areas with difficult to clean (e.g., porous), particle-generating, or visibly dirty (e.g., rusty) equipment or surfaces such as shelving, floors, walls, doors, window sills, and ceilings. For example, wood is both difficult to clean and particle-generating.
- Classified areas and segregated production areas surrounding the ISO 5 area that contains dust-collecting overhangs (e.g., utility pipes or ledges, such as windowsills).
- ISO 5 area open to the surrounding cleanroom with minimal or no physical barriers separating it from non-aseptic activities (e.g., non-aseptic weighing materials, gowning, container labeling).

Additionally:

There are multiple measures and assessments the FDA states that it expects to see to ensure compounding is being done under appropriate conditions. These include to:

- Conduct routine environmental monitoring, including a) nonviable airborne particulate sampling; b) viable airborne particulate sampling; c) personnel sampling (including glove fingertip sampling); and d) surface sampling, including but not limited to equipment, work surfaces, and room surfaces. Environmental monitoring provides information on the quality of the aseptic processing environment and, if problematic, the compounding.
- Certify the ISO 5 area every six months. If the ISO 5 area is not certified every six months or does not pass all certification requirements, there is no assurance that the ISO 5 area is working properly (e.g., generating unidirectional ISO 5 airflow). Smoke studies should be conducted as part of the certification to assess the airflow patterns necessary to maintain unidirectional flow from areas of higher air quality (e.g., ISO 5) to areas of lower air quality (e.g., ISO 7) to prevent microbial contamination of the sterile drug products during processing. Conducting smoke studies under dynamic conditions helps to ensure that unidirectional airflow is maintained while personnel are working in the ISO 5 area.
- Measure pressure differentials during operations to help ensure proper airflow (i.e., from areas of higher quality air to adjacent areas with lower quality air).
- Conduct media fill studies to closely simulate aseptic production operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations.

At this Meeting:

After discussion, the committee may recommend that the board submit comments with respect to the policies in this guidance document.

2. Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act -- Draft released 7/7/16

Attachment 10

This guidance pertains to compounding by an outsourcing facility. According to the FDA, a compounded drug product made by an outsourcing facility must not be “essentially a copy of one or more approved drug products,” as well as meeting other criteria.

The guidance states that outsourcing facilities must compound under current good manufacturing conditions. Drug products compounded by outsourcing facilities are exempt from FDA drug-approval requirements and the requirement to be labeled with adequate directions for use. Because of these and other criteria governing outsourcing facilities, the FDA states that compounded drug products by outsourcing facilities should only be distributed to health care facilities or dispensed to patients to fulfill the needs of patients whose medical needs cannot be met by an FDA-approved drug, unless drug is on a shortage list.

Outsourcing facilities cannot generally compound drugs that are essentially copies of approved drugs. Outsourcing facilities may not compound unapproved over-the-counter drug products under exemptions in 503B. The guidance focuses on describing how the FDA will apply these principles to drug products compounded by outsourcing facilities.

1. A compounded drug by an outsourcer is essentially a copy of an approved drug if the compounded drug is identical or nearly identical to an approved drug
UNLESS
2. The approved drug appears on the drug shortage list at the time of compounding, distribution and dispensing.

FDA intends to consider a compounded drug product to be identical or nearly identical to an approved drug if they both have the same:

1. active ingredients
2. route of administration
3. dosage form
4. dosage strength and
5. excipients

The FDA explains that when a product compounded by an outsourcer contains the same five criteria, the compounded product is the same as a manufactured drug and should not be compounded unless the manufactured product is on a shortage list. However, if the drug product differs in one or more of the five criteria, the FDA will generally not consider the product identical to a manufactured drug.

With respect to shortages, the FDA does not intend to take action against an outsourcer who compounds, distributes or dispenses a compounded similar drug within 60 days of

the drug appearing on a shortage list.

To differentiate compounded products from commercially manufactured products where one of the five criteria has changed and a quantity of compounded product is being provided for office use, relying on the prescriber's determination of clinical differences between the two products, the outsourcer should obtain a statement from prescriber that the compounded drug will be administered or dispensed only to a patient for whom the change produces a clinical difference.

At this Meeting:

After discussion, the committee may recommend that the board submit comments with respect to the policies in this guidance document (**Attachment 10**).

3. Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Attachment 11

A bulk drug substance is defined in part as a substance that “becomes an active ingredient or a finished dosage form of the drug, but does not include intermediates used in the synthesis of such substances.” The FDA is in the process of developing a “bulks list” for use in compounding and is currently evaluating the nominated items.

Attachment 11 contains information about this guidance.

Under the FD&C Act, a bulk drug substance that is not the subject of an application USP or NF monograph or is not a component of an FDA-approved drug cannot be used in compounding unless it appears on a bulks list promulgated as a regulation.

Once the evaluation of the nominated substances is completed, the FDA must adopt items to appear on the bulks list by regulation. Public comment on each item on this list will be possible as part of the rulemaking. Thereafter, the FDA will consult with the USP and develop the final list.

However, until a substance has been evaluated and identified in a final rule as being included or not included on the list, the FDA does not intend to take action against a pharmacy, federal facility or physician compounding a drug product that is not the subject of a USP or NF monograph if certain specified conditions are met. These are detailed in the proposal.

At this Meeting:

After discussion, the committee may recommend that the board submit comments with respect to the policies in this guidance document.

4. Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Attachment 12

This guidance updates the FDA's policies with respect to a pharmacy's compounding of human drug products. **Attachment 12** contains the guidance document.

A compounded drug product is exempt from sections 501(a)(2)(B), 502(f)(1) and 505 of the FD&C Act if it meets the conditions of section 503A. Specifically, the compounded drug product qualifies for the exemptions if:

1. The drug product is compounded for an identified individual patient based on the receipt of a valid prescription, or a notation, approved by a physician or other practitioner authorized to prescribe.
2. The compounding of the drug product is performed:
 - By a pharmacist in a pharmacy or federal facility or a physician,
 - By a pharmacist or physician in limited quantities before the receipt of a valid prescription order for an individual, provided:
 - The product produced is based on a history of pharmacist or physician received valid prescription orders for the compounding of the human drug product, and
 - Those orders have been generated solely within an established relationship between the pharmacist or physician either for a patient for whom the prescription order will be provided or the physician or other licensed practitioner who will write such prescription order.
 - The drug product is compounded in compliance with USP standards regarding pharmacy compounding with bulk drug substances that comply with USP or NF monograph standards.
 - Anticipatory compounding is not done in inordinate amounts
 - The drug product is compounded in a state with a signed MOU with the FDA or ships no more than 5 percent in states without a MOU for interstate shipments

Additionally the FDA will develop regulations in the future to:

- Add to the list of products that have been withdrawn or removed from the market and that cannot be compounded.
- Create a list of bulk drug substances that can be used in compounding
- Identify products with "demonstrable difficulties" for compounding
- Establish parameters for MOUs with the FDA and the states for to set limits for
- Interstate shipment of compounded products.

The FDA also will establish sanctions for those who violate the FDA's compounding requirements, including for violations involving producing adulterated drugs, unapproved new drug products, misbranded drugs

At this Meeting:

After discussion, the committee may recommend that the board submit comments with respect to the policies in this guidance document.

h. Articles in the News, Including Discussion and Consideration of “Fraud Concerns Grow as Spending on Handmade ‘Compounded’ Drugs Soar.”

Attachment 13

This article, which was published in the July 17, 2016, edition of *The Washington Post*, reports that government spending on compounded drugs under Medicare’s Part D rose 56 percent over the last year, with topical creams and gels among the costliest products. Over a four-year period, the federal workers’ compensation program reports an increase from 2.35 million to 214 million dollars.

According to a June report on Medicare spending, these increases, along with a sharp increase in the number of patients getting compounded drugs may indicate an emerging fraud trend. The report further states that some prescriptions may not have been medically necessary or even dispensed. Under the Medicare Part D drug program, the number of beneficiaries receiving compounded drugs has grown by 281 percent since 2006 to nearly 280,000 in 2015. Spending on drugs has reached 509 million, which is a 625 percent increase since 2006. Topical creams and gels, which are often used for pain, are among the fastest growing category of compounded drugs with a 3,466 percent increase over the last decade; the average cost of a prescription increased from \$40 in 2006 to \$331.

A copy of this article is provided in **Attachment 13**.

Attachment 1

Study of Expanded Use of an Automated Delivery Device

UPDATE
AUGUST 31, 2016



Jan D. Hirsch, BPharm, PhD

UCSD Skaggs School of Pharmacy & Pharmaceutical Sciences

UC San Diego
HEALTH SCIENCES

Update

- ScriptCenter Kiosk
 - Operations Update
- Update on Study
 - Reminder: Research Design & Questions
 - IRB Amendment
 - Study Timeline Requested Revision

ScriptCenter Kiosk Sharp Memorial Hospital

Location Change June 2016



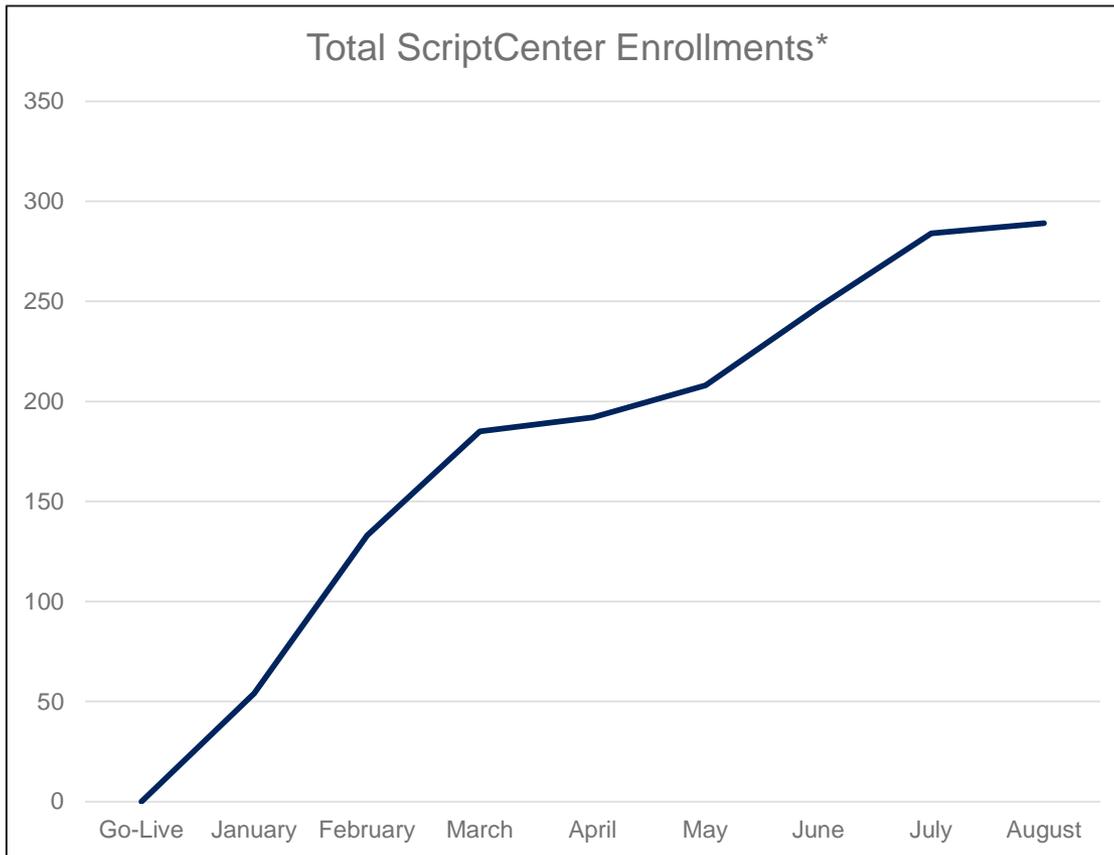
First Floor Lobby Sharp Memorial Hospital



ScriptCenter Kiosk Activity 1/20/16 through 8/9/16

Kiosk Go Live Date: 1/20/16
Study Start: 3/1/16

ENROLLMENT



289 users
(6% Campus Employees)

Total Campus Employees
4,820

Day Shift = 2,592

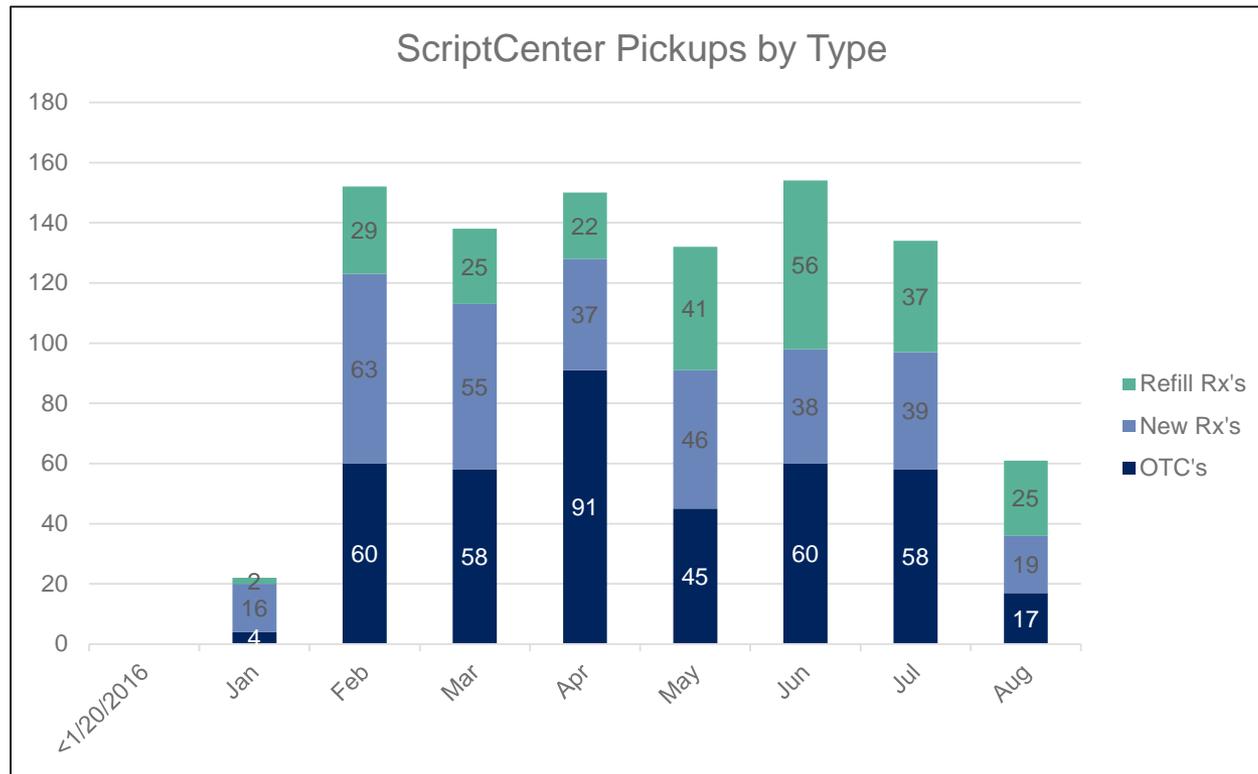
PM+ Variable = 2,228

If estimate 2 per household
= 9,640

ScriptCenter Kiosk Activity 1/20/16 through 8/9/16

Pick-ups by Type

Kiosk Go Live Date: 1/20/16
Study Start: 3/1/16



- About 80 Rxs per month
- On track for number needed for study (820)
- 376 Rxs in study period
- Data collection expected complete end of December

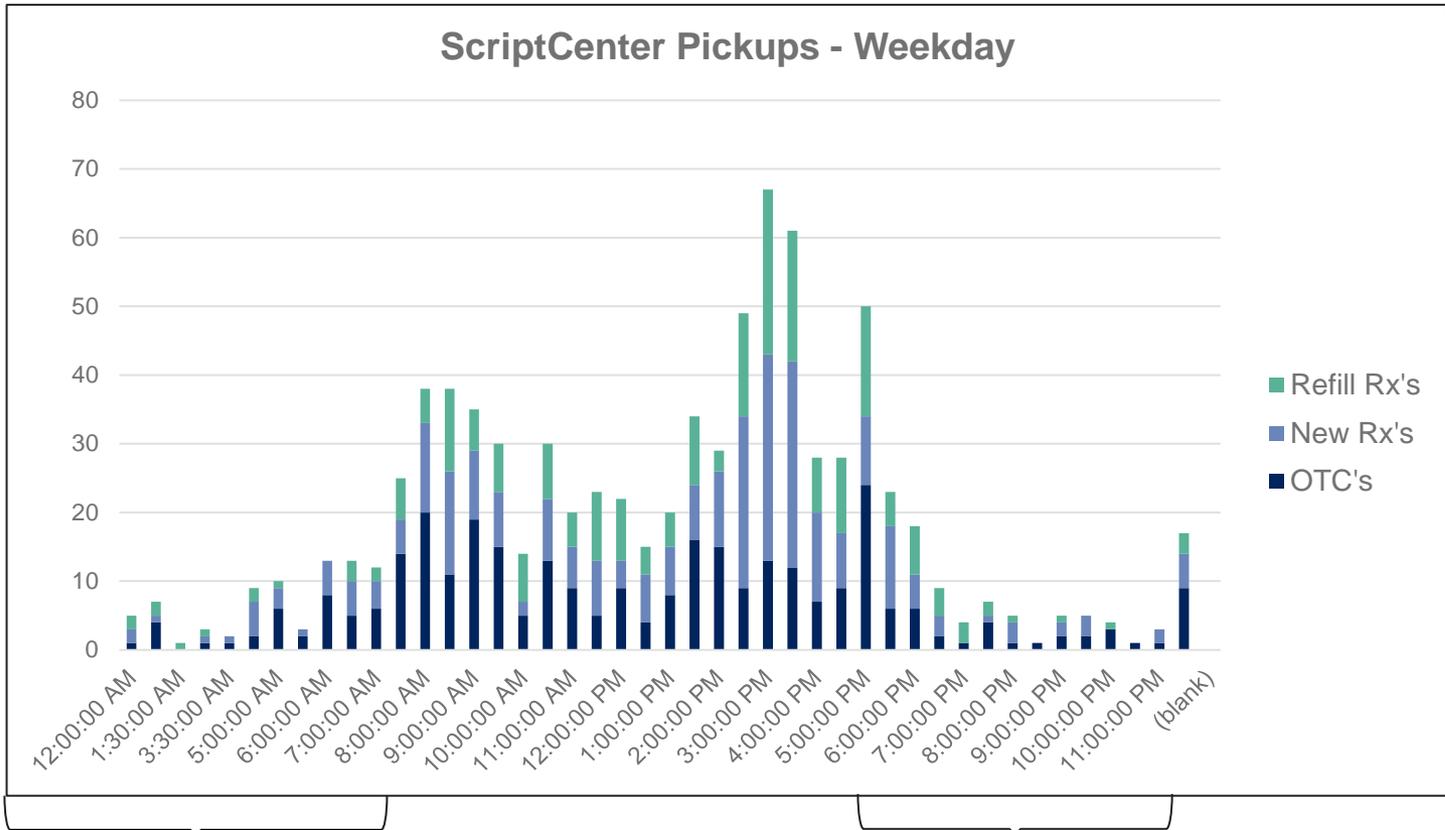
298 Users

Note: Higher 'new prescriptions' in the early months are due to a higher number of prescription transfers when went live. Many of these prescriptions are being turned into refills as time passes.

ScriptCenter Kiosk Activity 1/20/16 through 8/9/16

Pick-ups by Time Weekday

Kiosk Go Live Date: 1/20/16
Study Start: 3/1/16



Day Shift
2,592

PM +
Variable
2,228

298 Users

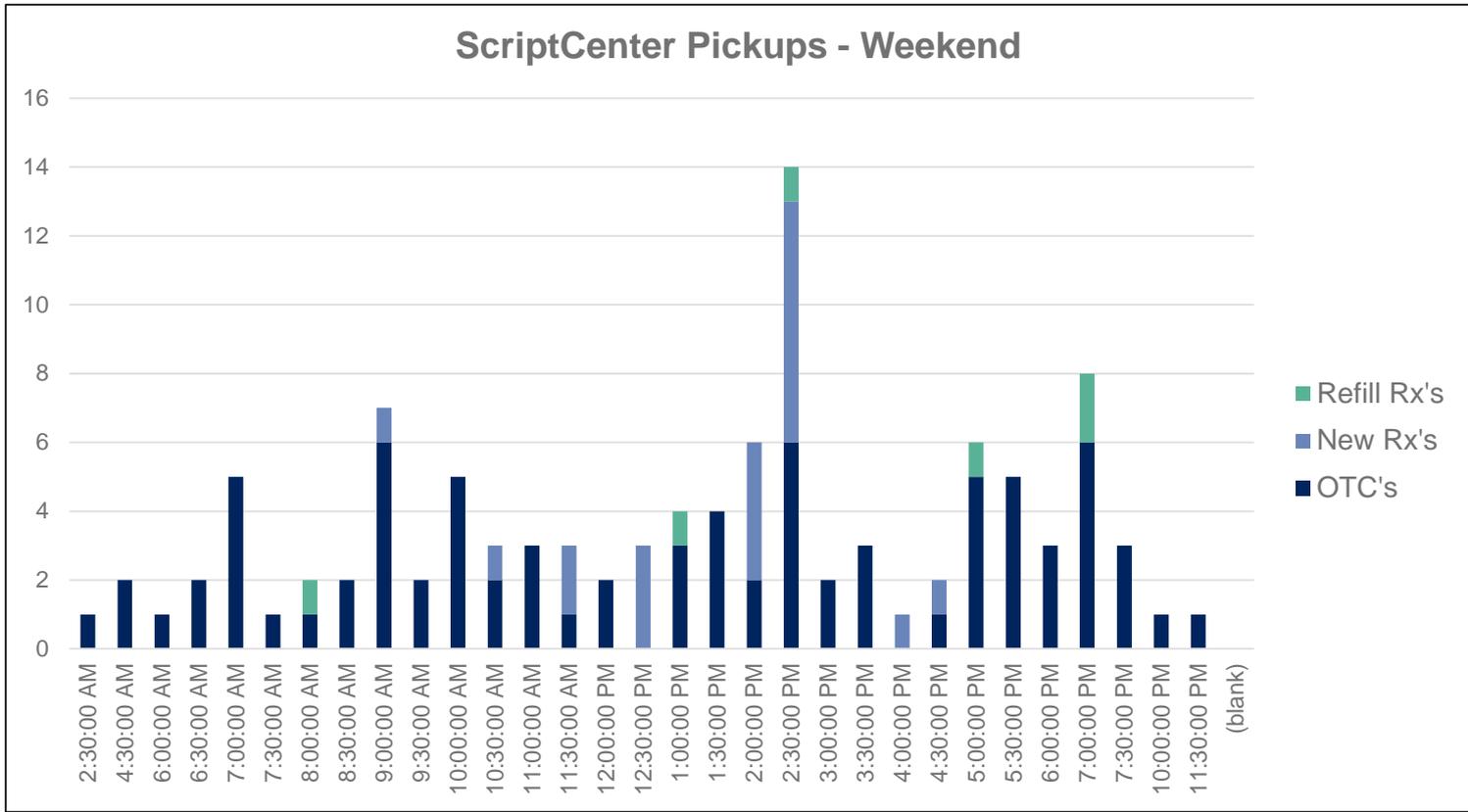
Pharmacy
Closed

Pharmacy
Closed

ScriptCenter Kiosk Activity 1/20/16 through 8/9/16

Pick-ups by Time Weekend

Kiosk Go Live Date: 1/20/16
Study Start: 3/1/16



Day Shift
2,592

PM +
Variable
2,228

298 Users



Pharmacy Closed

ScriptCenter Kiosk During vs. After Hours Pick-Up

Kiosk Go Live Date: 1/20/16
Study Start: 3/1/16

943 Total Pickups

683 (72%) During pharmacy hours
260 (28%) After pharmacy hours

313 New Rx Pickups

243 (78%) During pharmacy hours
70 (22%) After pharmacy hours

237 Refill Rx Pickups

197 (83%) During pharmacy hours
40 (17%) After pharmacy hours

393 OTC Pickups

243 (62%) During pharmacy hours
150 (38%) After pharmacy hours

Day Shift 2,592

PM + Variable
2,228

298 Users

Data is through 8/9/16.
After hours includes weekday & weekend times pharmacy is closed.

ScriptCenter Kiosk

Sharp Memorial Hospital



- No complaints received at Sharp
- Sample of testimonials *(have permission to share)*

“I work weekends and can now pick up my prescriptions when the Sharp Rees-Stealy pharmacy is closed. The 24/7 kiosk is so convenient that I no longer go to anywhere else. I am more comfortable managing my family’s prescriptions here at Sharp. The best part is the text notification alerting me that my medication is ready. This is one less call I have to make to the pharmacy to see if it was filled or if there were any problems. I got a co-worker to switch his pharmacy to Sharp. Very satisfied !!! ”

- *Alisa Valadez – LVN, Sharp Memorial Hospital*

“I love the ScriptCenter prescription pickup kiosk because I never wait in line like I did at other pharmacies. Transferring prescriptions for my family and me to Sharp Rees-Stealy was so easy. I work the night shift so this is super convenient for me. I have told my co-workers about ScriptCenter and highly recommend it for everyone.”

- *Wendell Hatten - Sharp Memorial Hospital Distribution Center*

Study Design

Quasi-experimental with
non-randomized control group

- Pre-Kiosk Implementation Survey (Sharp Employees)

Study Start

6 months pre-kiosk
(September 2015 – February 2016)

Month 1: March

Month 6: August

Month 10: December

Regular Counter

- RTS rate*

Kiosk Go Live Date: 1/20/16
Study Start: 3/1/16

Kiosk

- RTS rate
- Consultation Log
- Time to Pick-up
- Kiosk Patient Satisfaction

Regular Counter

- RTS rate*
- Consultation Log (Sample: New Rx's weeks of 5/23 & 6/6)
- Time to Pick-up*

RTS = Return to Stock

* For employees and dependents

Approved REVISED Study Timetable

- Q4 2015 Pre-kiosk 6-month data collection phase begins

- Q1 2016 Implement Kiosk device (1/20/16)
 Refine data collection tools & process
 Deployment of program/enroll patients

- Q2 - Q4 2016 Post-kiosk implementation
 March – December Data collection and analysis

- Q1 2017 Report Results to Board
 Continue Operate Kiosk



Questions?

UC San Diego
SKAGGS SCHOOL OF PHARMACY
AND PHARMACEUTICAL SCIENCES

Attachment 2

Individuals Registered	January 25, 2016	April 25, 2016	July 25, 2016	August 25, 2016
2.0 Prescribers	4,940	64,130	121,417	122,491
2.0 Dispensers	5,933	29,130	38,071	38,259
Pharmacists	N/A	17,219	29,639	30,096

Patient Activity Reports*				
*one month prior ending on the 25th of the indicated month	January 25, 2016	April 25, 2016	July 25, 2016	August 25, 2016
Prescribers	31,425	217,635	254,459	281,212
Dispensers	64,647	389,364	445,295	493,322

Access	January 25, 2016	April 25, 2016	July 25, 2016	August 25, 2016
Medical Doctor	49,881	142,106	161,499	173,484
Pharmacist	102,347	386,553	445,295	489,960

Attachment 3



CENTER FOR MEDICARE

DATE: October 28, 2013

TO: Employer Group Waiver Plan Sponsors

FROM: Cynthia G. Tudor, Ph.D., Director, Medicare Drug Benefit and C&D Data Group

RE: Clarifications to the 2014 Policy on Automatic Delivery of Prescriptions for Employer Group Waiver Plans

The Centers for Medicare and Medicaid Services (CMS) announced in the 2014 Call Letter that Part D sponsors should require their network retail and mail pharmacies to obtain beneficiary or authorized representative consent to deliver a prescription, new or refill, prior to each delivery. Beneficiaries cannot be required to use mail-order pharmacy, nor can plans auto-enroll Part D beneficiaries in automatic fill/automated refill and delivery programs (referred to in this memo generally as “automatic delivery programs”). This applies to all Employer Group Waiver Plans (EGWP) offered by Medicare Advantage-Prescription Drug Plan sponsors or stand-alone Part D sponsors.

CMS has been analyzing a request to allow EGWPs to continue offering automatic delivery programs, without obtaining consent prior to each delivery, if the automatic delivery program design supports beneficiary-directed care and minimizes beneficiary liability for unwanted shipments. CMS continues to track a large number of complaints related to automatic delivery programs. Complaints include beneficiaries reporting that they were auto-enrolled in automatic delivery programs, difficulty stopping auto-shipments, ongoing automatic credit card charges for unneeded/unwanted orders, and receiving unwanted items that their prescribing provider submitted directly to the pharmacy.

In a HPMS memo dated July 17, 2013, we proposed characteristics of EGWP automatic delivery programs that would meet CMS’ expectations for ensuring beneficiary-directed care and minimize beneficiary liability. After reviewing the comments submitted, we are now clarifying that for Calendar Year 2014 only, the policy for obtaining consent prior to each delivery is not required for beneficiaries in EGWP auto-ship programs if the following conditions are met and can be demonstrated upon request (including audit):

1. Enrollee participation in the automatic delivery program is voluntary and opt-in only;
2. The automatic delivery program only applies to prescription refills and does not apply to new prescriptions that are e-prescribed, faxed, mailed, or phoned-in directly to the pharmacy, even if the new prescription is a continuation of existing therapy;

3. The EGWP has easy to locate and easy to understand beneficiary materials on how to disenroll from automatic delivery programs, and the EGWP responds promptly to all disenrollment requests;
4. The EGWP will provide a full refund to the beneficiary and delete the prescription drug event (PDE) for any auto-shipped refill that the beneficiary reports as unneeded or otherwise unwanted. Beneficiary materials related to refunds must be easy to locate and easy to understand. Plans providing no-fee return of unneeded or unwanted drugs do not need to provide a full refund or delete the PDE when the prescription has been fully or partially used or consumed;
5. The EGWP will confirm whether the beneficiary wants to continue in the automatic delivery program at least annually and upon receipt of a new prescriptions from a provider, even if the new prescription is a continuation of existing therapy; and
6. The EGWP will promptly discontinue automatic delivery after notification that a beneficiary entered a skilled nursing facility, or elected hospice coverage.

EGWP sponsors interested in offering an automatic delivery program that does not feature obtaining consent prior to each delivery after January 1, 2014 must submit a request to PartDPolicy@cms.hhs.gov no later than December 18, 2013. EGWPs will need to submit the sponsor name, contract number(s), and whether the automatic delivery program will be applied to some or all of their EGWP contracts

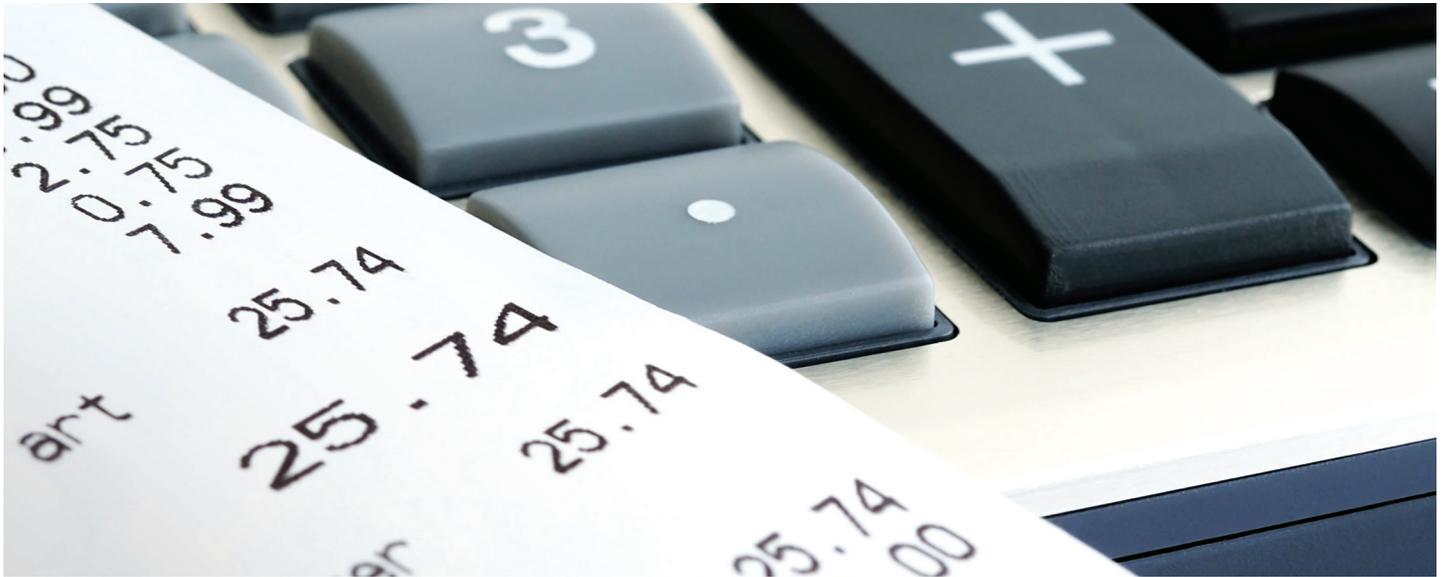
CMS will be closely monitoring this and other EGWP-specific policies in the coming year to determine the best course of action starting in 2015.

For further questions on automatic delivery policy for 2014, please contact Marie Manteuffel at (410) 786-3447 or Marie.Manteuffel@cms.hhs.gov.

Pharmacy Self-Auditing

Control Practices to Improve Medicaid Program Integrity and Quality Patient Care—Booklet 4: Billing Practices





Content Summary

This booklet is the fourth in a four-booklet series that discusses areas of pharmacy practice prone to triggering audits that pharmacy health care professionals should examine. This booklet focuses on billing practices. The other booklets examine provider prescribing practices, controlled substance management, and invoices and claims management. The four booklets may be used together or independently as a self-audit to identify areas of risk as well as opportunity for improvement.

The Affordable Care Act of 2010 expanded Medicaid eligibility in States that have adopted Medicaid expansion. In such States, Americans who earn less than 138 percent of the Federal poverty level, \$33,465 for a family of four in 2015, are eligible to enroll in Medicaid.[1] The National Health Expenditure Projections Forecast for 2014–2024 estimates Medicaid spending will grow by 5.9 percent on average annually from 2015 through 2024.[2]

The Medicaid expansion will impact Medicaid prescription drug utilization and expenditures. Private insurers lose about 1 to 1.5 percent of expenditures to fraud, while Medicaid may be closer to 10 to 15 percent.[3] Experts estimate another 20 to 30 percent of Medicaid dollars are lost to abuse or unnecessary services.[4]

According to the Kaiser Family Foundation, the Medicaid program paid 520 million prescription claims and spent \$20.6 billion in total utilization expenditures in 2012, after recouping rebates.[5] The sheer volume of claims and expenditures requires Medicaid to protect itself from fraud, waste, and abuse.

Pharmacists' unique role in the health care system often allows for intervention before fraud, waste, or abuse occurs. Due to the high risk for improper payments, the Centers for Medicare & Medicaid Services (CMS) developed this toolkit to educate pharmacy providers on self-audit precautions related to invoice management, controlled substances management, proper billing practices, and proper prescribing practices. In addition, this toolkit addresses potential fraud, waste, and abuse related to pharmacy services and how to report them.

Pharmacy providers can identify areas of practice that require further scrutiny and can use these tools to educate staff about potential fraud, waste, and abuse.

Title 18 of the United States Code defines health care fraud as knowingly and willfully executing, or attempting to execute, a scheme to defraud a health care program or obtain money or property from a health care program under false pretenses.[6] Medicaid fraud artists intentionally submit false claims or misrepresent facts to obtain funds to which they are not entitled.[7]

Federal Medicaid regulations do not define waste. Waste is similar to fraud, but it is not usually associated with criminal actions.[8] Think of waste as overutilization or misuse of services. Abuse may encompass waste and includes any action that may cost the Medicaid system unnecessary dollars. Abuse may include improper payment for services, payment for services that fail to meet professionally recognized standards of care, or payment for services that are medically unnecessary.[9] Abuse includes reimbursement for claims to which the provider is not entitled, but health care professionals guilty of abuse do not intentionally misrepresent facts to obtain payment. Like waste, abuse is not usually associated with criminal actions.

The Federal False Claims Act (FCA) is an important tool for combating fraud. In general, the FCA imposes civil liability on people who knowingly submit a false or fraudulent claim or engage in various types of misconduct involving Federal government money or property. From January 2009 through the end of the 2013 fiscal year, the Justice Department used the FCA to recover more than \$12.1 billion in health care fraud.[10]

A 2012 Office of Inspector General (OIG) report identified 2,637 retail pharmacies with questionable billing practices. The investigation found suspect pharmacies billed high dollar amounts per beneficiary, billed a high number of prescriptions per beneficiary, or billed for a high number of prescriptions per physician prescriber.[11] As a result, the OIG recommends CMS strengthen oversight of pharmacies and pharmacy audits.[12] Pharmacists can take the initiative to self-monitor practices within the pharmacy to prevent, identify, and correct potential fraud, waste, or abuse.

The audit process is a means of reviewing pharmacy practices to ensure staff members uphold operational procedures. State and Federal programs, such as Medicaid and Medicare Part D, State licensing boards, the

United States (U.S.) Drug Enforcement Administration (DEA), the U.S. Internal Revenue Service (IRS), and other third-party payers, conduct pharmacy audits. Through the pharmacy self-audit tool, pharmacy staff members can evaluate daily practices, pinpoint potential audit triggers, and proactively address vulnerabilities. Like any developing habit, a self-audit can become a part of daily, weekly, or monthly tasks.[13] Pharmacy managers can customize the pharmacy self-audit to ensure it addresses all pharmacy-specific compliance and operational procedures. When developing the blueprint for a customized pharmacy self-audit, consider the different forms of prescription drug fraud, waste, or abuse that may occur in the particular pharmacy setting, and focus on these vulnerabilities.

Fraud, waste, or abuse may occur as a result of billing miscalculations—quantity miscalculations or days’ supply miscalculations. Fraud, waste, or abuse may also occur in the pharmacy as a result of inappropriate practices, including refill practices, overrides, partial fills, delivery documentation, or package size selection.

Pharmacists can help protect State Medicaid patients from harm and State Medicaid dollars from waste by educating staff members, providing billing job aids, and making sure all pharmacy staff members know what to do in the event a Medicaid billing error is discovered.

Billing Practices Self-Audit

This booklet (Booklet 4—Billing Practices) contains 15 of the 50 steps to conduct a pharmacy self-audit and examines common quantity and days’ supply billing errors. In addition, inappropriate refill practices, overrides, partial fill procedures, and package size selection are discussed. A thorough review of these steps as they pertain to pharmacy practice will help pharmacies preserve State Medicaid program integrity and improve the quality of patient care for State Medicaid beneficiaries. Consider each step, answer the questions listed, and examine existing policies and procedures to identify any audit triggers related to billing practices.

The three additional booklets in the “Pharmacy Self-Auditing: Control Practices to Improve Medicaid Program Integrity and Quality” Toolkit (Booklet 1—Prescribing Practices, Booklet 2—Controlled Substances Management, and Booklet 3—Invoice Management) contain the remaining steps, with audit questions and detailed information regarding each step. The steps in the four booklets correspond to the steps in the document titled “Pharmacy Auditing and Dispensing: The Self-Audit Control Practices to Improve Medicaid Program Integrity and Quality Patient Care Checklist.”

Pharmacists represent a unique line of defense against fraud, waste, and abuse. Pharmacists may help uncover unnecessary costs to the Medicaid system by taking a close look at billing practices that include billing units, refill practices, overrides, partial fill procedures, package size selection, and proof of delivery documentation. If the following self-audit steps reveal potential overpayments, the self-audit toolkit explains what to do next.

36. Discuss billing procedures with staff to determine whether staff members correctly submit claims for drugs commonly submitted with improper billing units. Provide staff members with job aids associated with common types of quantity and/or days’ supply miscalculations. The examples below are not comprehensive but suggest potential targets for job aids.
 - Oral products;
 - Anti-migraine agents;
 - Bowel preparations;
 - Multi-drug/multi-month packs; and
 - Osteoporosis agents.

- Other dosage forms;
 - Inhalers;
 - Ophthalmic products;
 - Topical products; and
 - Vaginal products.
- Injections; and
- Kits.

Reimbursements and rebates are two components of Medicaid prescription drug programs. When a pharmacy dispenses a prescription for a Medicaid beneficiary, the State Medicaid agency (SMA) reimburses the pharmacy, and then pharmaceutical manufacturers provide statutorily-defined rebates to the SMA for each unit of drug that was dispensed. SMAs reimburse pharmacies using the National Council for Prescription Drug Program’s Billing Unit Standard (BUS), while pharmaceutical manufacturers submit rebates to SMAs using CMS unit of measure standards. Because SMAs must convert BUS units to CMS units, a pharmacy BUS claim submission error may also result in inaccurate pharmaceutical manufacturer rebates to the SMA.[14] If a pharmacy submits a claim for a drug with a National Drug Code (NDC) other than the NDC for the drug the pharmacy actually dispensed, the SMA may receive a rebate to which the State was not entitled or may not receive a rebate to which the State was entitled.

37. Review prescription requirements for non-controlled and controlled substances.[15, 16, 17]

- Date of issuance;
- Prescriber’s signature;
- Prescriber’s authority to prescribe (For example: mid-level prescribers versus physicians; State regulations versus Federal days’ supply regulations; and authorization to prescribe specific controlled drug schedules);
- Drug name;
- Drug strength;
- Drug dosage form;
- Quantity of drug prescribed;
- Directions for use;
- Number of refills authorized by the prescriber (if any);
- “Brand name medically necessary” if no generic substitution is allowed;
- If handwritten, controlled substance prescriptions must be written in ink or pencil that cannot be erased; and
- Prescribers must manually sign controlled substance prescriptions on the date issued.

38. Ensure staff members are able to correctly calculate a day’s supply for prescriptions.

- Multiply the number of doses per day by the number of days of therapy to determine the correct quantity to dispense; and
- Reverse-verify by dividing the quantity dispensed by the number of doses per day to determine the number of days’ supply.

39. Talk to pharmacy staff members about prescriptions written for odd quantities.

- Reduce the quantity dispensed to correspond to a number of days equal to or less than the plan-imposed maximum if the days' supply calculated by dividing the quantity dispensed by the number of doses per day exceeds the plan-imposed maximum allowable days' supply.

Upon review of the prescription, pharmacists may see quantities and days' supplies that do not align. Inaccurate claim submission of these types of discrepancies may lead to negative audit findings. For example, if the prescription presented is written for 100 tablets for a 30 days' supply, but the sig code states the drug should be taken three times daily, the pharmacist must either adjust the dispensed quantity to 90 tablets for 30 days or adjust the days' supply to 33.

40. Talk to pharmacy staff members about prescriptions written for doses that exceed Food and Drug Administration (FDA) labeling.

- Examine high doses with scrutiny;
- Consult the FDA label;
- Contact the prescriber to verify the dose if it exceeds FDA recommendations; and
- Document all communication on the hard copy.

Pharmacists should consult a drug reference if a prescribed dose appears in excess to determine if the dose prescribed is within FDA-labeled guidelines. The National Library of Medicine provides a free drug reference, DailyMed, accessible at <https://dailymed.nlm.nih.gov/dailymed/index.cfm> on the National Institutes of Health website. In addition, the FDA maintains a database of approved prescription labeling, Drugs@FDA, accessible at <https://www.accessdata.fda.gov/scripts/cder/drugsatfda/> on the FDA website. Simply enter the name of the drug, navigate to the drug in question, and consider the dosage and administration guidelines listed in the product label. If the dose prescribed exceeds FDA-labeled recommendations, contact the prescriber to verify the dose. Document the verification on the hard copy. Include the diagnosis and the reason for override on the hard copy, if available.

41. Talk to pharmacy staff members about prescriptions that include the use-as-directed sig code for dispensed quantities more than one billing unit per month.

- Shampoos—Document frequency of use and size of area to be treated;
- Creams and ointments—Document frequency of use and size of area to be treated;
- Migraine medications—Document number of headaches treated per month;
- Insulin—Document exact regular dosage and maximum daily dosage for any sliding scale directions; and
- Diabetic syringes, test strips, or lancets—Document maximum use per day.

Prescriptions that require more than one billing unit per month require more concise directions to accurately represent the days' supply. Contact the prescriber to determine the maximum daily dose and gather detailed information for each of these types of medications.

42. Talk to pharmacy staff members about refill practices.

- Do not push-bill or auto-refill without patient consent or request or when prohibited by State law;
- Do not refill and mail to patients without request or patient consent, and only perform patient outreach to initiate refills in attempts to improve medication adherence and clinical outcomes; and



- Do not use financial incentives to influence beneficiary decisions about when or where to fill prescriptions paid by a federally funded program.

Consider the risk for fraud, waste, or abuse if pharmacy staff members use inappropriate refill practices (for example: push-billing and auto-refills, refilling and mailing to patients without request or consent, or financial incentives). Push-billing occurs when pharmacy providers auto-refill prescriptions without beneficiary consent or request. The U.S. Department of Justice’s Civil Fraud Division investigated auto-refill practices at a major retail chain and alleged the chain auto-refilled and billed prescriptions without patient consent while pressuring pharmacists to meet 40 percent auto-refill enrollment goals.[18]

A suspect refill tactic targeted at Medicaid beneficiaries includes refilling prescriptions without a patient request and mailing the completed prescriptions to the beneficiary. Pharmacy providers should not auto-refill without a request from the beneficiary. Providers should only contact a beneficiary to solicit requests for medication refills if the pharmacy provider has assessed the beneficiary’s prescription history and the patient outreach is an attempt to improve the patient’s medication adherence and clinical outcome.[19]

Financial incentives influence a patient’s choice of pharmacy services for prescription refills and are prohibited. “Pharmacies are not allowed to improperly influence the decision-making of Medicare and Medicaid patients about where to fill prescriptions,” said Special Agent in Charge Glenn R. Ferry for the U.S. Department of Health and Human Services, Office of Inspector General (HHS-OIG). “Pharmacy chains that manipulate patient choices in this way will be held accountable.”[20] Financial incentives may include shopper loyalty programs that provide cents off gallons of gas or store credit, gift cards, or merchandise. Pharmacies should not waive copayments (if applicable) as an incentive for the patient to refill unneeded prescriptions. However, most States require a pharmacy to fill and dispense a Medicaid prescription, even if the beneficiary cannot pay the copayment or refuses to pay the copayment.

43. Consider possible patient-driven inappropriate refill practices.

- Counsel patients if stockpiling is suspected;
- Be aware of red flags that may indicate diversion and require further scrutiny; and

- If diversion is suspected, report concerns to the proper authorities.

Patients may stockpile—accumulate excessive and inappropriate amounts of prescription and over-the-counter drugs—for future use. Patient motives for stockpiling vary from fear of drug shortages or unexpected changes in prescription drug benefits to accumulation of drugs for the purpose of diversion or abuse.[21] Patients who stockpile may seek prescriptions from multiple prescribers, and unnecessarily accumulating drugs contributes to waste and abuse in the health care system.[22]

Drug diversion occurs when patients or other individuals divert drugs from the legal supply chain to an illegal supply chain for unlawful, often recreational, purposes. Drug diversion may occur anywhere along the supply chain: manufacturer, distributor, wholesaler, pharmacy, or end-user. Illicit drug distribution occurs in absence of a legal and medically necessary purpose. Costs of the prescription drug diversion epidemic to State Medicaid programs go far beyond the cost of the drug itself. Diversion results in additional costs to the SMA associated with emergency room visits, physician’s visits, and rehabilitation services.[23] Ensure pharmacy staff members are familiar with ways patients commonly divert prescription drugs, including: card sharing, medication sharing, prescription pad theft, forged or altered prescriptions, doctor shopping, and theft.

Red flags that may indicate diversion include:

- The patient requests to pay cash when insurance coverage exists;
- One patient drops off or picks up multiple similar prescriptions for two or more patients;
- Similar or identical prescriptions originate from the same prescriber or practice for inordinately large quantities of medications typically diverted;
- Groups of patients drop off similar or identical prescriptions for commonly diverted medications, often written by a prescriber who practices in another city or county;
- The patient is unable to provide identification when requested;
- The diagnosis given by the patient does not match the diagnosis given by the prescriber;
- The prescriber is unable or unwilling to give a diagnosis or provides the same diagnosis for all patients, such as back pain or degenerative disc disease;
- The prescriber is unavailable to speak directly with the pharmacist, will not return calls, or takes an unusual amount of time to respond to the pharmacist;
- The prescriber has not committed his or her DEA registration number to memory;
- The prescription does not contain all federally-mandated information; or
- The prescription does not comply with tamper-resistance industry standards or appears tampered with.

The DEA will hold accountable prescribers who issue prescriptions outside of legitimate medical use. The DEA also expects a pharmacist to exercise a corresponding responsibility to question prescriptions that do not appear to have been issued for a legitimate medical use.[24] Pharmacists should report their suspicions. Agencies that may be notified include:

- Local law enforcement;
- U.S. DEA;
- State Medicaid Fraud Control Unit; and
- State licensing board if a health care professional is involved.



Or contact:

U.S. Department of Health and Human Services, Office of Inspector General

ATTN: Hotline

P.O. Box 23489

Washington, DC 20026

Phone: 1-800-HHS-TIPS (1-800-447-8477)

TTY: 1-800-377-4950

Fax: 1-800-223-8164

Email: HHSTips@oig.hhs.gov

Website: <https://forms.oig.hhs.gov/hotlineoperations/>

44. Talk to pharmacy staff members about overrides at the point of sale (POS).

- Submit claims with vacation supply override codes only if the patient is on vacation; and
- Submit claims with known prior authorization (PA) override codes only if the patient meets the PA criteria.

Consider the risk for fraud, waste, or abuse if pharmacy staff members use override codes to adjudicate claims without appropriate substantiation. Inappropriate overrides for vacation supplies or PA at the POS are another potential source of risk for fraud. Recently, CareMed, a specialty pharmacy in New York, agreed to pay \$9.5 million in fees to the Federal government and roughly \$450,000 to the State of New York for falsifying PA information to process claims for Medicare and Medicaid beneficiaries. Pharmacy employees, with knowledge of the criteria at various insurance companies, would provide clinical information to the insurance representatives so the patient would “meet” the necessary requirements to have the medication covered.[25] Talk to staff members about when overrides are appropriate.

45. Talk to pharmacy staff members about prescription origin codes.

- Do not alter prescription origin codes; and
- Verify the prescriber DEA number and office telephone number for all controlled substance prescriptions received by telephone. If the caller or prescriber is unknown, confirm the contact information with a



secondary source. If the contact information differs, call the prescriber’s office at a published telephone number to confirm the prescription.

Prescription Origin Codes[26]

Code	Appropriate Use
1	Written—Prescription is presented to the pharmacy on a paper prescription pad.
2	Telephone—Prescription is conveyed to the pharmacy verbally by telephone call, voicemail, or other electronically recorded verbal message.
3	Electronic—Prescription is transmitted to the pharmacy by the National Council for Prescription Drug Programs’ SCRIPT Standard or Health Level 7 (HL7) Standard transactions.
4	Facsimile—Prescription is transmitted to the pharmacy by facsimile machine.
5	Pharmacy—A prescription origin code value of 5 is used when a pharmacy staff member must create a new prescription number from an existing prescription. This may occur due to prescription transfer between pharmacies, prescription transfer between pharmacies in the same parent organization, sale of prescription records from one pharmacy to another, or changes in pharmacy software requirements. A prescription code value of 5 is also appropriate when a pharmacist has prescriptive authority and dispenses a pharmacist-prescribed product, such as emergency contraceptives or Controlled Substances Act Schedule V cough preparations.

Consider the risk for fraud, waste, or abuse if pharmacy staff members adjudicate a claim with an origin code that does not apply. A prescription origin code identifies the method by which a pharmacy receives a prescription. It is important to note any changes made to the original prescription do not change the origin code.[27] Prescriptions received via phone may be particularly vulnerable given the capability to misrepresent a physician’s office and provide a callback number that does not belong to the physician.[28] In one case

involving the New York Medicaid program, 69 of 172 prescriptions indicated as phoned-in from an initial sample audit were found to be improper.[29]

46. Talk to pharmacy staff members about product selection (dispense as written—DAW) codes.
- Only use the DAW 1 product selection code when the prescriber has indicated product substitution is not allowed on the prescription; and
 - Only use the DAW 2 product selection code when the patient has requested to receive the brand name drug rather than the generic equivalent.

Prescription Selection Codes[30]

DAW Code	Appropriate Use
0	Appropriate when the prescriber indicates product substitution is allowed or when the prescriber does not include a product selection code on the written prescription. The pharmacy provider may dispense multi-source and single-source generic drugs or single-source brand name drugs using this product selection code.
1	Appropriate only when the prescriber indicates verbally or on the written prescription that substitution is not allowed— “substitution is not allowed,” “dispense as written,” or “brand name medically necessary.” The pharmacy provider may only dispense the brand name version of the drug prescribed using this product selection code.
2	Appropriate only when the patient indicates he or she requests the brand name version of the drug prescribed. The pharmacy provider may dispense only the brand name version of the drug prescribed using this product selection code and may do so even though the prescriber did not indicate substitution is not allowed.
3	Appropriate if a generic drug is available, but the pharmacist opted to dispense the brand name drug even though the generic drug was in stock.
4	Appropriate if a generic drug is available, but the pharmacist opted to dispense the brand name drug because the generic drug was not in stock.
5	Appropriate if a generic drug is available, but the pharmacist opted to dispense the brand name drug and elected to be reimbursed for the generic drug.
6	Appropriate when an override DAW code is required.
7	Appropriate when substitution is not allowed because the brand name drug is required to be dispensed by State law. This may occur if State law requires drug testing of generic drugs that has not yet been completed.
8	Appropriate when the generic drug is not available. This may occur if the generic drug has been approved by the FDA but not yet manufactured and distributed.
9	Appropriate when the prescriber indicates product substitution is allowed, but the beneficiary’s prescription drug plan requires the pharmacy to dispense the brand name product.[31] For example, the SMA may require the pharmacy to dispense the brand name product to meet the requirements of a statutorily defined manufacturer rebate agreement.



Consider the risk for fraud, waste, or abuse if pharmacy staff members adjudicate claims with inaccurate product selection codes. The DAW product selection code designation references the reason a particular brand is dispensed based upon direction from the prescriber.[32] Excessive use of certain DAW codes may raise red flags from an audit perspective, especially the use of DAW 1 on multi-source products. Review acceptable use of DAW 1 and DAW 9 codes with staff and emphasize appropriate documentation procedures. Proper documentation on prescriptions, especially those received via phone, is critical to withstand audit scrutiny and avoid fraudulent accusations of modifying the prescription to increase revenue. The phrases “brand name medically necessary” or “dispense as written” are needed in the cases of DAW 1 prescriptions. In some situations, SMAs may request a brand instead of generic substitution. In these instances with proper documentation, DAW 9 is appropriate.

47. Talk to pharmacy staff members about partial fill procedures.

- Adjudicate partial fills appropriately. Do not “owe” patients any drug quantity if the full quantity to be dispensed has already been billed;
- Only use the partial fill functionality of the billing system when unable to fill the full quantity to be dispensed;
- Do not bill the payer for the full amount of a partial refill; and
- Do not bill the payer for a second dispensing fee when completing a partial refill.

Consider the risk for fraud, waste, or abuse if pharmacy staff members bill for the entire prescribed quantity but dispense a partial supply while waiting for additional stock to be delivered. A partial fill occurs when a pharmacy does not dispense the total quantity of the medication indicated on the prescription. Potential fraud exists because the pharmacy may receive reimbursement to which it was not entitled. If the pharmacy bills and receives reimbursement for a complete fill and “owes” the beneficiary the remainder of the fill, the beneficiary may not pick up the owed portion, or the pharmacy may not be able to obtain additional supply of the medication. When the medication is returned to stock, the pharmacy inventory is inaccurate, and Medicaid has overpaid the pharmacy. This topic was the subject of an OIG investigation related to \$25 million in overpayments by Medicare Part D for Schedule II prescriptions partial fill completions billed as refills.[33] In addition, pharmacies may create partial fill claims as a means to generate a second dispensing fee. As is

the case with other potential audit red flags, an excess of partial fills has the potential to trigger an audit. Implement a sound partial-fill protocol, including proper documentation, to avoid accusations of partially filling prescriptions in an effort to generate dispensing fee revenue.

48. Talk to pharmacy staff members about how they select package sizes when more than one size is available.
- Select the smallest commercially available package size to address the prescription requirements;
 - Ensure the NDC dispensed matches the NDC billed, particularly for generic and compounded medications;
 - Adhere to State-specific Medicaid compound prescription billing requirements;
 - Bill accurate quantities of medications used in compounded medications; and
 - Confirm that commercially available equivalents do not exist and that the compounded medications are treating a medically necessary indication.

Consider the risk for fraud, waste, or abuse if pharmacy staff members select a package size larger than is necessary. Areas that are particularly vulnerable to audit findings include topical preparations, reconstituted products, and compounds. Review with staff the importance of selecting the smallest commercially available package size, and in cases where this does not occur, document the reason for the larger package size on the prescription (for example: affected area for topical preparations). Staff must ensure the NDC dispensed matches the NDC billed. For compounded medication in particular, if a staff member bills for the entire contents of a package to create a compound when a smaller volume would have been adequate to create the compound, potential for fraud, waste, or abuse exists. In addition, pharmacy staff members may inappropriately flag non-compound products as compounds to increase revenue. A pharmacy owner in West Virginia recently pleaded guilty to defrauding Medicare and Medicaid for dispensing compounded generic medications and billing for the brand. Medicare and West Virginia Medicaid will recover \$1.1 million from a settlement with the pharmacy.[34] Review compound prescription billing procedures with staff to ensure the correct package size and NDC are selected and billed appropriately and to prevent future audit recovery.

49. Talk to pharmacy staff members about how they document beneficiary receipt of prescriptions.
- Always obtain signatures from patients or their agents at the time of prescription pickup.

Consider the risk for fraud, waste, or abuse if pharmacy staff members do not document proof of delivery. Routine examination of signature logs is worthwhile to prepare for potential audits or to uncover fraud in the form of forged signatures. The potential for fraud exists when no records demonstrate proof of delivery because pharmacy employees may forge a beneficiary's signature for a prescription that never reaches the beneficiary.[35]

50. If a Medicaid overpayment is identified, take one of the following steps:
- Reverse any claim within the last year;
 - Send a check and an explanation for any older claim; or
 - Self-disclose the overpayments to your SMA or the OIG.

Pharmacies must report the overpayment within 60 days from the date the overpayment is identified.[36] Overpayments usually include the following situations:[37]

- At the time of the service, the individual receiving the service was not eligible for Medicare or Medicaid;
- Medicare or Medicaid mistakenly paid as primary where another third-party payer was properly primary;
- The payment amount was miscalculated and excessive;

- The service did not fall within one of the statutory benefits or was subject to a statutory exclusion; or
- The service was not medically necessary.

The FCA contains a whistleblower provision allowing an individual, known as a “relator,” to file a lawsuit on behalf of the Federal government against a person or business based on evidence of fraud against Federal programs or contracts. The whistleblower is entitled to a portion of any monies recovered.[38] The FCA includes a treble damages provision (a tripling of actual and compensatory damage) for persons who have “actual knowledge, deliberate ignorance of the truth or falsity of the information, or reckless disregard of the truth or falsity of the information.”[39] In addition, persons may be found to have violated the FCA in reverse—not by receiving money to which the person is not entitled, but by avoiding payment of monies due the Federal government.[40] In addition, a pharmacy may be terminated as a Medicaid provider for cause because the pharmacy has engaged in fraud for abusing billing privileges (for example: billing for services that were not provided or failing to repay a Medicaid overpayment).[41] Identifying and reporting overpayments in a timely manner will prevent negative consequences and offers the pharmacy the opportunity to provide staff training to prevent future overpayments.

Conclusion

CMS is committed to educating pharmacy providers about potential fraud, waste, and abuse related to pharmacy services. The four Pharmacy Self-Auditing booklets in the “Pharmacy Self-Auditing: Control Practices to Improve Medicaid Program Integrity and Quality” Toolkit provide self-audit steps to identify potential audit triggers in a pharmacy practice. The booklets address areas prone to potential fraud, waste, and abuse related to pharmacy services, and provide instruction on how to report suspected fraud, waste, and abuse. Pharmacy providers can use audit findings to identify areas of practice that require further scrutiny as well as use these tools to educate pharmacy personnel about potential fraud, waste, and abuse.

This booklet discusses how evaluating billing practices can be incorporated into a pharmacy self-audit. The booklet contains 15 of the 50 steps to conduct a pharmacy self-audit and examines common quantity and days’ supply billing errors. In addition, inappropriate refill practices, overrides, partial fill procedures, and package size selection are discussed. A thorough review of these steps as they pertain to pharmacy practice will help pharmacies preserve State Medicaid program integrity and improve the quality of patient care for State Medicaid beneficiaries.

To review any of the three additional booklets in the “Pharmacy Self-Auditing: Control Practices to Improve Medicaid Program Integrity and Quality” Toolkit (Booklet 1—Prescribing Practices, Booklet 2—Controlled Substances Management, and Booklet 3—Invoice Management), with audit questions and detailed information regarding each step, visit <https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/edmic-landing.html> on the CMS website. The steps in the four booklets correspond to the steps in the document titled “Pharmacy Auditing and Dispensing: The Self-Audit Control Practices to Improve Medicaid Program Integrity and Quality Patient Care Checklist.”

To see the electronic version of this booklet and the other products included in the “Pharmacy Self-Auditing: Control Practices to Improve Medicaid Program Integrity and Quality” Toolkit, visit the Medicaid Program Integrity Education page at <https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/edmic-landing.html> on the CMS website.

Follow us on Twitter  [#MedicaidIntegrity](https://twitter.com/MedicaidIntegrity)

References

- 1 Centers for Medicare & Medicaid Services. (n.d.). Medicaid & CHIP. Medicaid Expansion & What it Means for You. Retrieved March 18, 2015, from <https://www.healthcare.gov/medicaid-chip/medicaid-expansion-and-you/>
- 2 Centers for Medicare & Medicaid Services. National Health Expenditure Projections 2014-2024. Retrieved October 1, 2015, from <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/Proj2014.pdf>
- 3 Matthews, M. (2012, May 31). Medicare and Medicaid Fraud Is Costing Taxpayers Billions. Forbes. Retrieved March 18, 2015, from <http://www.forbes.com/sites/merrillmatthews/2012/05/31/medicare-and-medicaid-fraud-is-costing-taxpayers-billions/>
- 4 U.S. House of Representatives. Committee on Oversight and Government Reform. (2012, April 25). Uncovering Waste, Fraud, and Abuse in the Medicaid Program. Retrieved March 18, 2015, from <https://oversight.house.gov/wp-content/uploads/2012/04/Uncovering-Waste-Fraud-and-Abuse-in-the-Medicaid-Program-Final-3.pdf>
- 5 Bruen, B. & Young, K. (2014, December 10). What Drives Spending and Utilization on Medicaid Drug Benefits in States? The Henry J. Kaiser Family Foundation. Retrieved March 18, 2015, from <http://kff.org/report-section/what-drives-spending-and-utilization-on-medicaid-drug-benefits-in-states-issue-brief/>
- 6 Health Care Fraud, 18 U.S.C. § 1347 (2010). Retrieved March 17, 2015, from <http://www.gpo.gov/fdsys/pkg/USCODE-2011-title18/pdf/USCODE-2011-title18-partI-chap63-sec1347.pdf>
- 7 Definitions, 42 C.F.R. § 455.2. (2011). Retrieved March 17, 2015, from http://www.ecfr.gov/cgi-bin/text-idx?SID=079196713a1d27e688ca77d9927a9f4a&node=pt42.4.455&rgn=div5#se42.4.455_12
- 8 National Association of Medicaid Directors. (2012, March). Rethinking Medicaid Program Integrity: Eliminating Duplication and Investing in High-Value Tools. Retrieved March 17, 2015, from http://medicaiddirectors.org/wp-content/uploads/2015/08/namd_medicaid_pi_position_paper_final_120319.pdf
- 9 National Association of Medicaid Directors. (2012, March). Rethinking Medicaid Program Integrity: Eliminating Duplication and Investing in High-Value Tools. Retrieved March 17, 2015, from http://medicaiddirectors.org/wp-content/uploads/2015/08/namd_medicaid_pi_position_paper_final_120319.pdf
- 10 Staman, J. (2014, September 8). Health Care Fraud and Abuse Laws Affecting Medicare and Medicaid: An Overview. Congressional Research Service. Retrieved March 19, 2015, from <http://fas.org/sgp/crs/misc/RS22743.pdf>
- 11 U.S. Department of Health and Human Services. Office of Inspector General. (2012, May). Retail Pharmacies With Questionable Part D Billing. Retrieved March 18, 2015, from <https://oig.hhs.gov/oei/reports/oei-02-09-00600.pdf>
- 12 U.S. Department of Health and Human Services. Office of Inspector General. (2012, May). Retail Pharmacies With Questionable Part D Billing. Retrieved March 18, 2015, from <https://oig.hhs.gov/oei/reports/oei-02-09-00600.pdf>
- 13 Baird, J. (2011, January). Self-Audits: The ‘Canary in the Mine Shaft’ for Avoiding Recoupments. Pharmacy Law. Retrieved March 17, 2015, from <http://www.americaspharmacist.net/issues/APJAN11-PharmacyLaw.pdf>
- 14 U.S. Department of Health and Human Services. Office of Inspector General. (2007, November). Unit of Measure Inconsistencies in the Medicaid Prescription Drug Program. Retrieved March 24, 2015, from <https://oig.hhs.gov/oei/reports/oei-05-07-00050.pdf>
- 15 Administrative Rules of Montana. (2011, June 24). Prescription Requirements, Rule 24.174.510. Retrieved March 30, 2015, from <http://www.mtrules.org/gateway/ruleno.asp?RN=24.174.510>
- 16 Administrative Rules of North Dakota. (2012, October). Requirements of a Prescription Order for Noncontrolled Drugs, Chapter 61-04-06-02. Retrieved March 30, 2015, from <http://www.legis.nd.gov/information/acdata/pdf/61-04-06.pdf?20150330074620>
- 17 21 C.F.R. § 1306.05. Retrieved April 15, 2015, from http://www.ecfr.gov/cgi-bin/text-idx?rgn=div5;node=21%3A9.0.1.1.7#se21.9.1306_105
- 18 Lazarus, D. (2012, October 19). U.S. Investigating CVS Prescription Refills. Los Angeles Times. Retrieved March 17, 2015, from <http://articles.latimes.com/2012/oct/19/business/la-fi-lazarus-20121019>
- 19 Minnesota Department of Human Services. (2014, May 6). Pharmacy Services: Automatic Refills. Retrieved March 23, 2015, from http://www.dhs.state.mn.us/main/idcplg?IdcService=GET_DYNAMIC_CONVERSION&RevisionSelectionMethod=LatestReleased&DocName=id_008992#P193_17710

- 20 U.S. Department of Justice. (2014, December 3). Rite Aid Corporation Pays \$2.99 Million for Alleged Use of Gift Cards to Induce Medicare and Medicaid Business. Retrieved March 16, 2015, from <http://www.justice.gov/opa/pr/rite-aid-corporation-pays-299-million-alleged-use-gift-cards-induce-medicare-and-medicaid>
- 21 AMCP. (n.d.). The Academy of Managed Care Pharmacy's Concepts in Managed Care Pharmacy: Medication Stockpiling. Retrieved March 23, 2015, from <http://amcp.org/WorkArea/DownloadAsset.aspx?id=9792>
- 22 AMCP. (n.d.). The Academy of Managed Care Pharmacy's Concepts in Managed Care Pharmacy: Medication Stockpiling. Retrieved March 23, 2015, from <http://amcp.org/WorkArea/DownloadAsset.aspx?id=9792>
- 23 U.S. Department of Health and Human Services. Centers for Medicare & Medicaid Services. (2012, January). Drug Diversion in the Medicaid Program: State Strategies for Reducing Prescription Drug Diversion in Medicaid. Retrieved March 23, 2015, from <https://www.cms.gov/medicare-medicare-coordination/fraud-prevention/medicaidintegrityprogram/downloads/drugdiversion.pdf>
- 24 U.S. Department of Justice. Drug Enforcement Administration. Office of Diversion Control. (n.d.). Section IX – Valid Prescription Requirements. Retrieved May 7, 2015, from [http://www.dea.gov/diversion.usdoj.gov/pubs/manuals/pharm2/pharm_content.htm#9](http://www.dea.gov/diversion/usdoj.gov/pubs/manuals/pharm2/pharm_content.htm#9)
- 25 The United States Attorney's Office. Southern District of New York. (2014, October 9). Manhattan U.S. Attorney Settles Civil Fraud Claims Against Caremed [sic] Pharmaceutical Services for Engaging in Fraudulent Conduct. Retrieved March 17, 2015, from <http://www.justice.gov/usao/nys/pressreleases/October14/CareMedSettlementPR.php>
- 26 National Council for Prescription Drug Programs. (2013, November). Telecommunication Version D and Above Questions, Answers and Editorial Updates (p. 22). Retrieved March 24, 2015, from <http://www.ncdp.org/members/pdf/versiond.editorial.pdf>
- 27 National Council for Prescription Drug Programs. (2013, November). Telecommunication Version D and Above Questions, Answers and Editorial Updates (p. 22). Retrieved March 24, 2015, from <http://www.ncdp.org/members/pdf/versiond.editorial.pdf>
- 28 U.S. Department of Justice. Drug Enforcement Administration. Office of Diversion Control. (2000, February). A Pharmacist's Guide to Prescription Fraud. Retrieved March 24, 2015, from <http://www.dea.gov/diversion.usdoj.gov/pubs/brochures/pharmguide.htm>
- 29 New York State Office of the State Comptroller Thomas P. DiNapoli. Division of State Government Accountability. (2013, August). Payments for Fraudulent and Improper Claims Submitted by Davis Ethical Pharmacy. Retrieved March 24, 2015, from <http://osc.state.ny.us/audits/allaudits/093013/12s11.pdf>
- 30 University of Kansas School of Pharmacy. (n.d.). Dispensing (DAW) Codes. Retrieved March 24, 2015, from <http://pskills.pharm.ku.edu/rxgenerator/tp/DAWCodes.html>
- 31 National Council for Prescription Drug Programs. (2013, November). Telecommunication Version D and Above Questions, Answers and Editorial Updates (p. 19). Retrieved March 24, 2015, from <http://www.ncdp.org/members/pdf/versiond.editorial.pdf>
- 32 National Council for Prescription Drug Programs. (2005, October 4). NCPDP Reference Manual. Chapter 3: NCPDP Flat File Format. Retrieved March 24, 2015, from <https://www.cms.gov/Medicare/Billing/ElectronicBillingEDITrans/downloads/NCPDPflatfile.pdf>
- 33 U.S. Department of Health and Human Services. Office of Inspector General. (2012, September). Inappropriate Medicare Part D Payments for Schedule II Drugs Billed as Refills. Retrieved March 24, 2015, from <https://oig.hhs.gov/oei/reports/oei-02-09-00605.pdf>
- 34 The United States Attorney's Office. Southern District of West Virginia. (2015, February 25). Trivillian's Pharmacy, Owner Plead Guilty to Federal Health Care and Drug Crimes. Retrieved March 30, 2015, from <http://www.justice.gov/usao-sdvw/pr/trivillians-pharmacy-owner-plead-guilty-federal-health-care-and-drug-crimes>
- 35 The United States Attorney's Office. District of Maryland. (2014, December 15). Federal Jury Convicts Pharmacy Store Owner of Health Care Fraud and Identity Theft. Retrieved March 17, 2015, from <http://www.justice.gov/usao-md/pr/federal-jury-convicts-pharmacy-store-owner-health-care-fraud-and-identity-theft>
- 36 Reporting and Returning of Overpayments, 42 U.S.C. § 1320d. Retrieved March 30, 2015, from <http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title42-section1320a-7k&num=0&edition=prelim>
- 37 Robertson, B. (2011, September/October). Reporting and Returning Medicare and Medicaid Overpayments. [Reprinted from Journal of Healthcare Compliance, 13(5).] Retrieved March 31, 2015, from http://www.huschblackwell.com/~media/files/businessinsights/businessinsights/2011/09/reporting%20and%20returning%20medicare%20and%20medicaid%20ov___/files/reporting%20and%20returning%20medicare%20and%20medicaid%20ov___/fileattachment/jhcc_05-11_robertson.p
- 38 Romano, D.H. (2010, March). Compliance 101. The Fraud and Abuse Laws That Compliance Professionals Need to Know. Health Care Compliance Association. Retrieved April 1, 2015, from http://www.hcca-info.org/Portals/0/PDFs/Resources/Conference_Handouts/Compliance_Institute/2010/703handout7.pdf

39 U.S. Department of Justice. (n.d.). False Claims Act: A Primer. Retrieved March 31, 2015, from http://www.justice.gov/sites/default/files/civil/legacy/2011/04/22/C-FRAUDS_FCA_Primer.pdf

40 Romano, D.H. (2010, March). Compliance 101. The Fraud and Abuse Laws That Compliance Professionals Need to Know. Health Care Compliance Association. Retrieved April 1, 2015, from http://www.hcca-info.org/Portals/0/PDFs/Resources/Conference_Handouts/Compliance_Institute/2010/703handout7.pdf

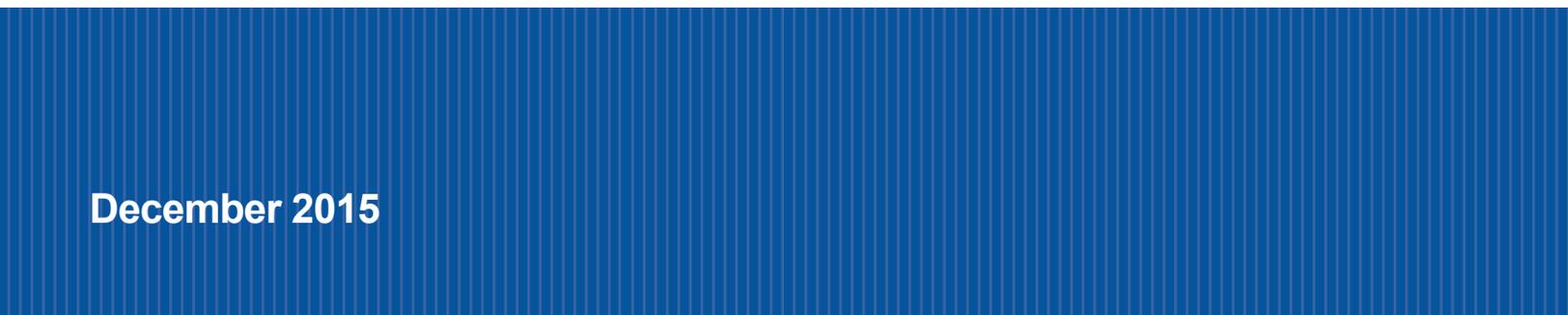
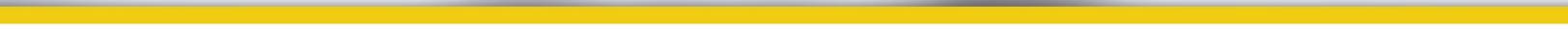
41 Center for Program Integrity and Center for Medicaid and CHIP Services. (2012, January 20). CPI-CMCS Informational Bulletin. Retrieved April 1, 2015, from <http://www.medicaid.gov/Federal-Policy-Guidance/downloads/CIB-01-20-12.pdf>

Disclaimer

This booklet was current at the time it was published or uploaded onto the web. Medicaid and Medicare policies change frequently so links to the source documents have been provided within the document for your reference.

This booklet was prepared as a service to the public and is not intended to grant rights or impose obligations. This booklet may contain references or links to statutes, regulations, or other policy materials. The information provided is only intended to be a general summary. Use of this material is voluntary. Inclusion of a link does not constitute CMS endorsement of the material. We encourage readers to review the specific statutes, regulations, and other interpretive materials for a full and accurate statement of their contents.

December 2015



December 2015

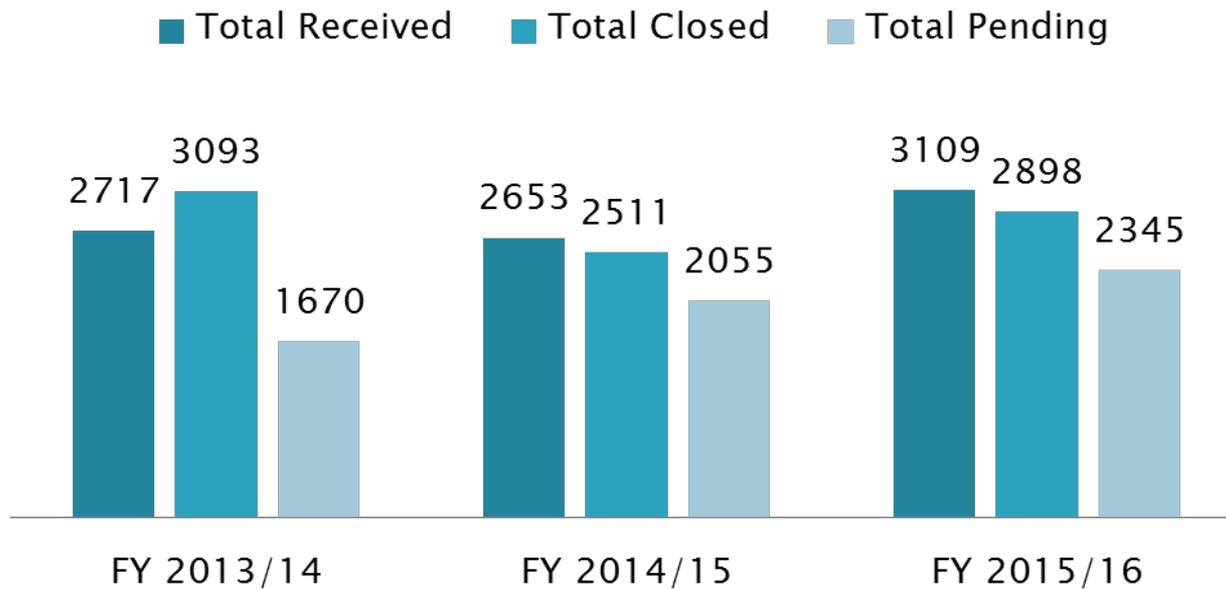
Attachment 4

Enforcement Committee Meeting Citation and Fine Presentation

California State Board of Pharmacy

Julia G. Ansel
Chief of Enforcement
August 31, 2016

Total COMPLAINTS



Total FINES ASSESSED

	FY13/14	FY 14/15	FY 15/16
Total Citations Issued	1985	1180	1976
Total Fines Assessed	\$13,011,000	\$1,694,080	\$2,264,285
Total Med Error Citations Issued*	638	377	578
<small>*One citation may include more than one med error violation.</small>			
Total Med Error Fines Assessed	\$286,750	\$202,600	\$394,450

Total CITATIONS ISSUED BY LICENSE TYPE

	FY 2015/16
Pharmacist with Citation and Fine	718
Pharmacist with Citation and no Fine	85
Pharmacy with Citation and Fine	381
Pharmacy with Citation and no Fine	252
Technician with Citation and Fine	319
Technician with Citation and no Fine	2
Wholesalers	23
Designated Representative	17
Clinics	5
Drug Room	1
Hospital or Pharmacy - Government Owned	12
Hospital	18
Miscellaneous (Intern, Correctional Facility, Non-Resident Pharmacy and Vet Retailers)	113
Unlicensed Activity	30
Total Citations FY 2015/16	1976

Closed

WITH CITATION AND FINE

	FY 13/14	FY14/15	FY 15/16
Pharmacist	339	224	352
PIC	363	196	366
Pharmacy	375	186	381
Total Closed with Citation and Fine	1077	606	1099

T OP TEN VIOLATIONS BY PHARMACIST Fiscal Year 2015/16

Violation	Percentage
CCR 1716 Variation from Prescription	43%
CCR 1714(d) Operational Standards and Security; pharmacist responsible for pharmacy security	17%
CCR 1764 / Civil Code 56.10 (a) Unauthorized Disclosure of Prescription Medical Information	7%
CCR 1707.2(b)(1)(A) In addition to obligation to consult...a pharmacist shall provide oral consultation to his or her patients...whenever the prescription drug has not been previously disclosed to the patient	6%
CCR 1707.3 Duty to review drug therapy	5%
BPC 4301 (h) Unprofessional Conduct; the administering to oneself, of any controlled substance, or use and any dangerous drug or of alcoholic beverages to the extent or in a manner as to be dangerous	5%
CCR 1714 (b) Operational Standards and Security; pharmacy responsible for pharmacy security	4%
BPC 4301(l) Unprofessional Conduct; conviction of a crime substantially related to the practice of pharmacy	4%
CCR 1711(d) Quality Assurance program finding shall be used to develop systems to prevent medication errors	4%
BPC 4231d)/ CCR1732.5 Failure to provide documentation substantiating completion of continuing education/ renewal requirements for pharmacist	4%

T OP TEN VIOLATIONS BY PHARMACIES

Fiscal Year 2015/16

Violation	Percentage
CCR 1716 Variation from Prescription	39%
CCR 1714 (b) Operational Standards and Security; pharmacy responsible for pharmacy security	21%
BPC 4113(d) Every pharmacy shall notify the board in writing within 30 days of the date of a change in PIC	10%
BPC 4113(a) PIC: Notification to the board; responsibilities, every pharmacy shall designate a PIC within 30days in writing of the identity of the license number of that pharmacist	7%
CCR 1764 / Civil Code 56.10 (a) Unauthorized Disclosure of Prescription Medical Information	6%
CCR 1707.3 Duty to review drug therapy	4%
CCR 1707.2(b)(1)(A) In addition to obligation to consult...a pharmacist shall provide oral consultation to his or her patients...whenever the prescription drug has not been previously disclosed to the patient	4%
CCR 1711(d) Quality Assurance program finding shall be used to develop systems to prevent medication errors	3%
BPC 4081 (a) records of dangerous drugs and devices kept open for inspection; maintenance of records, current inventory	3%
BPC 4305 (b) Disciplinary grounds: failure of pharmacy or pharmacist to notify of termination of PIC; continuing to operate without pharmacist; operation of pharmacy for more than 30 days without supervision or management by PIC	3%

T OP TEN VIOLATIONS BY PIC

Fiscal Year 2015/16

Violation	Percentage
CCR 1714(d) Operational Standards and Security; pharmacist responsible for pharmacy security	33%
CCR 1716 Variation from Prescription	25%
CCR 1764 / Civil Code 56.10 (a) Unauthorized Disclosure of Prescription Medical Information	7%
BPC 4081 (a) records of dangerous drugs and devices kept open for inspection; maintenance of records, current inventory	7%
CCR 1714 (b) Operational Standards and Security; pharmacy responsible for pharmacy responsible for pharmacy security	6%
CCR 1707.2(b)(1)(A) In addition to obligation to consult...a pharmacist shall provide oral consultation to his or her patients...whenever the prescription drug has not been previously disclosed to the patient	5%
CCR 1714 (c) Operational standards and security; the pharmacy must be maintained in a sanitary condition	5%
CCR 1711(d) Quality Assurance program finding shall be used to develop systems to prevent medication errors	5%
CCR 1735.2(j) Compounding requirements – PIC shall complete a compounding self assessment prior to any sterile injectable compounding is performed in pharmacy	5%
BPC 4081 (a) / CCR 1718 Records of dangerous drugs and devices kept open for inspection; maintenance of records, current inventory/ current inventory defined	4%

P RESCRIPTION ERRORS VIOLATION DATA

Fiscal Year 2015–16

Fine Amount	Number	Percent of total Violations
\$0	264	41%
\$100 - \$999	192	29%
\$1,000 - \$2,000	161	25%
\$2,500 - \$5,000	32	5%
Total Number of Med Error Violations	649	100%

MEDICATION ERROR DATA

Fiscal Year 2015/16

Look-alike / Sound-alike Errors		Lipitor	Lexapro
Clonazepam	Lorazepam	L-Thyroxine	Liothyronine
Clomid	Clomipramine	Lovaza	Lorazepam
Clomiphene	Clomipramine	Metformin	Metoprolol
Clomiphene	Clonazepam	Methadone	Metadate
Duricef	Fioricet	Methotrexate	Metolazone
Hydralazine	Hydroxyzine	Risperidone	Ropinirole
Hydrochlorothiazide	Hydroxyzine	Rocaltrol	Ropinirole
Ketorolac	Ketoconazole	Subocone	Suboxone
Labetalol	Lamotrigine	Tramadol	Trazodone

P RESCRIPTION ERROR CASES FY 2015/16

\$500 Fine

- # **Case 1:** A pharmacist-in-charge dispensed Clonidine .1mg to a patient instead of Trihexyphenidyl 2mg tablets. Patient ingested wrong medication.
 - # **Case 2:** A pharmacy dispensed a dry powder for Amoxicillin 125mg/5ml bottle, without mixing with water. Oral suspension for a child was given to patient in a powder form.
 - # **Case 3:** A pharmacy dispensed Boost Kid Essentials .03-1 gram-kcal/ml liquid instead of Pediasure .06-1.5 gram-kcal/ml liquid.
- 

P RESCRIPTION ERROR CASES FY 2015/16

\$750 Fine

- # **Case 1:** A pharmacist dispensed a prescription written for Xanax 1mg but filled it with Lorazepam 1mg tablets.
 - # **Case 2:** A pharmacist verified a prescription for Diethylpropion 75mg tablets labeled with directions for use of 1 tablet in the morning, despite being prescribed with direction for use of ½ to 1 tablet in the morning.
 - # **Case 3:** A pharmacist incorrectly dispensed one 5ml box of Erythromycin eye drops instead of the prescribed Gentamicin eye drops.
- 

P RESCRIPTION ERROR CASES FY 2015/16

\$1,000 Fine

- # **Case 1:** A pharmacy dispensed Montelukast 4mg tablets which had some Montelukast 5mg tablets co-mingled in the same bottle.
 - # **Case 2:** A pharmacy dispensed Picato .05% gel instead of prescribed Picato .015% gel.
 - # **Case 3:** A pharmacist dispensed Fioricet with codeine instead of the prescribed Fioricet plain.
- 

P RESCRIPTION ERROR CASES FY 2015/16

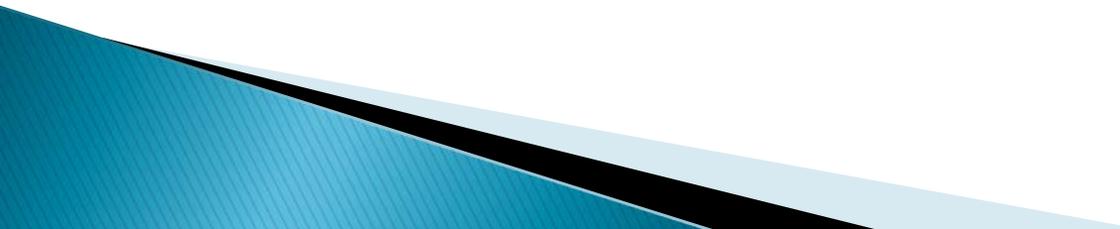
\$1,500 Fine

Case 1: Patient "Ira T." was dispensed medication meant for patient "Irma T".

Case 2: A pharmacy dispensed Cephalexin 500mg versus the prescribed Amoxicillin 500mg. Quality Assurance Review was not completed.

\$2,500 Fine

Case 1: A pharmacy allowed the compounding of drug products but failed to maintain a compounding log for each of the compounded drug products.



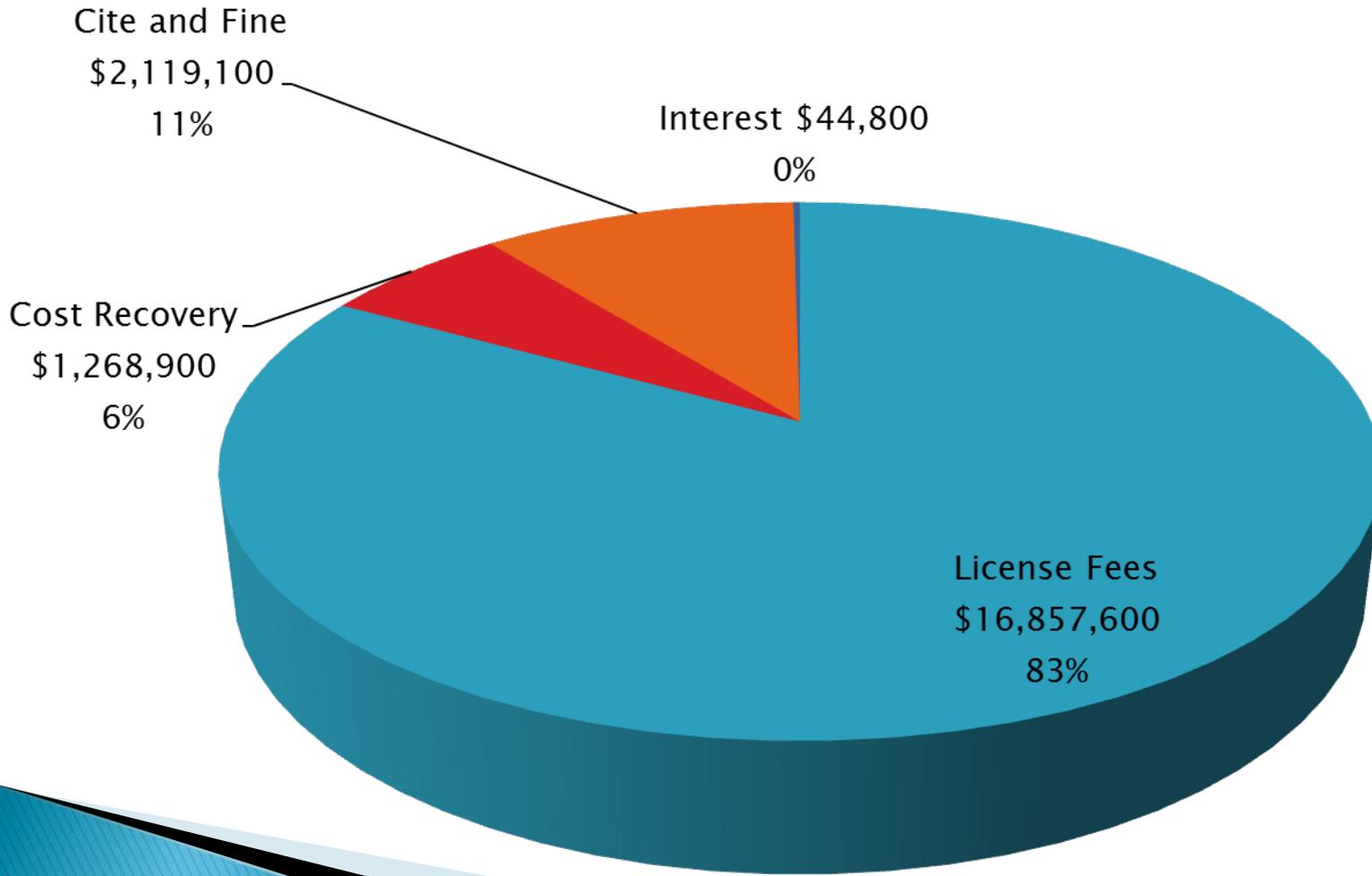
P RESCRIPTION ERROR CASES FY 2015/16

\$5,000 Fine

- # **Case 1:** A pharmacy dispensed clomipramine capsules instead of clomiphene tablets to a patient. Consumer ingested medication and became sick for two days. Patient was dispensed clomipramine capsules without oral consultation.
- # **Case 2:** A pharmacist dispensed a prescription for Metformin 1000mg, two tablets, twice a day versus prescribed Metformin 500mg, two tablets, twice a day. Pharmacists at this location failed to provide consultation to patients. Also failed to document medication errors.

Total Revenue

Fiscal Year 2015/16 FM 12



Attachment 5

Sterile Compounding Inspections Overview

Presented on 8/31/16
Enforcement & Compounding Committee
By Christine Acosta PharmD.

Number of LSC/NSC licenses

- 7/1/13: 365

- LSC: 272

- NSC: 93

- 7/1/14: 989

- LSC: 901

- NSC: 88

- 7/1/15: 1,026

- LSC: 936

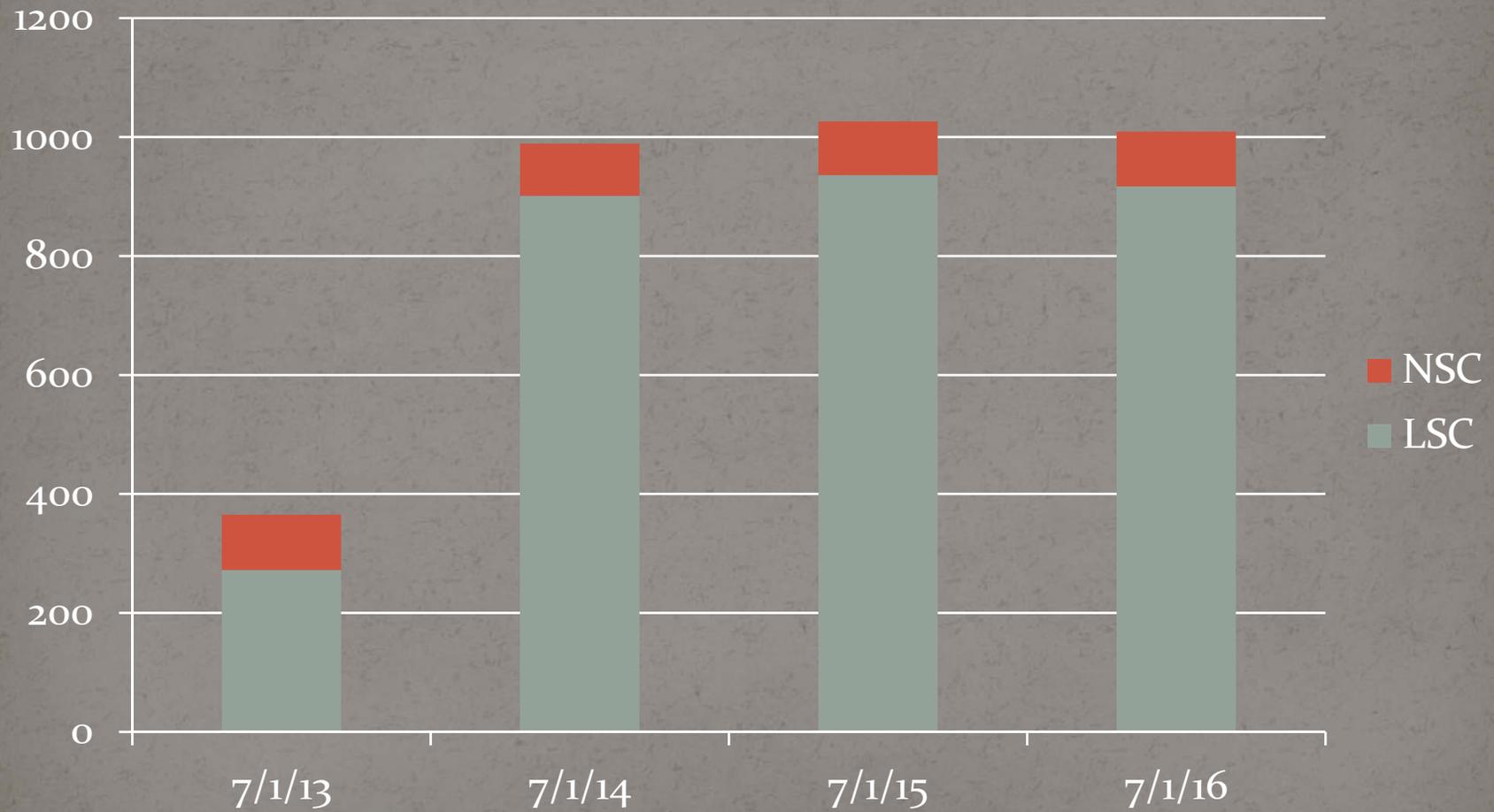
- NSC: 90

- 7/1/16: 1,009

- LSC: 917

- NSC: 92

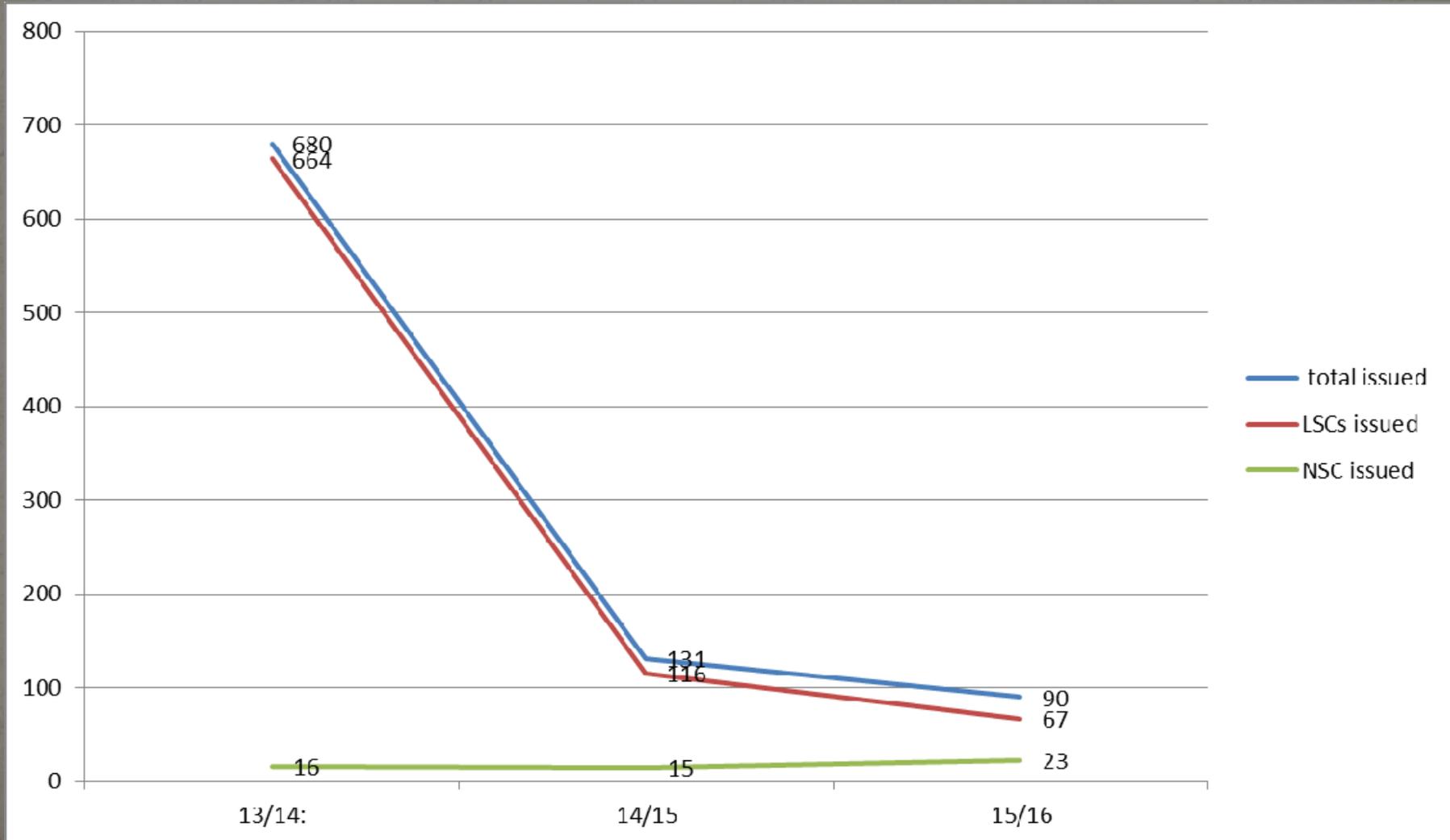
Total NSC and LSC Licenses By Year 2013-2016



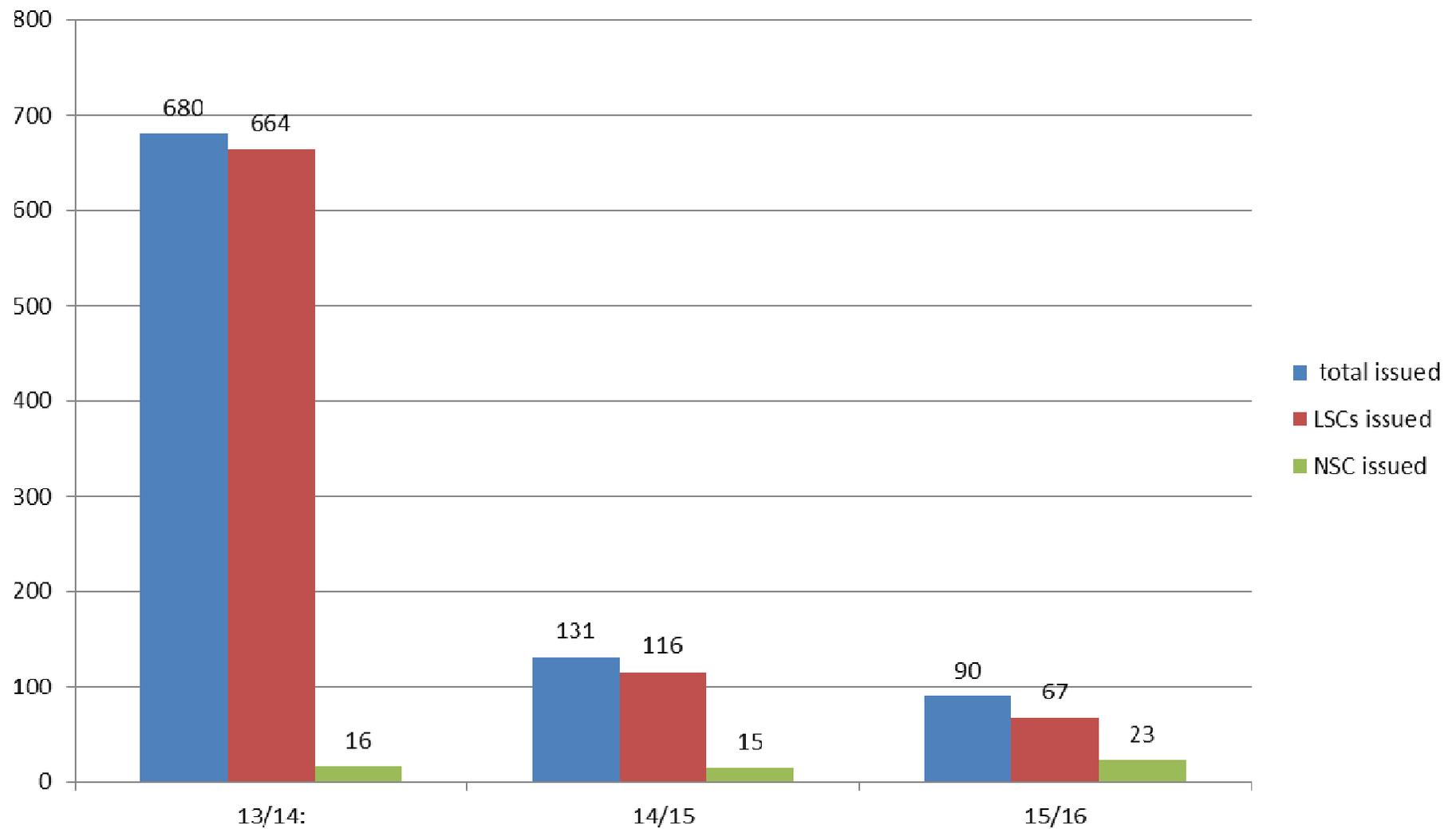
Number of NEW LSC issued

- FY 13/14: 680
 - LSC: 664
 - NSC: 16
- FY 14/15: 131
 - LSC: 116
 - NSC: 15
- FY 15/16: 90
 - LSC: 67
 - NSC: 23

Number of LSC issued

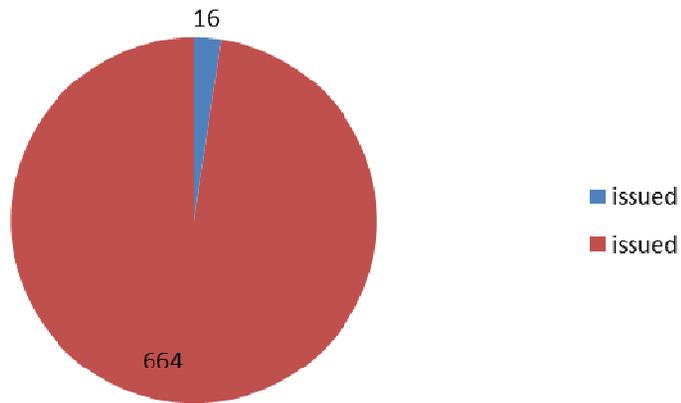


Number of LSC issued

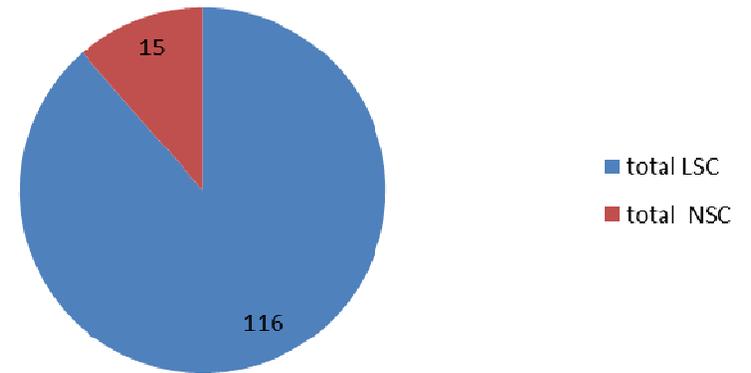


Number of LSC issued

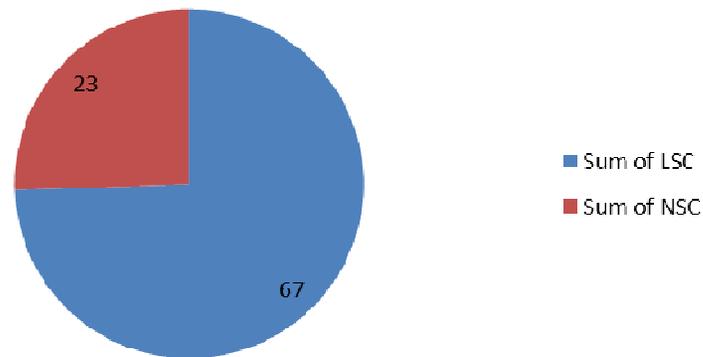
Licenses issued in FY13/14:



Licenses issued in FY 14/15



Licensed issued in FY 15/16



Number of LSC inspections done

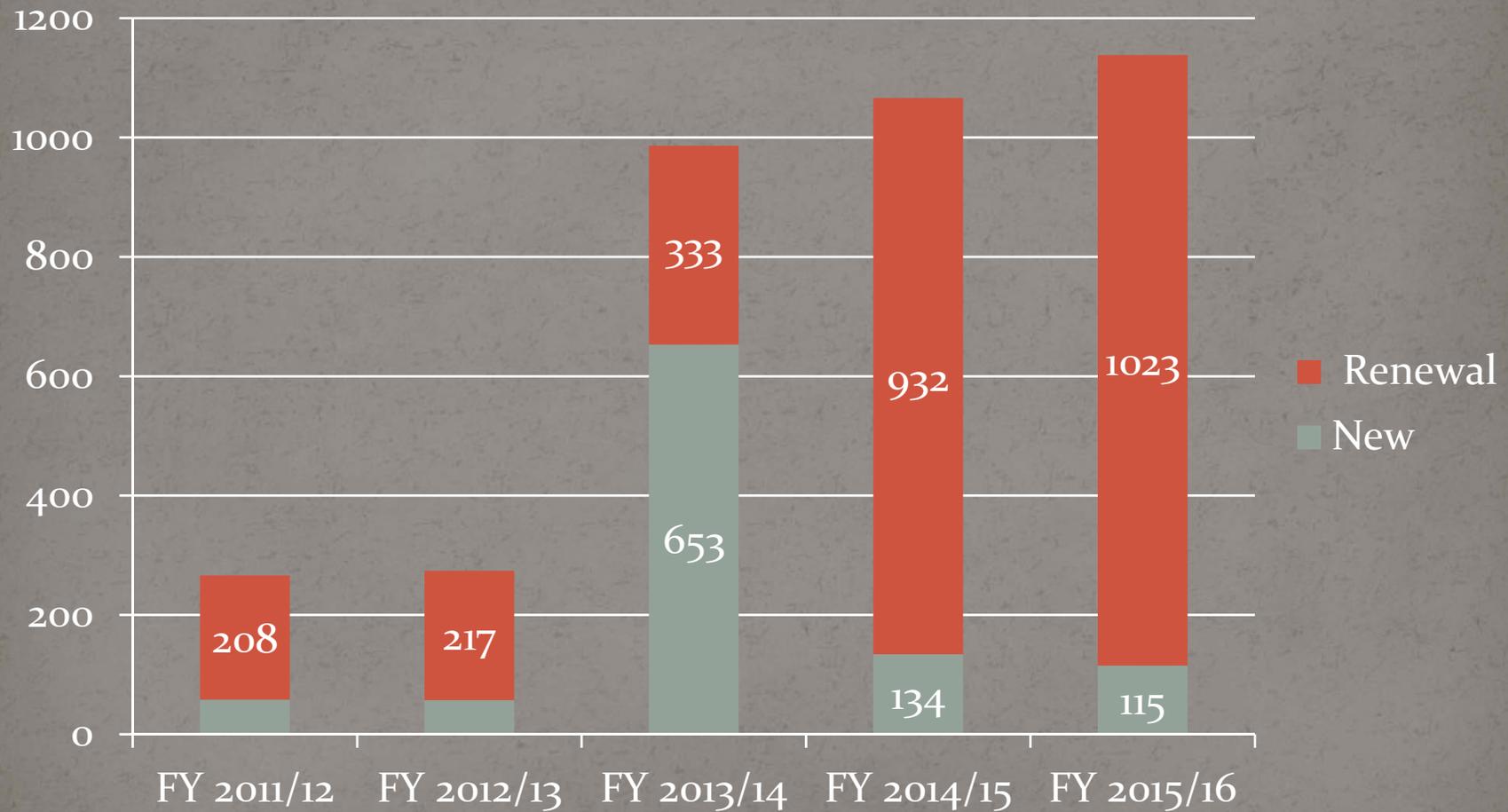
NEW

- FY11/12: 58
- FY: 12/13: 57
- FY 13/14: 653
- FY 14/15: 134
- FY 15/16: 115

Renewal

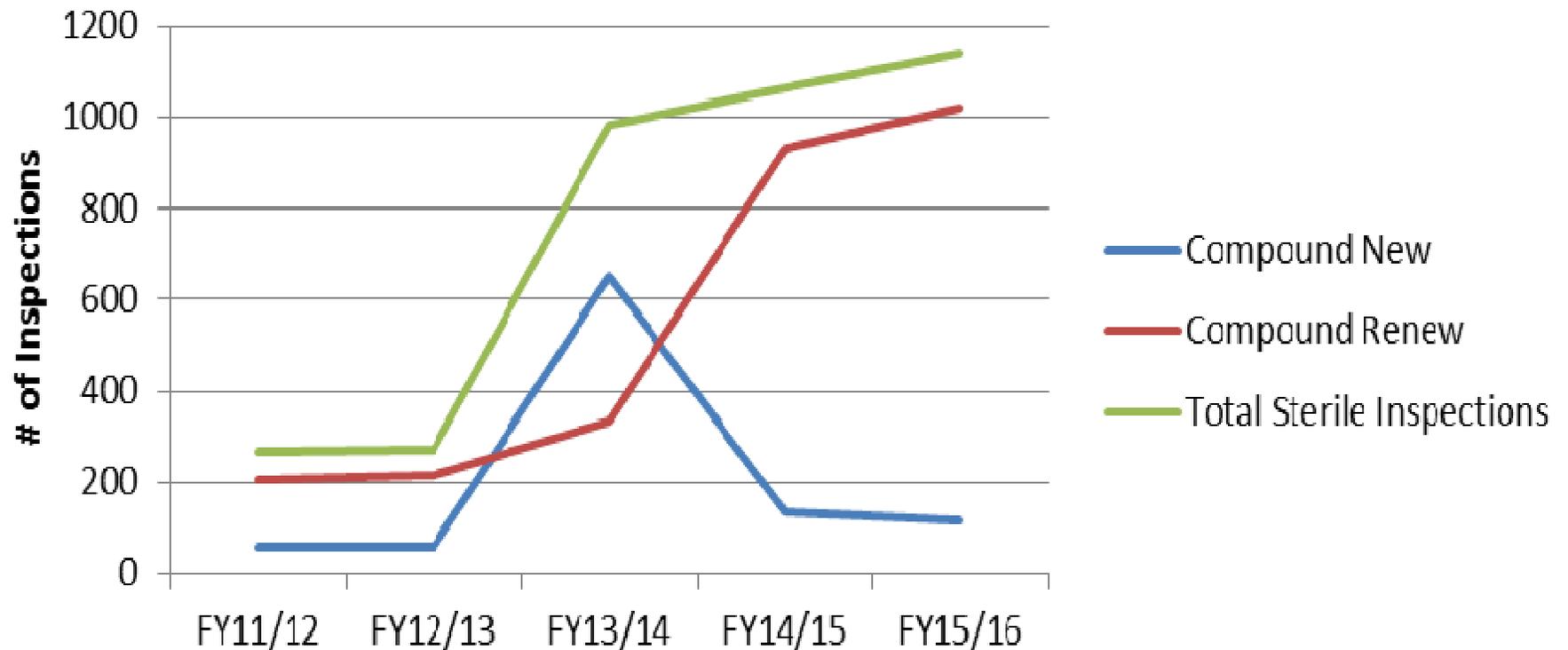
- FY: 11/12: 208
- FY: 12/13: 217
- FY 13/14: 333
- FY 14/15: 932
- FY 15/16: 1,023

Total LSC Inspections Performed FY 2012/13 to FY 2015/16



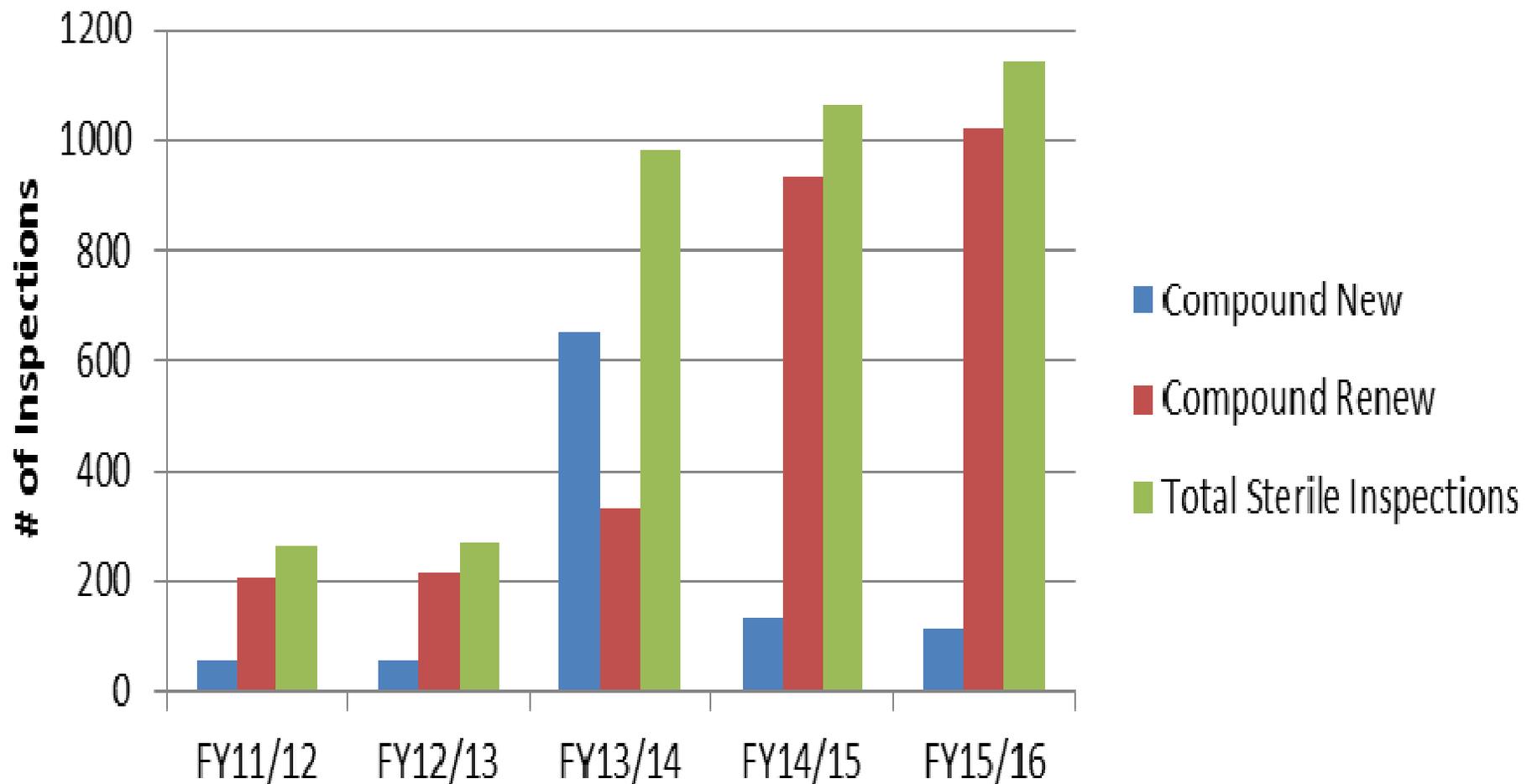
Number of LSC inspections done

Sterile Compounding New and Renewal Inspections

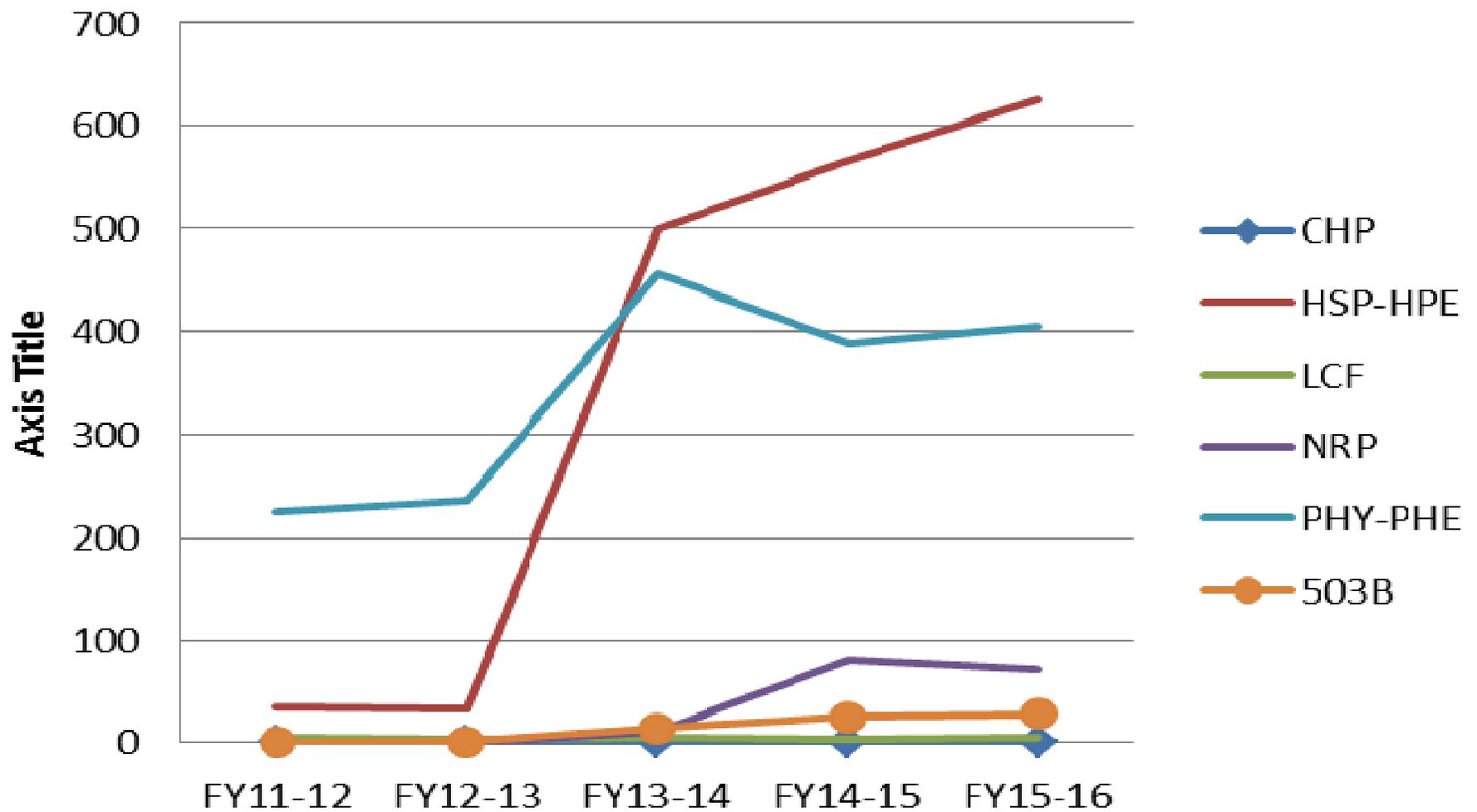


Number of LSC inspections done

Sterile Compounding New and Renewal Inspections



Sterile Compounding Inspections by License Type

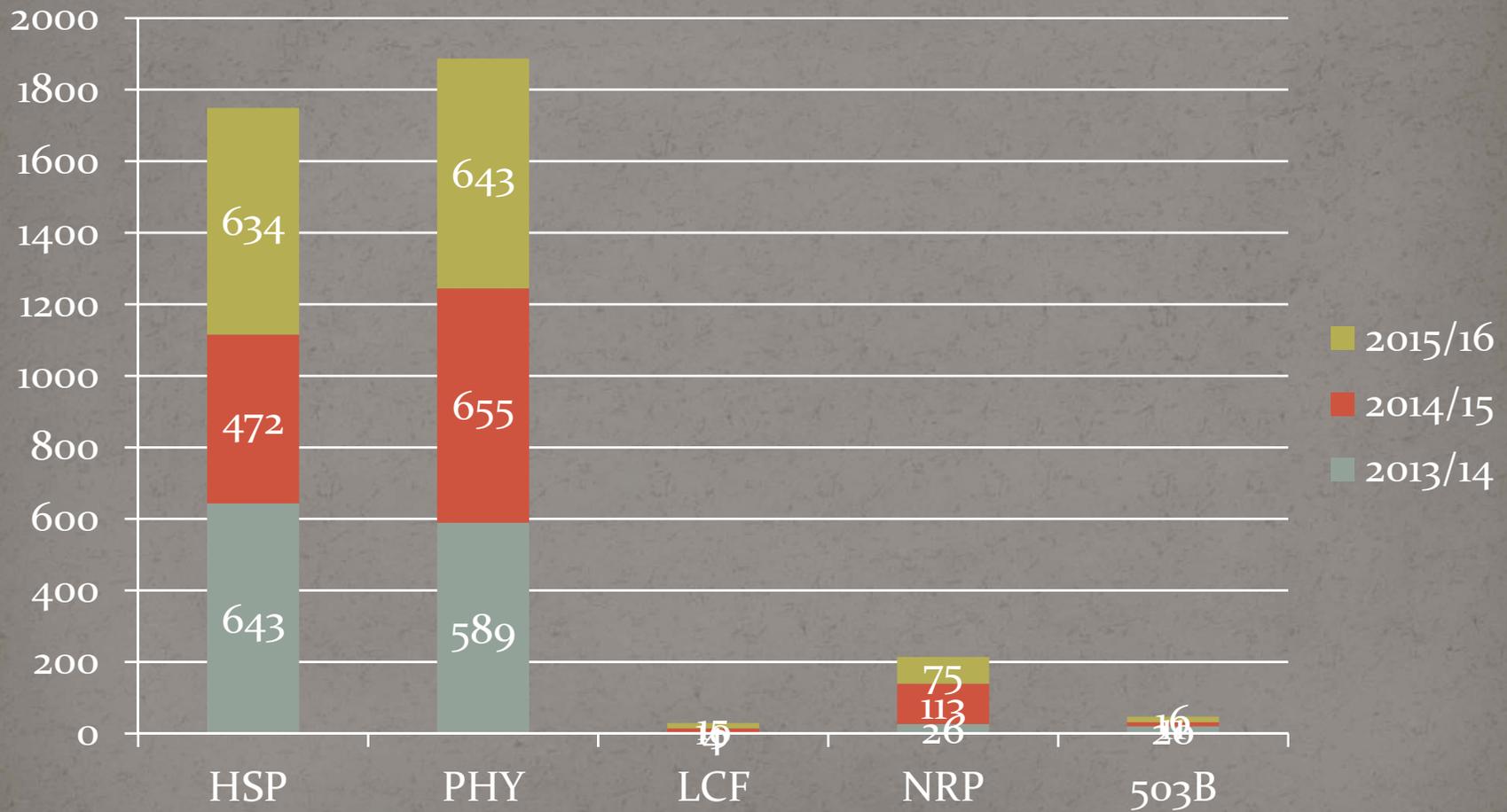


Number of violations:

- FY 13/14: 1,282
 - HSP: 643
 - PHY: 589
 - LCF: 4
 - NRP: 26
 - 503b: 20

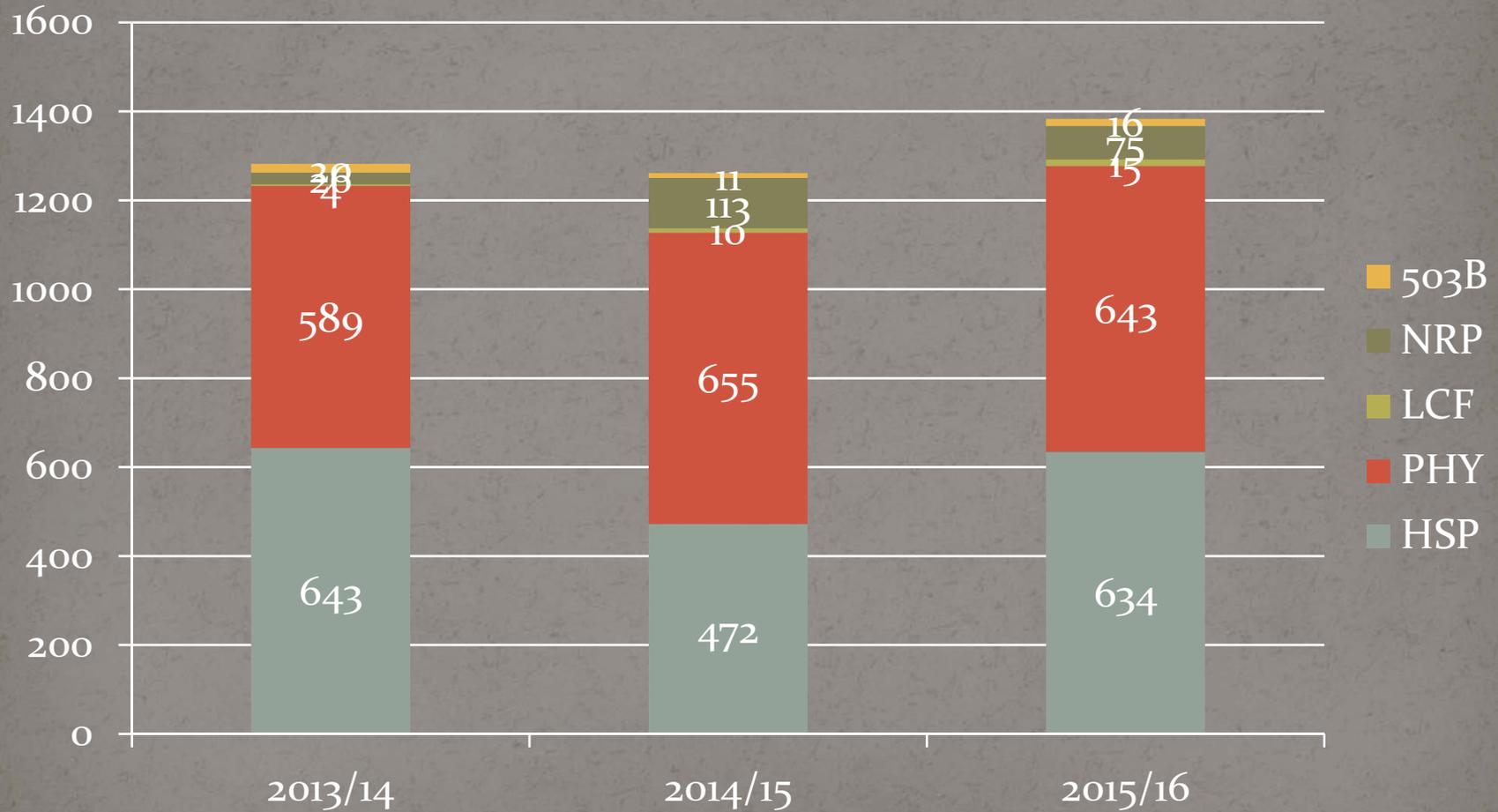
Violations by License Type

FY 2013/14, 2014/15, 2015/16



Total Violations by Year

FY 2013/14, 2014/15 and 2015/16



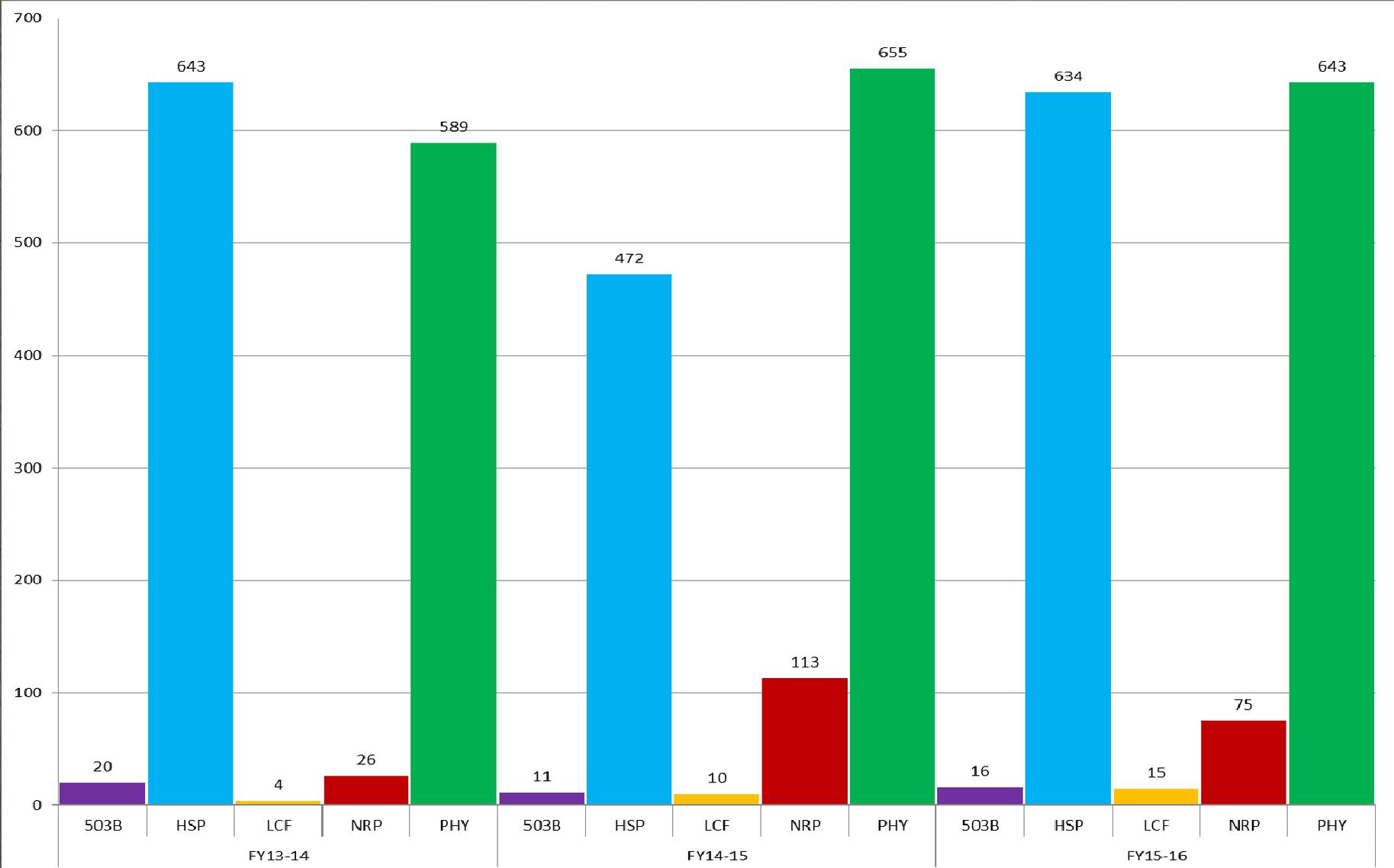
number of violations by

- FY 14/15: 1,261
 - HSP: 472
 - PHY: 655
 - LCF: 10
 - NRP: 113
 - 503b: 11

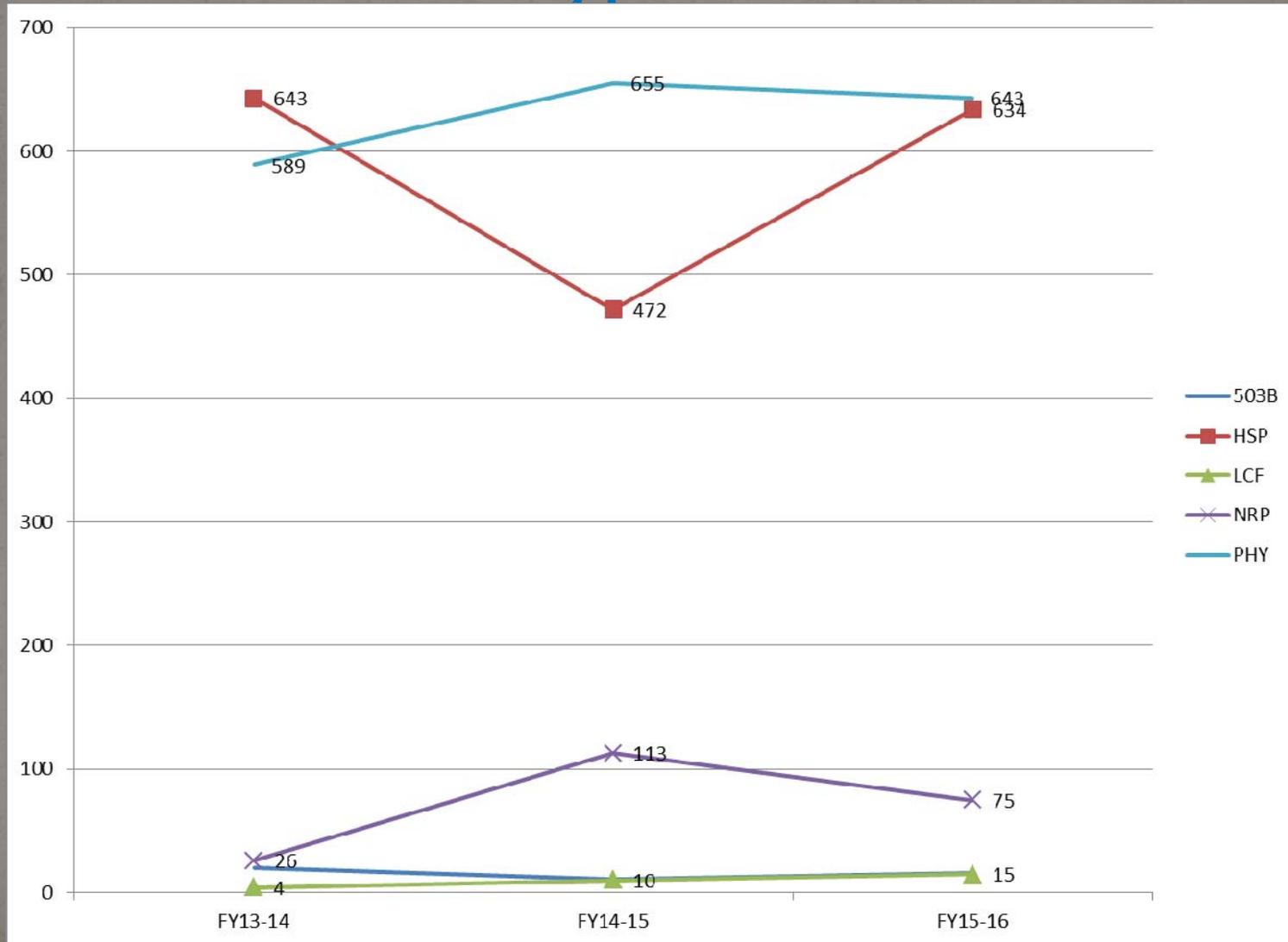
Number of violations

- FY 15/16: 1,383
 - HSP: 634
 - PHY: 643
 - LCF: 15
 - NRP: 75
 - 503b: 16

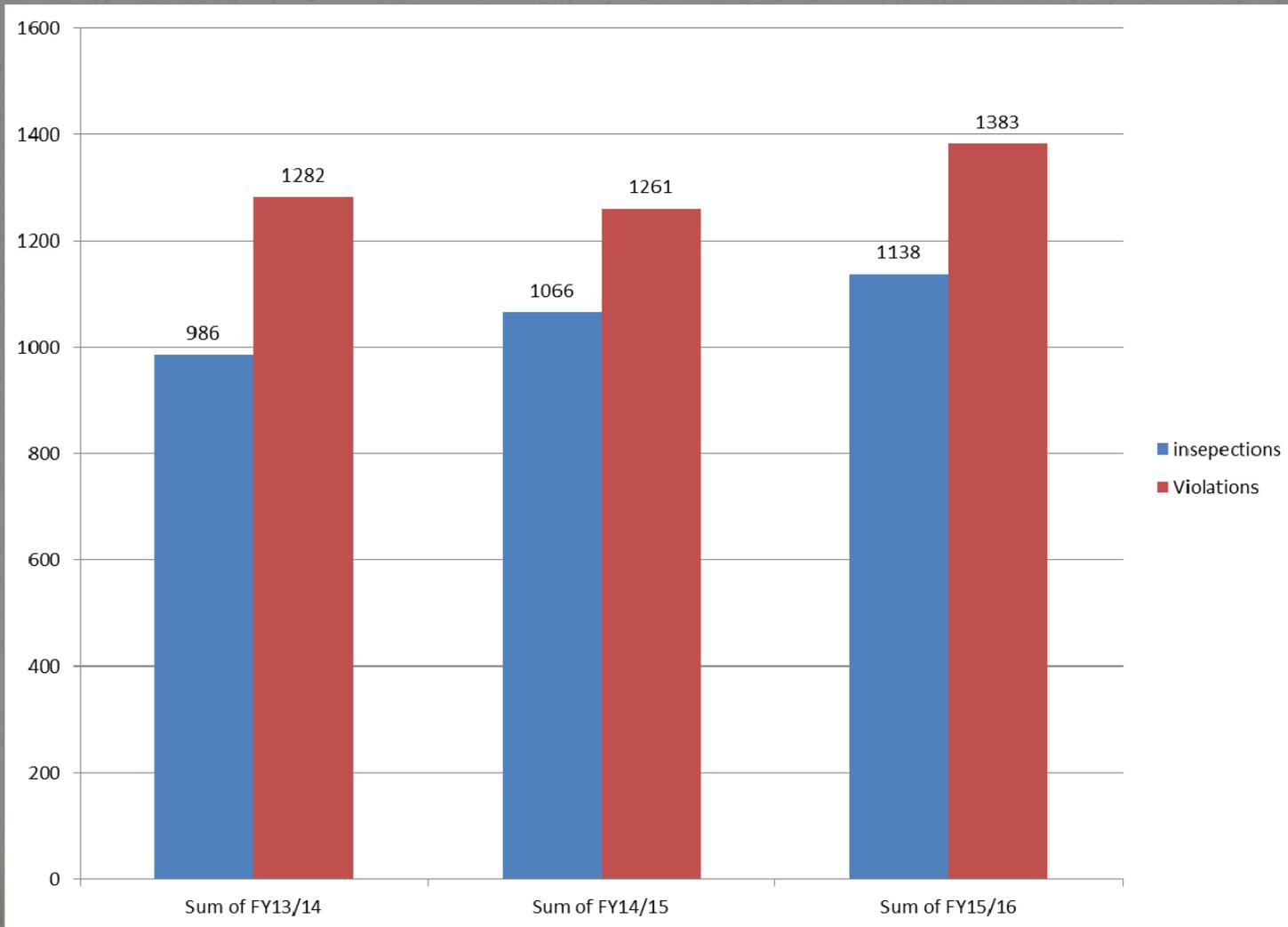
Number of violations by FY and license type



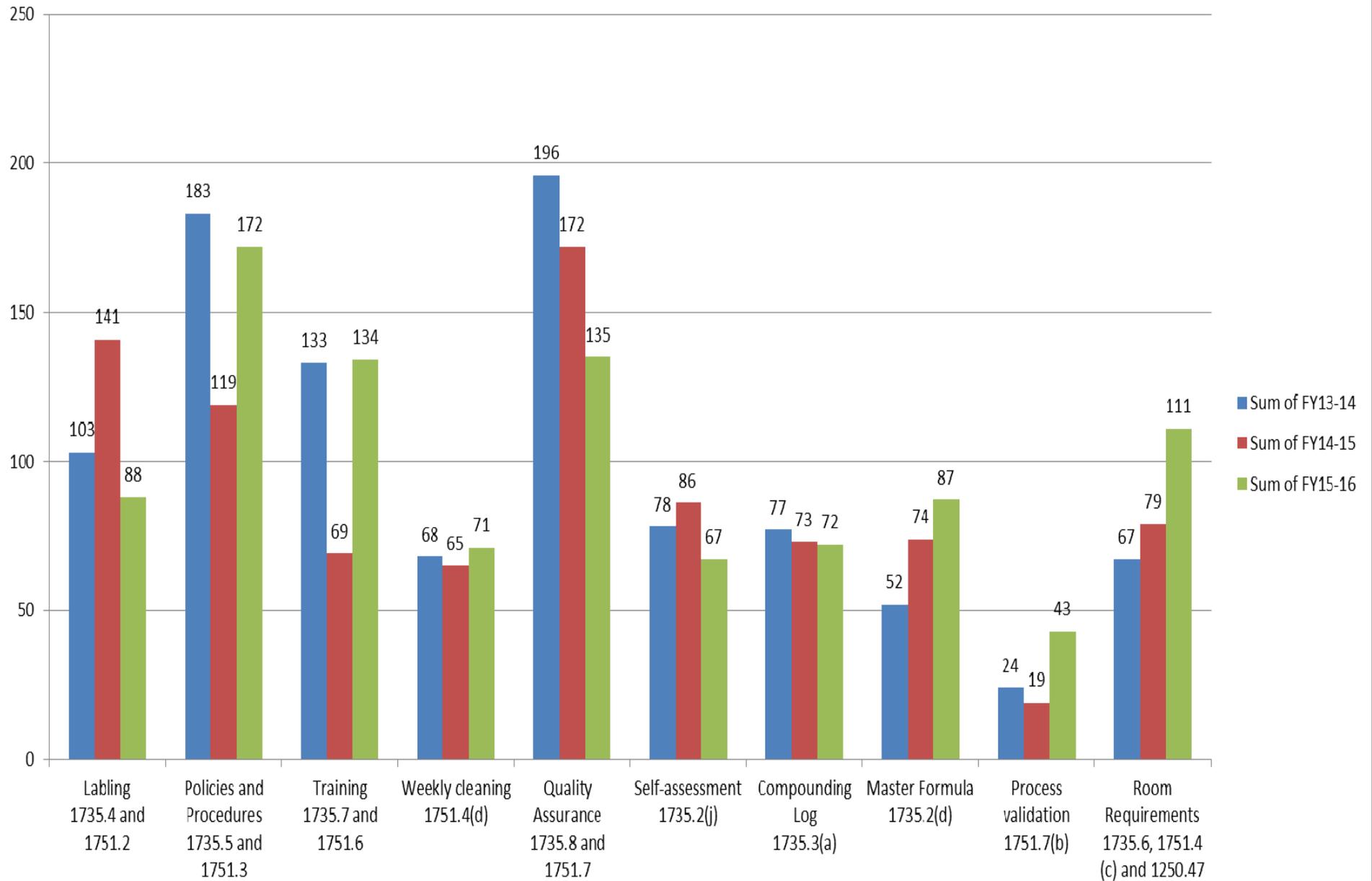
Number of violations by FY and license type



number of violations by related to the number of inspection done



Top Violations



Number of LSC on probation on 7/1

	FY13/14	FY14/15	FY15/16
• PHY	2	5	9
• HSP	0	0	0
• NRP	1	1	0

Number of LSCs with actions during each FY

	FY13/14	FY14/15	FY15/16
• Revocation	0	0	0
• Probation	4	0	1
• Voluntary Surrender	2	3	1
• Public Reprimand	0	0	2

Number of LSCs referred to the AG

	FY13/14	FY14/15	FY15/16
• LSC	2	1	0
• NSC	0	1	1

Sterile Compounding Inspections: Overview

THE END

Attachment 6

Board of Pharmacy

To Amend § 1735 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1735. Compounding in Licensed Pharmacies.

(a) "Compounding" means any of the following activities occurring in a licensed pharmacy, by or under the supervision of a licensed pharmacist, pursuant to a prescription:

- (1) Altering the dosage form or delivery system of a drug
- (2) Altering the strength of a drug
- (3) Combining components or active ingredients
- (4) Preparing a compounded drug product preparation from chemicals or bulk drug substances

(b) "Compounding" does not include reconstitution of a drug pursuant to a manufacturer's direction(s) ~~for oral, rectal, topical, or injectable administration~~, nor does it include the sole act of tablet splitting or crushing, capsule opening, or the addition of flavoring agent(s) to enhance palatability.

~~(c) "Compounding" does not include, except in small quantities under limited circumstances as justified by a specific, documented, medical need, preparation of a compounded drug product that is commercially available in the marketplace or that is essentially a copy of a drug product that is commercially available in the marketplace~~

~~(d)~~(c) 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 1751 et seq.).

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

To Amend § 1735.1 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1735.1. Compounding Definitions.

(a) “Ante-area” means an area with ISO Class 8 or better air quality where personnel hand hygiene and garbing procedures, staging of components, and other high-particulate-generating activities are performed, that is adjacent to the area designated for sterile compounding. It is a transition area that begins the systematic reduction of particles, prevents large fluctuations in air temperature and pressures in the cleanroom, and maintains air flows from clean to dirty areas. ISO Class 7 or better air quality is required for ante-areas providing air to a negative pressure room.

(b) “Beyond use date” means the date, or date and time, after which administration of a compounded drug preparation shall not begin, the preparation shall not be dispensed, and the preparation shall not be stored (other than for quarantine purposes).

(c) “Biological Safety Cabinet (BSC)” means a ventilated cabinet for compounding sterile drug preparations, having an open front with inward airflow for personnel protection, downward HEPA-filtered laminar airflow for product protection, and HEPA-filtered exhausted air for environmental protection. Where hazardous drugs are prepared, the exhaust air from the biological safety cabinet shall be appropriately removed by properly designed external building ventilation. This external venting should be dedicated to one BSC or CACI.

(d) “Bulk drug substance” means any substance that, when used in the preparation of a compounded drug preparation, processing, or packaging of a drug, is an active ingredient or a finished dosage form of the drug, but the term does not include any intermediate used in the synthesis of such substances.

(e) “Cleanroom or clean area or buffer area” means a room or area with HEPA-filtered air that provides ISO Class 7 or better air quality where the primary engineering control (PEC) is physically located.

(1) For nonhazardous compounding a positive pressure differential of 0.02- to 0.05-inch water column relative to all adjacent spaces is required.

(2) For hazardous compounding at least 30 air changes per hour of HEPA-filtered supply air and a negative pressure of between 0.01 to 0.03 inches of water column relative to all adjacent spaces is required.

(f) "Compounding Aseptic Containment Isolator (CACI)" means a unidirectional HEPA-filtered airflow compounding aseptic isolator (CAI) designed to provide worker protection from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes and to provide an aseptic environment for compounding sterile preparations. Air exchange with the surrounding environment should not occur unless the air is first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Where hazardous drugs are prepared, the exhaust air from the isolator shall be appropriately removed by properly designed external building ventilation. This external venting should be dedicated to one BSC or CACI. Air within the CACI shall not be recirculated nor turbulent.

(g) "Compounding Aseptic Isolator (CAI)" means a form of isolator specifically designed for non-hazardous compounding of pharmaceutical ingredients or preparations while bathed with unidirectional HEPA-filtered air. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless the air has first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded. Air within the CAI shall not be recirculated nor turbulent.

(h) "Controlled cold temperature" means 2 degrees to 8 degrees C (35 degrees to 46 degrees F).

(i) "Controlled freezer temperature" means -25 degrees to -10 degrees C (-13 degrees to 14 degrees F) or at a range otherwise specified by the pharmaceutical manufacturer(s) for that product.

(j) "Controlled room temperature" means 20 degrees to 25 degrees C (68 degrees to 77 degrees F).

(k) "Copy or essentially a copy" of a commercially available drug product includes all preparations that are comparable in active ingredients to commercially available drug

products, except that it does not include any preparations in which there has been a change, made for an identified individual patient, which produces for that patient a clinically significant difference, as determined by a prescribing practitioner, between that compounded preparation and the comparable commercially available drug product.

(l) "Daily" means occurring every day the pharmacy is operating, except when daily monitoring of refrigerator and freezer temperature are required, then daily means every 24 hours.

(m) "Displacement airflow method" means a concept which utilizes a low pressure differential, high airflow principle to maintain segregation from the adjacent ante-area by means of specific pressure differentials. This principle of displacement airflow shall require an air velocity of 40 ft per minute or more, from floor to ceiling and wall to wall, from the clean area across the line of demarcation into the ante-area. The displacement concept may not be used to maintain clean area requirements for sterile compounds which originate from any ingredient that was at any time non-sterile, regardless of intervening sterilization of the ingredient, or for hazardous compounds.

(n) "Dosage unit" means a quantity sufficient for one administration to one patient.

(o) "Equipment" means items that must be calibrated, maintained or periodically certified.

(p) "First air" means the air exiting the HEPA filter in a unidirectional air stream that is essentially particle free.

(q) "Gloved fingertip sampling" means a process whereby compounding personnel lightly press each fingertip and thumb of each hand onto appropriate growth media, which are then incubated at a temperature and for a time period conducive to multiplication of microorganisms, and then examined for growth of microorganisms.

(r) "Hazardous" means all anti-neoplastic agents identified by the National Institute for Occupational Safety and Health (NIOSH) as meeting the criteria for a hazardous drug and any other drugs, compounds, or materials identified as hazardous by the pharmacist-in-charge.

(s) "Integrity" means retention of potency until the ~~expiration~~ beyond use date ~~noted~~ provided on the label, so long as the preparation is stored and handled according to the label directions.

(t) "Lot" means one or more compounded drug preparation(s) prepared during one uninterrupted continuous cycle of compounding from one or more common active

ingredient(s).

(u) "Media-fill test" means a test used to measure the efficacy of compounding personnel in aseptic techniques whereby compounding procedures are mimicked using a growth-based media and then the resulting preparation is evaluated for sterility. The media-fill test must mimic the most complex compounding procedures performed by the pharmacy.

(v) "Non-sterile-to-sterile batch" means any compounded drug preparation containing two (2) or more dosage units with any ingredient that was at any time non-sterile, regardless of intervening sterilization of that ingredient.

(w) "Parenteral" means a preparation of drugs administered in a manner other than through the digestive tract. It does not include topical, sublingual, rectal or buccal routes of administration.

(x) "Personal protective equipment" means clothing or devices that protect the employee from exposure to compounding ingredients and/or potential toxins and minimize the contamination of compounded preparations. These include shoe covers, head and facial hair covers, face masks, gowns, and gloves.

(y) "Potency" means active ingredient strength within +/- 10% (or the range specified in USP37-NF32, 37th Revision, Through 2nd Supplement Effective December 1, 2014) of the labeled amount. Sterile injectable products compounded solely from commercially manufactured sterile pharmaceutical products in a health care facility licensed under section 1250 of the Health and Safety Code are exempt from this definition. For those exempt, the range shall be calculated and defined in the master formula.

(z) "Preparation" means a drug or nutrient compounded in a licensed pharmacy; the preparation may or may not be sterile.

(aa) "Prescriber's office" or "prescriber office" means an office or suite of offices in which a prescriber regularly sees patients for outpatient diagnosis and treatment. This definition does not include any hospital, pharmacy, or other facility, whether or not separately licensed, that may be affiliated with, adjacent to, or co-owned by, the prescriber's practice environment.

(ab) "Primary Engineering Control (PEC)" means a device that provides an ISO Class 5 or better environment through the use of non-turbulent, unidirectional HEPA-filtered first air for

compounding sterile preparations. Examples of PEC devices include, but are not limited to, laminar airflow workbenches, biological safety cabinets, sterile compounding automated robots, compounding aseptic isolators, and compounding aseptic containment isolators.

(ac) "Process validation" means demonstrating that when a process is repeated within specified limits, the process will consistently produce preparations complying with predetermined requirements. If any aspect of the process is changed, the process would need to be revalidated.

(ad) "Product" means a commercially manufactured drug or nutrient evaluated for safety and efficacy by the FDA.

(ae) "Quality" means the absence of harmful levels of contaminants, including filth, putrid, or decomposed substances, and the absence of active ingredients other than those listed on the label, and the absence of inactive ingredients other than those listed on the master formula document.

(af) "Segregated sterile compounding area" means a designated space for sterile-to-sterile compounding where a PEC is located within either a demarcated area (at least three foot perimeter) or in a separate room. Such area or room shall not contain and shall be void of activities and materials that are extraneous to sterile compounding. The segregated sterile compounding area shall not be in a location that has unsealed windows or doors that connect to the outdoors, in a location with high traffic flow, or in a location that is adjacent to construction sites, warehouses, or food preparation. The segregated sterile compounding area shall not have a sink, other than an emergency eye-washing station, located within three feet of a PEC. The segregated sterile compounding area shall be restricted to preparation of sterile-to-sterile compounded preparations.

(1) The BUD of a sterile drug preparation made in a segregated sterile compounding area is limited to 12 hours or less as defined by section 1751.8(d).

(2) When the PEC in the segregated sterile compounding area is a CAI or a CACI and the documentation provided by the manufacturer shows it meets the requirements listed in section 1751.4(f)(1)-(3), the assigned BUD shall comply with section 1751.8(a-b) or (d).

(ag) "Strength" means amount of active ingredient per unit of a compounded drug product

preparation.

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

To Amend § 1735.2 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1735.2. Compounding Limitations and Requirements; Self-Assessment.

(a) Except as specified in (b) and (c), no drug ~~product~~ preparation shall be compounded prior to receipt by a pharmacy of a valid prescription for an individual patient where the prescriber has approved use of a compounded drug ~~product~~ preparation either orally or in writing. Where approval is given orally, that approval shall be noted on the prescription prior to compounding.

(b) A pharmacy may prepare and store a limited quantity of a compounded drug ~~product~~ preparation in advance of receipt of a patient-specific prescription where and solely in such quantity as is necessary to ensure continuity of care for an identified population of patients of the pharmacy based on a documented history of prescriptions for that patient population.

(c) A “reasonable quantity” ~~as used in~~ that may be furnished to a prescriber for office use by the prescriber as authorized by Business and Professions Code section 4052, subdivision (a)(1), means that amount of compounded drug ~~product~~ preparation that:

(1) ~~is~~ ordered by the prescriber or the prescriber’s agent using a purchase order or other documentation received by the pharmacy prior to furnishing that lists the number of patients seen or to be seen in the prescriber’s office for whom the drug is needed or anticipated, and the quantity for each patient that is sufficient for office administration or application to patients in the prescriber’s office, or for distribution of not more than a 72-hour supply to the prescriber’s patients, as estimated by the prescriber; and

(2) Is delivered to the prescriber’s office and signed for by the prescriber or the prescriber’s agent; and

(3) Is sufficient for administration or application to patients solely in the prescriber's office, or

for furnishing of not more than a 120-hour supply for veterinary medical practices, solely to the prescriber's own veterinary patients seen as part of regular treatment in the prescriber's office, as fairly estimated by the prescriber and documented on the purchase order or other documentation submitted to the pharmacy prior to furnishing; and

~~(2)~~(4) That the pharmacist has a credible basis for concluding it is a reasonable quantity for office use ~~is reasonable~~ considering the intended use of the compounded medication and the nature of the prescriber's practice; and

~~(3)~~ (5) for With regard to any individual prescriber to whom the pharmacy furnishes, and with regard to ~~for~~ all prescribers to whom the pharmacy furnishes, taken as a whole, is an amount which the pharmacy is capable of compounding in compliance with pharmaceutical standards for integrity, potency, quality and strength of the compounded drug product preparation; and

(6) Does not exceed an amount the pharmacy can reasonably and safely compound.

(d) No pharmacy or pharmacist shall compound a drug preparation that:

(1) Is classified by the FDA as demonstrably difficult to compound;

(2) Appears on an FDA list of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective; or

(3) Is a copy or essentially a copy of one or more commercially available drug products, unless that drug product appears on an ASHP (American Society of Health-System Pharmacists) or FDA list of drugs that are in short supply at the time of compounding and at the time of dispense, and the compounding of that drug preparation is justified by a specific, documented medical need made known to the pharmacist prior to compounding. The pharmacy shall retain a copy of the documentation of the shortage and the specific medical need in the pharmacy records for three years from the date of receipt of the documentation.

~~(d)~~(e) A drug product preparation shall not be compounded until the pharmacy has first prepared a written master formula-record document that includes at least the following elements:

(1) Active ingredients to be used.

(2) Equipment to be used.

(3) ~~Expiration dating requirements.~~ The maximum allowable beyond use date for the preparation, and the rationale or reference source justifying its determination.

(4) Inactive ingredients to be used.

(5) ~~Process and/or procedure~~ Specific and essential compounding steps used to prepare the drug.

(6) Quality reviews required at each step in preparation of the drug.

(7) Post-compounding process or procedures required, if any.

(8) Instructions for storage and handling of the compounded drug preparation.

~~(e)(f)~~ Where a pharmacy does not routinely compound a particular drug ~~product~~ preparation, the master formula record for that ~~product~~ preparation may be recorded on the prescription document itself.

~~(f)(g)~~ The pharmacist performing or supervising compounding is responsible for the integrity, potency, quality, and labeled strength of a compounded drug ~~product~~ preparation until ~~it~~ the beyond use date indicated on the label, so long as label instructions for storage and handling are followed after the preparation is dispensed.

~~(g)(h)~~ 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.

~~(h)(i)~~ Every compounded drug ~~product~~ preparation shall be given an ~~expiration~~ beyond use date representing the date or date and time beyond which the compounded drug preparation should not be used, stored, transported or administered, and determined based on the professional judgment of the pharmacist performing or supervising the compounding. ~~in the professional judgment of the pharmacist performing or supervising the compounding, it should not be used.~~

(1) For non-sterile compounded drug preparation(s), ~~the beyond use date~~ This “beyond use date” of the compounded drug product shall not exceed any of the following: 180 days from preparation or

(A) the shortest expiration date or beyond use date of any component ingredient in the compounded drug product preparation,

- (B) the chemical stability of any one ingredient in the compounded drug preparation;
- (C) the chemical stability of the combination of all ingredients in the compounded drug preparation,
- (D) 180 days for non-aqueous formulations,
- (E) 14 days for water-containing oral formulations, and
- (F) 30 days for water-containing topical/dermal and mucosal liquid and semisolid formulations.

(2) For sterile compounded drug preparations, the beyond use date shall not exceed any of the following:

- (A) The shortest expiration date or beyond use date of any ingredient in the sterile compounded drug product preparation,
- (B) The chemical stability of any one ingredient in the sterile compounded drug preparation,
- (C) The chemical stability of the combination of all ingredients in the sterile compounded drug preparation, and
- (D) The beyond use date assigned for sterility in section 1751.8.

(3) Extension of a beyond use date is only allowable when supported by the following:

- (A) Method Suitability Test,
- (B) Container Closure Integrity Test, and
- (C) Stability Studies

~~unless a longer later date is supported by stability studies of~~

(4) In addition to the requirements of paragraph three (3), the ~~finished~~ drugs or compounded drug ~~products~~ preparations tested and studied shall be using the same identical components in ingredients, specific and essential compounding steps, quality reviews, and packaging as the finished drug or compounded drug preparation.

(5) Shorter dating than set forth in this subsection may be used if it is deemed appropriate in the professional judgment of the responsible pharmacist.

~~(j)~~ (j) The pharmacist performing or supervising compounding is responsible for the proper preparation, labeling, storage, and delivery of the compounded drug ~~product~~ preparation.

~~(k)~~ (k) Prior to allowing any drug product preparation to be compounded in a pharmacy, the pharmacist-in-charge shall complete a self-assessment for compounding pharmacies developed

by the board (Incorporated by reference is “Community Pharmacy & Hospital Outpatient Pharmacy Compounding Self-Assessment” Form 17M-39 Rev. 02/12.) as required by Section 1715 of Title 16, Division 17, of the California Code of Regulations. That form contains a first section applicable to all compounding, and a second section applicable to sterile injectable compounding. The first section must be completed by the pharmacist-in-charge before any compounding is performed in the pharmacy. The second section must be completed by the pharmacist-in-charge before any sterile ~~injectable~~ compounding is performed in the pharmacy. The applicable sections of the self-assessment shall subsequently be completed before July 1 of each odd-numbered year, within 30 days of the start date of a new pharmacist-in-charge or change of location, and within 30 days of the issuance of a new pharmacy license. The primary purpose of the self-assessment is to promote compliance through self-examination and education.

(l) Packages of ingredients, both active and inactive, that lack a supplier’s expiration date are subject to the following limitations:

(1) such ingredients cannot be used for any non-sterile compounded drug preparation more than three (3) years after the date of receipt by the pharmacy.

(2) such ingredients cannot be used for any sterile compounded drug preparation more than one (1) year after the date of receipt by the pharmacy.

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code, Sections 1735, 1735.1, 1735.8, and 1751.1-1751.8 of Title 16, Division 17, of the California Code of Regulations.

To Amend § 1735.3 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1735.3. ~~Records~~ Recordkeeping of for Compounded Drug Products Preparations.

(a) For each compounded drug ~~product preparation~~, the pharmacy records shall include:

(1) The master formula ~~record~~ document.

(2) A compounding log consisting of a single document containing all of the following:

(A) Name and Strength of the compounded drug preparation.

(B) The date the drug ~~product preparation~~ was compounded.

~~(3)(C) The identity of the any pharmacy personnel who compounded the~~ engaged in compounding the drug ~~product preparation~~.

~~(4)(D) The identity of the pharmacist reviewing the final drug ~~product preparation~~.~~

~~(5)(E) The quantity of each component ingredient used in compounding the drug ~~product preparation~~.~~

~~(6)(F) The manufacturer, expiration date and lot number of each component. If the manufacturer name is demonstrably unavailable, the name of the supplier may be substituted. If the manufacturer does not supply an expiration date for any component, the records shall include the date of receipt of the component in the pharmacy, and the limitations of section 1735.2, subdivision (l) shall apply.~~

(i) Exempt from the requirements in this paragraph (1735.3(a)(2)(F)) are sterile ~~products preparations~~ compounded ~~on a one-time basis in a single lot~~ for administration within seventy-two (72) hours to a patient in a health care facility licensed under section 1250 of the Health and Safety Code and stored in accordance with standards for “Redispensed CSPs” found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP37-NF32) Through 2nd Supplement (35 37th Revision, Effective ~~May~~ December 1, 2012-2014), hereby incorporated by reference, ~~to an inpatient in a health care facility licensed under section 1250 of the Health and Safety Code.~~

~~(7)(G) A pharmacy-assigned unique reference or lot number for the compounded drug ~~product preparation~~.~~

~~(8)(H)~~ The expiration beyond use date or beyond use date and time of the final compounded drug product preparation, expressed in the compounding record document in a standard date and time format.

~~(9)(I)~~ The final quantity or amount of drug product preparation compounded for dispensing.

(J) Documentation of quality reviews and required post-compounding process and procedures.

(b) Pharmacies shall maintain records of the proper acquisition, storage, and destruction of chemicals, bulk drug substances, drug products, and components used in compounding.

(c) Active ingredients shall be obtained from a supplier registered with the Food and Drug Administration (FDA). All other ~~C~~chemicals, bulk drug substances, and drug products, and components used to compound drug products preparations shall be obtained, whenever possible, from reliable FDA- registered suppliers. The pharmacy shall acquire and retain any available certificates of purity or analysis, either written in English or translated into English, for chemicals, bulk drug substances, and drug products, and components used in compounding. Certificates of purity or analysis are not required for drug products that are approved by the FDA. Any certificates of purity or analysis acquired by the pharmacy shall be matched to the corresponding chemical, bulk drug substance, or drug products received.

(d) 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~~ last in effect. If only recorded and stored electronically, on magnetic media, or in any other computerized form, the records shall be maintained as specified by Business and Professions Code section 4070 subsection (c).

Authority cited: Sections 4005, 4127, and 4169, Business and Professions Code.

Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

To Amend § 1735.4 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1735.4. Labeling of Compounded Drug ~~Products~~ Preparations.

(a) Each compounded drug preparation shall be affixed with a container label prior to dispensing that contains at least:

(1) Name of the compounding pharmacy and dispensing pharmacy (if different);

(2) Name (brand or generic) and strength, volume, or weight of each active ingredient. For admixed IV solutions, the intravenous solution utilized shall be included;

(3) Instructions for storage, handling, and administration. For admixed IV solutions, the rate of infusion shall be included;

(4) The beyond use date for the drug preparation;

(5) The date compounded; and

(6) The lot number or pharmacy reference number.

~~In addition to the labeling information required under Business and Professions Code section 4076 and under California Code of Regulations section 1707.5, the label of a compounded drug product preparation shall contain the generic or brand name(s) of the principal all active ingredient(s).~~

(b) Any compounded drug preparation dispensed to a patient or readied for dispensing to a patient shall also include on the label the information required under Business and Professions Code section 4076 and California Code of Regulations, title 16, section 1707.5.

~~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) Any compounded drug preparation dispensed to a patient or readied for dispensing to a patient shall also include, on the container label or on a receipt provided to the patient, a statement that the drug has been compounded by the pharmacy. ~~Drug products preparations compounded into unit dose containers that are too small or otherwise impractical for full compliance with subdivisions (a) and (b) shall be labeled with at least the name(s) of the active ingredient(s), concentration or strength, volume or weight of the~~

~~preparation, pharmacy reference or lot number, and expiration date.~~

(d) Prior to dispensing drug preparations compounded into unit-dose containers that are too small or otherwise impractical for full compliance with subdivisions (a), (b), and (c) shall be labeled with at least the name of the compounding pharmacy and dispensing pharmacy, if different, the name(s) of the active ingredient(s), strength, volume or weight of the preparation, pharmacy reference or lot number, and beyond use date, and shall not be subject to minimum font size requirements. Once dispensed, outer packaging must comply with 1735.4(a) – (c).

(e) All hazardous agents shall bear a special label which states “Chemotherapy - Dispose of Properly” or “Hazardous – Dispose of Properly.”

Note: Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4076 and 4127, Business and Professions Code.

To Amend § 1735.5 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1735.5. Compounding Policies and Procedures.

(a) Any pharmacy engaged in compounding shall maintain ~~a~~ written policies and procedures ~~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. Any material failure to follow the pharmacy’s written policies and procedures shall constitute a basis for disciplinary action.

(b) The policies and procedures ~~manual~~ shall be reviewed and such review shall be documented on an annual basis by the pharmacist-in-charge. ~~and~~ The policies and procedures manual shall be updated whenever changes in policies and procedures ~~processes~~ are implemented.

(c) The policies and procedures ~~manual~~ shall include at least the following:

- (1) Procedures for notifying staff assigned to compounding duties of any changes in ~~processes~~ or to the policies or procedures manual.
- (2) ~~Documentation of a~~ A written plan for recall of a dispensed compounded drug product preparation where subsequent verification information demonstrates the potential for adverse effects with continued use of a compounded drug product. The plan shall ensure that all affected doses can be accounted for during the recall and shall provide steps to identify which patients received the affected lot or compounded drug preparation(s).
- (3) ~~The p~~ 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) Procedures for evaluating, maintaining, certifying, cleaning, and disinfecting the facility (physical plant) used for compounding, and for training on these procedures as part of the staff training and competency evaluation process.
- (45) Documentation of the methodology used to ~~test~~ validate integrity, potency, quality, and labeled strength of compounded drug ~~products~~ preparations. The methodology must be appropriate to compounded drug preparations.
- (56) Documentation of the methodology and rationale or reference source used to determine appropriate ~~expiration~~ beyond use dates for compounded drug ~~products~~ preparations.
- (7) Dates and signatures reflecting all annual reviews of the policies and procedures by the pharmacist-in-charge.
- (8) Dates and signatures accompanying any revisions to the policies and procedures approved by the pharmacist-in-charge.
- (9) Policies and procedures for storage of compounded drug preparations in the pharmacy and daily documentation of all room, refrigerator, and freezer temperatures within the pharmacy.
- (10) Policies and procedures regarding ensuring appropriate functioning of refrigeration devices, monitoring refrigeration device temperatures, and actions to take regarding any out of range temperature variations within the pharmacy.
- (11) Policies and procedures for proper garbing when compounding with hazardous products. This shall include when to utilize double shoe covers.

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, ~~and 4127~~, and 4301, Business and Professions Code.

To Amend § 1735.6 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

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 compounding of compounded drug ~~products~~ preparations. This shall include records of maintenance and cleaning of the facilities and equipment. Where applicable, this shall also include records of certification(s) of facilities or equipment.

(b) Any equipment used to compound drug ~~products~~ preparations shall be stored, used, ~~and~~ maintained, and cleaned in accordance with manufacturers' specifications.

(c) Any equipment that weighs, measures, or transfers ingredients used to compound drug ~~products~~ preparations for which calibration or adjustment is appropriate shall be calibrated prior to use, on a schedule and by a method determined by the manufacturer's specifications, to ensure accuracy. Documentation of each such calibration shall be recorded in writing in a form which is not alterable and these records of calibration shall be maintained and retained in the pharmacy.

(d) Any pharmacy engaged in any hazardous drug compounding shall maintain written documentation regarding appropriate cleaning of facilities and equipment to prevent cross-contamination with non-hazardous drugs.

(e) Hazardous drug compounding shall be completed in an externally vented physically separate room with the following requirements:

(1) Minimum of 30 air changes per hour except that 12 air changes per hour are acceptable for segregated compounding areas with a BSC or CACI when products are assigned a BUD of 12 hrs or less or when non sterile products are compounded; and

(2) Maintained at a negative pressure of 0.01 to 0.03 inches of water column relative to all adjacent spaces (rooms, above ceiling, and corridors); and

(3) Each PEC in the room shall also be externally vented; and

(4) All surfaces within the room shall be smooth, seamless, impervious, and non-shedding.

(f) Where compliance with the January 1, 2017 amendments to Article 4.5 or Article 7, requires physical construction or alteration to a facility or physical environment, the board or its designee may grant a waiver of such compliance for a period of time to permit such physical change(s). Application for any waiver shall be made by the licensee in writing, and the request shall identify the provision(s) requiring physical construction or alteration, and the timeline for any such change(s). The board or its designee may grant the waiver when, in its discretion, good cause is demonstrated for such waiver.

Note: Authority cited: Sections 4005 and 4127, Business and Professions Code.

Reference: Sections 4005, 4036, 4037, 4051, 4052 and 4127, Business and Professions Code.

To Amend § 1735.7 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1735.7. Training of Compounding Staff.

(a) A pharmacy engaged in compounding shall maintain documentation demonstrating that personnel involved in compounding have the skills and training required to properly and accurately perform their assigned responsibilities and documentation demonstrating that all personnel involved in compounding are trained in all aspects of policies and procedures. This training shall include but is not limited to support personnel (e.g. institutional environmental services, housekeeping), maintenance staff, supervising pharmacist and all others whose jobs are related to the compounding process. ~~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 ongoing 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 prior to compounding any drug ~~product~~ preparation.

Note: Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052 and 4127, Business and Professions Code.

To Amend § 1735.8 in Article 4.5 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

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~~ preparations.

(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 analysis of compounded drug preparations to ensure integrity, potency, quality, and labeled strength, ~~including the frequency of testing~~ ~~analysis of compounded drug products~~. All qualitative and quantitative analysis reports for compounded drug ~~products~~ preparations shall be retained by the pharmacy and ~~collected~~ maintained along with the compounding ~~log record~~ and master formula document. The quality assurance plan shall include a schedule for routine testing and analysis of specified compounded drug preparations to ensure integrity, potency, quality, and labeled strength, on at least an annual basis.

(d) The quality assurance plan shall include a written procedure for scheduled action in the

event any compounded drug ~~product~~ preparation is ever discovered to be ~~below~~ outside minimum standards for integrity, potency, quality, or labeled strength.

(e) The quality assurance plan shall include a written procedure for responding to out-of-range temperature variations within the pharmacy and within patient care areas of a hospital where furnished drug is returned for redispensing.

Note: Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052 and 4127, Business and Professions Code.

To Amend § 1751 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

Article 7. Sterile ~~Injectable~~ Compounding

1751. Sterile ~~Injectable~~ Compounding; Compounding Area; Self-Assessment.

(a) Any pharmacy engaged in compounding sterile ~~injectable~~ drug ~~products~~ preparations 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~~ preparations shall have a ~~designated~~ compounding area designated for the preparation of sterile ~~injectable~~ drug products preparations that is in a restricted location where traffic has no impact on the performance of the PEC(s). The cleanroom, including the walls, ceilings, and floors, shall be constructed in accordance with Section 1250.4 of Title 24, Part 2, Chapter 12, of the California Code of Regulations. The pharmacy shall be ventilated in a manner in accordance with Section 505.5 of Title 24, Part 4, Chapter 5 of the California Code of Regulations. ~~which shall meet the following standards:~~ The environments within the pharmacy shall meet the following standards:

~~(1) Clean Room and Work Station Requirements, shall be in accordance with Section 1250 of Title 24, Part 2, Chapter 12, of the California Code of Regulations.~~

~~(2) Walls, ceilings and floors shall be constructed in accordance with Section 1250 of Title 24, Part 2, Chapter 12, of the California Code of Regulations.~~

~~(3) Be ventilated in a manner in accordance with Section 505.12 of Title 24, Chapter 5 of the California Code of Regulations.~~

~~(4) Be Each ISO environment shall be certified annually at least every six months by a qualified technician who is familiar with the methods and procedures for certifying laminar air flow hoods and clean room requirements, in accordance with standards adopted by the United States General Services Administration in accordance with Section 1751.4. Certification records must be retained for at least 3 years in the pharmacy.~~

~~(5)-(2) The pharmacy shall be arranged in accordance with Section 1250 of Title 24, Part 2, Chapter 12, of the California Code of Regulations. Items related to the compounding of sterile injectable drug products preparations within the compounding area shall be stored in such a way as to maintain the integrity of an aseptic environment.~~

~~(6)-(3) A sink shall be included in accordance with Section 1250.4 of Title 24, Part 2, Chapter 12, of the California Code of Regulations. Sinks and drains shall not be present in any ISO Class 7 or better cleanroom, nor in a segregated sterile compounding area within three feet of an ISO Class 5 or better PEC, with the exception of emergency eye-rinsing stations. A sink may be located in an ante-area. When the PEC in the segregated sterile compounding area is a CAI or CACI and the documentation provided by the manufacturer shows it meets the requirements listed in 1751.4(f)(1)-(3) the sterile compounding area is exempt from the room requirement listed in 1751(b)(3).~~

~~(7)-(4) There shall be a refrigerator and, ~~for~~ where appropriate, a freezer, of sufficient capacity to meet the storage requirements for all material requiring refrigeration or freezing, and a backup plan to ensure continuity of available compounded drug preparations in the event of a power outage.~~

~~(c) Any pharmacy compounding a sterile injectable drug product preparation from one or more non-sterile ingredients shall comply with Business and Professions Code section 4127.7.~~

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127 and ~~4127.7~~, Business and Professions Code; Sections 1735, 1735.1-1735.8., and 1751.1-1751.8. of Title 16, Division 17, of the California Code of

Regulations; and Section 18944, Health and Safety Code.

To Amend § 1751.1 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.1. Sterile ~~Injectable~~ Compounding Recordkeeping Requirements.

(a) ~~Pharmacies compounding sterile injectable products for future use pursuant to section 1735.2 shall, in addition to those records required by section 1735.3, make and keep records indicating the name, lot number, amount, and date on which the products were provided to a prescriber.~~

~~(b) In addition to the records required by section 1735.3 and subdivision (a), any pharmacy engaged in any compounding of for sterile drug products preparations compounded from one or more non-sterile ingredients, shall maintain the following records, which must be made and kept by~~ readily retrievable, within the pharmacy:

(1) ~~The~~ Documents evidencing training and competency evaluations of employees in sterile product drug preparation policies and procedures.

(2) Results of hand hygiene and garbing assessments with integrated gloved fingertip testing.

(3) Results of assessments of personnel for aseptic techniques including results of media-fill tests and gloved fingertip testing performed in association with media-fill tests.

(4) Results of viable air and surface sampling.

(5) Video of smoke studies in all ISO certified spaces.

(6) Documents indicating daily documentation of room, R refrigerator, and freezer temperatures appropriate for sterile compounded drug preparations consistent with the temperatures listed in section 1735.1 for:

(A) Controlled room temperature.

(B) Controlled cold temperature.

(C) Controlled freezer temperature.

(7) Certification(s) of the sterile compounding environment(s).

(8) Documents indicating daily documentation of air pressure differentials or air velocity

measurements between all adjoining ISO rooms or areas, including those associated with compounding aseptic (containment) isolators, and air pressure differentials or air velocity measurements between all rooms or spaces with an immediate entry or opening to ISO rooms or areas.

(9) Other facility quality control logs records specific to the pharmacy's policies and procedures (e.g., cleaning logs for facilities and equipment).

(10) Logs or other documentation of inspections for expired or recalled ~~pharmaceutical products or raw ingredients~~ chemicals, bulk drug substances, drug products, or other ingredients.

(11) Preparation records including the master formula document work sheet, the preparation compounding log work sheet, and records of end-product evaluation testing and results.

(b) Pharmacies compounding sterile drug preparations for future use pursuant to section 1735.2 shall, in addition to those records required by section 1735.3, make and keep records indicating the name, lot number, and amount of any drug preparation compounded for future use, the date on which any preparation was provided to a prescriber, and the name, address, license type and number of the prescriber.

(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. If only recorded and stored electronically, on magnetic media, or in any other computerized form, the records shall be maintained as specified by Business and Professions Code section 4070 subsection (c).

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

To Amend § 1751.2 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.2. Sterile ~~Injectable~~ Compounding Labeling Requirements.

In addition to the labeling information required under Business and Professions Code section 4076 and California Code of Regulations, title 16, sections 1707.5 and 1735.4, a pharmacy ~~which that~~ compounds sterile injectable drug products preparations shall include the following information on the labels for each such those products preparation:

- (a) ~~The~~ Telephone number of the pharmacy. ~~, except~~ The telephone number is not required on the label for sterile injectable drug products preparations dispensed administered for to inpatients of a within the hospital pharmacy.
- ~~(b) Name and concentration of ingredients contained in the sterile injectable drug product.~~
- ~~(c)~~ Instructions for storage, and handling, and administration.;
- ~~(d)~~ All cytotoxic hazardous agents shall bear a special label which states "Chemotherapy - Dispose of Properly" or "Cytotoxic Hazardous – Dispose of Properly."

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, 4076 and 4127, Business and Professions Code.

To Amend § 1751.3 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.3. Sterile ~~Injectable~~ Compounding Policies and Procedures.

(a) Any pharmacy engaged in compounding sterile drug preparations shall maintain written policies and procedures for compounding. Any material failure to follow the pharmacy's written policies and procedures shall constitute a basis for disciplinary action. In addition to the elements required by section 1735.5, there shall be written policies and procedures regarding the following:

- (1) Action levels for colony-forming units (CFUs) detected during viable surface sampling, glove

fingertip, and viable air sampling and actions to be taken when the levels are exceeded.

(2) Airflow considerations and pressure differential monitoring.

(3) An environmental sampling plan and procedures specific to viable air, surface and gloved fingertip sampling as well as nonviable particle sampling.

(4) Cleaning and maintenance of ISO environments and segregated compounding areas.

(5) Compounded sterile drug preparation stability and beyond use dating.

(6) Compounding, filling, and labeling of sterile drug preparations.

(7) Daily and monthly cleaning and disinfection schedule for the controlled areas and any equipment in the controlled area as specified in section 1751.4.

(8) Depyrogenation of glassware (if applicable)

(9) Facility management including certification and maintenance of controlled environments and related equipment.

(10) For compounding aseptic isolators and compounding aseptic containment isolators, documentation of the manufacturer's recommended purge time.

(11) Hand hygiene and garbing.

(12) Labeling of the sterile compounded drug preparations based on the intended route of administration and recommended rate of administration.

(13) Methods by which the supervising pharmacist will fulfill his or her responsibility to ensure the quality of compounded drug preparations.

(14) Orientation, training, and competency evaluation of staff in all aspects of the preparation of sterile drug preparations including didactic training and knowledge/competency assessments that include at minimum: hand hygiene and garbing; decontamination (where applicable); cleaning and disinfection of controlled compounding areas; and proper aseptic technique, demonstrated through the use of a media-fill test performed by applicable personnel; and aseptic area practices.

(15) Preparing sterile compounded drug preparations from non-sterile components (if applicable). This shall include sterilization method suitability testing for each master formula document.

(16) Procedures for handling, compounding and disposal of hazardous agents. The written

policies and procedures shall describe the pharmacy protocols for cleanups and spills in conformity with local health jurisdiction standards.

(17) Procedures for handling, compounding and disposal of infectious materials. The written policies and procedures shall describe the pharmacy protocols for cleanups and spills in conformity with local health jurisdiction standards.

(18) Proper use of equipment and supplies.

(19) Quality assurance program compliant with sections 1711, 1735.8 and 1751.7.

(20) Record keeping requirements.

(21) Temperature monitoring in compounding and controlled storage areas.

(22) The determination and approval by a pharmacist of ingredients and the compounding process for each preparation before compounding begins.

(23) Use of automated compounding devices (if applicable).

(24) Visual inspection and other final quality checks of sterile drug preparations.

~~(a) Any pharmacy engaged in compounding sterile injectable drug products shall maintain a written policy and procedures 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 compounded drug preparations 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 drug products preparations shall have written policies and procedures for the disposal of infectious materials and/or materials containing cytotoxic hazardous residues. The written policies and procedures shall describe the pharmacy~~

~~protocols for cleanups and spills in conformity with local health jurisdiction standards.~~

(b) For lot compounding, the pharmacy shall maintain written policies and procedures that includes, in addition to the elements required by section 1735.5 and 1751.3(a), written policies and procedures regarding the following:

(1) Use of master formula documents and compounding logs.

(2) Appropriate documentation.

(3) Appropriate sterility and potency testing.

(c) For non-sterile-to-sterile batch compounding, the pharmacy shall maintain written policies and procedures for compounding that includes, in addition to the elements required by section 1735.5, 1751.3(a), and 1751.7(e), written policies and procedures regarding the following:

(1) Process validation for chosen sterilization methods.

(2) End-product evaluation, quantitative, and qualitative testing.

~~(d)(1) All written p~~olicies and procedures shall be immediately available to all personnel involved in these compounding activities and to board inspectors.

~~(d)(2)(e) All personnel involved must read the policies and procedures before compounding sterile injectable products-drug preparations, and any~~All personnel involved must read all additions, revisions, and deletions to the written policies and procedures-must be communicated to all personnel involved in sterile compounding. Each review must be documented by a signature and date.

~~(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 direct compounding 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 areas 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.~~

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

To Amend § 1751.4 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.4. Facility and Equipment Standards for Sterile ~~Injectable~~ Compounding.

(a) No sterile ~~injectable drug product~~ preparation shall be compounded if it is known, or reasonably should be known, that the compounding environment fails to meet criteria specified in the pharmacy's written policies and procedures for the safe compounding of sterile ~~injectable drug products~~ preparations.

(b) During the compounding of preparation of sterile ~~injectable drug products~~ preparations, access to the areas designated ~~area or cleanroom~~ for compounding must be limited to those individuals who are properly attired.

(c) All equipment used in the areas designated ~~area or cleanroom~~ for compounding must be made of a material that can be easily cleaned and disinfected.

(d) Cleaning shall be done using a germicidal detergent and sterile water. The use of a sporicidal agent is required to be used at least monthly.

(1) All ISO Class 5 surfaces, work table surfaces, carts, counters, and the cleanroom floor shall be cleaned at least daily. After each cleaning, disinfection using a suitable sterile agent shall occur on all ISO Class 5 surfaces, work table surfaces, carts, and counters.

(2) Walls, ceilings, storage shelving, tables, stools, and all other items in the ISO Class 7 or ISO Class 8 environment shall be cleaned at least monthly.

(3) Cleaning shall also occur after any unanticipated event that could increase the risk of contamination.

(4) All cleaning materials, such as wipers, sponges, and mops, shall be non-shedding and dedicated to use in the cleanroom, or ante-area, and segregated sterile compounding areas and shall not be removed from these areas except for disposal.

(e) Disinfection, using a suitable sterile agent, shall also occur on all surfaces in the ISO Class 5 PEC frequently, including:

(1) At the beginning of each shift;

(2) At least every 30 minutes when compounding involving human staff is occurring or before each lot;

(3) After each spill; and

(4) When surface contamination is known or suspected.

~~(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.~~

(f) Pharmacies preparing sterile compounded preparations require the use of a PEC that provides ISO Class 5 air or better air quality. Certification and testing of primary and secondary engineering controls shall be performed no less than every six months and whenever the device or area designated for compounding is relocated, altered or a service to the facility is performed that would impact the device or area. Certification must be completed by a qualified technician who is familiar with certification methods and procedures in accordance with CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2006-13, Revised May 20, 2015).

Certification records must be retained for at least 3 years. Unidirectional compounding aseptic isolators or compounding aseptic containment isolators may be used outside of an ISO Class 7 cleanroom if the isolator is certified to meet the following criteria:

(1) Particle counts sampled approximately 6-12 inches upstream of the critical exposure site shall maintain ISO Class 5 levels during compounding operations.

(2) Not more than 3520 particles (0.5 um and larger) per cubic meter shall be counted during material transfer, with the particle counter probe located as near to the transfer door as possible without obstructing transfer.

(3) 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.

Compounding aseptic isolators that do not meet the requirements as outlined in this subdivision or are not located within an ISO Class 7 cleanroom may only be used to compound preparations that meet the criteria specified in accordance with subdivision (d) of Section 1751.8 of Title 16, Division 17, of the California Code of Regulations.

(g) Pharmacies preparing parenteral cytotoxic sterile hazardous agents shall do so in accordance with Section 505.125.1 of Title 24, Chapter 5, of the California Code of Regulations, requiring a ~~laminar air flow hood~~ negative pressure PEC. Additionally, each PEC used to compound hazardous agents shall be externally vented. The ~~hood~~ negative pressure PEC must be certified ~~annually~~ every six months by a qualified technician who is familiar with CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2006-13, Revised May 20, 2015). ~~the methods and procedures for certifying laminar air flow hoods and cleanroom requirements, in accordance with National Sanitation Foundation Standard 49 for Class II (Laminar Flow) Biohazard Cabinetry, as revised May, 1983 (available from the National Sanitation Foundation, 3475 Plymouth Road, P.O. Box 1468, Ann Arbor, Michigan 48106, phone number (313) 769-8010) or manufacturer's specifications. Certification records must be retained for at least 3 years.~~ Any drug preparation that is compounded in a PEC where hazardous drugs are prepared must be labeled as hazardous, regardless of whether the drug ingredients are considered hazardous.

(1) During the hazardous drug compounding that is performed in a compounding aseptic containment isolator, full hand hygiene and garbing must occur. Garbing shall include hair cover, facemask, beard cover (if applicable), polypropylene or low shedding gown that closes in the back, shoe covers, and two pairs of sterile ASTM D6978-05 standard gloves.

(h) If a compounding aseptic isolator is certified by the manufacturer to maintain ISO Class 5

air quality during dynamic operation conditions during compounding as well as during the transfer of ingredients into and out of the compounding aseptic isolator, then it may be placed into a non-ISO classified room. Individuals that use compounding aseptic isolators in this manner must ensure appropriate garbing, which consists of donning sterile gloves over the isolator gloves immediately before non-hazardous compounding. These sterile gloves must be changed by each individual whenever continuous compounding is ceased and before compounding starts again.

(i) Compounding aseptic isolator and compounding aseptic containment isolator used in the compounding of sterile drug preparations shall use non-turbulent unidirectional air flow patterns. A smoke patterned test shall be used to determine air flow patterns.

(j) Viable surface sampling shall be done at least every six months for all sterile-to-sterile compounding and quarterly for all non-sterile-to-sterile compounding. Viable air sampling shall be done by volumetric air sampling procedures which test a sufficient volume of air (400 to 1,000 liters) at each location and shall be done at least once every six months. Viable surface and viable air sampling shall be performed by a qualified individual who is familiar with the methods and procedures for surface testing and air sampling. Viable air sampling is to be performed under dynamic conditions that simulate actual production. Viable surface sampling is to be performed under dynamic conditions of actual compounding. When the environmental monitoring action levels are exceeded, the pharmacy shall identify the CFUs at least to the genus level in addition to conducting an investigation pursuant to its policies and procedures. Remediation shall include, at minimum, an immediate investigation of cleaning and compounding operations and facility management.

(k) The sterile compounding area in the pharmacy shall have a comfortable and well-lighted working environment, which includes a room temperature of 20-24 degrees Celsius (68-75 degrees Fahrenheit) or cooler to maintain comfortable conditions for compounding personnel when attired in the required compounding garb.

(l) A licensee may request a waiver of these provisions as provided in section 1735.6(f).

Note: Authority Cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052 and 4127, Business and Professions Code; and Section 18944, Health and Safety Code.

To Amend § 1751.5 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.5. Sterile ~~Injectable~~ Compounding Attire.

~~(a) When preparing cytotoxic agents, gowns and gloves shall be worn.~~

~~(b) (a) When compounding sterile drug products preparations from one or more non-sterile ingredients the following standards must be met:~~

~~(1) Cleanroom garb Personal protective equipment consisting of a ~~low~~ non-shedding coverall gown, head cover, face mask, facial hair covers (if applicable), and shoe covers must be worn inside the designated area at all times. For hazardous compounding double shoe covers are required.~~

~~(2) Cleanroom garb Personal protective equipment must be donned and removed ~~outside the designated area~~ in an ante-area or immediately outside the segregated compounding area.~~

~~(3) Personnel shall don personal protective equipment in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. The following order is to be followed unless the pharmacy has a procedure in place that documents a method equivalent to or superior to the method described here: The donning of shoe covers or dedicated shoes, head and facial hair covers and face masks shall be followed by the washing of hands and forearms up to the elbows for 30 seconds with soap and water, drying hands, and then the donning of a non-shedding gown.~~

~~(3)-(4) Compounding personnel shall not wear any wrist, Hhand, finger, and or wrist other visible jewelry must be eliminated jewelry, piercing, headphones, earbuds, or personal electronic device. 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.~~ Sterile gloves that have been tested for compatibility with disinfection with isopropyl alcohol are required. Hand cleansing with a persistently active alcohol-based product followed by the donning of sterile gloves may occur within the ante or cleanroom. Gloves are to be routinely disinfected with sterile 70 percent isopropyl alcohol before entering or re-entering the PEC and after contact with non-sterile objects. Gloves shall also be routinely inspected for holes, punctures, or tears and replaced immediately if such are detected.

(6) Individuals experiencing exposed rashes, sunburn, weeping sores, conjunctivitis, active respiratory infections or other communicable disease, or those wearing cosmetics, nail polish, or artificial nails shall be excluded from the ISO Class 5 and ISO Class 7 compounding areas until their conditions are remedied.

~~(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.~~

(b) When preparing hazardous agents, appropriate gowns and personal protective equipment shall be worn regardless of the PECs used (e.g., biological safety cabinet and compounding aseptic containment isolator).

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

To Amend § 1751.6 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.6 Training of Sterile Injectable Compounding Staff, Patient, and Caregiver. Sterile Compounding Consultation; Training of Sterile Compounding Staff.

(a) Consultation shall be available to the patient and/or primary caregiver concerning proper use, storage, handling, and disposal of sterile injectable drug products preparations and related supplies furnished by the pharmacy.

(b) The pharmacist-in-charge shall ~~be responsible to~~ ensure that all pharmacy personnel

engaging in compounding sterile ~~injectable drug products~~ preparations shall have training and demonstrated competence in the safe handling and compounding of sterile ~~injectable drug products~~ preparations, including ~~cytotoxic~~ hazardous agents if the pharmacy compounds products with ~~cytotoxic~~ hazardous 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.

(d) The pharmacist-in-charge shall be responsible to ensure the continuing competence of pharmacy personnel engaged in compounding sterile ~~injectable drug products~~ preparations.

(e) Pharmacies that compound sterile ~~drug products from one or more non-sterile ingredients~~ preparations 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~~ preparation compounding documentation.

(D) Quality assurance procedures.

(E) Aseptic preparation procedures.

(F) Proper hand hygiene, gowning and gloving technique.

(G) General conduct in the controlled area (aseptic area practices).

(H) Cleaning, sanitizing, and maintaining of the equipment and ~~used in~~ the controlled area.

(I) Sterilization techniques for compounding sterile drug preparations from one or more non-sterile ingredients.

(J) Container, equipment, and closure system selection.

(2) Each person ~~assigned to the controlled area~~ engaged in sterile compounding must successfully complete practical skills training in aseptic technique and aseptic area practices using models that are comparable to the most complex manipulations to be performed by the individual. Each pharmacist responsible for, or directly supervising and controlling, aseptic

techniques or practices, must demonstrate the skills needed to ensure the sterility of compounded drug preparations. 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 at least every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years.

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

To Amend § 1751.7 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.7. Sterile ~~Injectable~~ Compounding Quality Assurance and Process Validation.

(a) Any pharmacy engaged in compounding sterile ~~injectable drug products~~ preparations 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) Procedures for ~~C~~leaning and sanitization of the ~~parenteral medication~~ sterile preparation area.

~~(2) The storage of compounded sterile injectable products in the pharmacy and periodic documentation of refrigerator temperature.~~

~~(3)~~(2) Actions to be taken in the event of a drug recall.

~~(4)~~(3) Written justification of ~~Documentation justifying the chosen expiration~~ beyond use dates for compounded sterile ~~injectable drug products~~ preparations.

(b)(1) The pharmacy and each individual involved in the compounding of sterile drug

preparations must successfully demonstrate competency on aseptic technique and aseptic area practices before being allowed to prepare sterile drug preparations. 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 the types of manipulations, products and batch sizes the individual is expected to prepare and include a media-fill test. The validation process shall be as complicated as the most complex manipulations performed by staff and contain the same amount or greater amount of volume transferred during the compounding process. The same personnel, procedures, equipment, and materials must be used in the testing. Media used must have demonstrated the ability to support and promote growth. Completed medium samples must be incubated in a manner consistent with the manufacturer's recommendations. If microbial growth is detected, then each individual's sterile preparation process must be evaluated, corrective action taken and documented, and the validation process repeated.

(2) Each individual's competency must be revalidated at least every twelve months for sterile to sterile compounding and at least every six months for individuals compounding sterile preparations from non-sterile ingredients.

(3) The pharmacy's validation process on aseptic technique and aseptic area practices must be revalidated whenever:

(A) the quality assurance program yields an unacceptable result,

(B) there is any change in the compounding process, the Primary Engineering Control (PEC), or the compounding environment. For purposes of this subsection, a change includes, but is not limited to, when the PEC is moved, repaired or replaced, when the facility is modified in a manner that affects airflow or traffic patterns, or when improper aseptic techniques are observed.

(4) The pharmacy must document the validation and revalidation process.

~~Each individual involved in the preparation of sterile injectable drug products preparations must first successfully demonstrate competency by successfully performing aseptic media fill tests complete a validation process on technique before being allowed to prepare sterile~~

~~injectable drug products preparations. 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 media fill testing process shall be as complicated as the most complex manipulations performed by staff and contain the same amount or greater of volume transferred during the compounding process. The same personnel, procedures, equipment, and materials must be involved. Media used must have demonstrated the ability to support and promote growth. Completed medium media samples must be incubated in a manner consistent with the manufacturer's recommendations. If microbial growth is detected, then the employee's sterile preparation process must be evaluated, corrective action taken and documented, and the validation process media fill testing repeated. Personnel competency must be revalidated at least every twelve months for sterile to sterile compounding and at least every six months for individuals compounding sterile products from non-sterile ingredients. Aseptic work practice assessments via media fill tests must be revalidated, as appropriate to the circumstance or personnel found to be deficient, whenever the quality assurance program yields an unacceptable result, when the compounding process changes, equipment used in the compounding of sterile injectable drug products preparations 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.~~

(c) All sterile compounding personnel must successfully complete an initial competency evaluation. In addition, immediately following the initial hand hygiene and garbing procedure, each individual who may be required to do so in practice must successfully complete a gloved fingertip (all fingers on both hands) sampling procedure (zero colony forming units for both hands) at least three times before initially being allowed to compound sterile drug preparations.

(d) Re-evaluation of garbing and gloving competency shall occur at least every 12 months for personnel compounding products made from sterile ingredients and at least every six months for personnel compounding products from non-sterile ingredients.

~~(e)~~(1) Batch-produced sterile drug preparations compounded from one or more non-sterile ingredients, except as provided in paragraph (2), 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. Sterility testing shall be USP chapter 71 compliant and pyrogens testing shall confirm acceptable levels of pyrogens per USP chapter 85 limits, before dispensing. This requirement of end product testing confirming sterility and acceptable levels of pyrogens prior to dispensing shall apply regardless of any sterility or pyrogen testing that may have been conducted on any ingredient or combination of ingredients that were previously non-sterile. Exempt from pyrogen testing are topical ophthalmic and inhalation preparations.

(2) The following non-sterile-to-sterile batch drug preparations do not require end product testing for sterility and pyrogens:

(A) Preparations for self-administered ophthalmic drops in a quantity sufficient for administration to a single patient for 30 days or less pursuant to a prescription.

(B) Preparations for self-administered inhalation in a quantity sufficient for administration to a single patient for 5 days or less pursuant to a prescription.

~~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.~~

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

To Amend § 1751.8 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.8. Beyond Use Dating for Sterile Compounded Drug Preparations.

In conformity with and in addition to the requirements and limitations of section 1735.2, subdivision (h), every sterile compounded drug preparation shall be given and labeled with a beyond use date that does not exceed the shortest expiration date or beyond use date of any ingredient in sterile compounded drug preparation, nor the chemical stability of any one ingredient in the sterile compounded drug preparation, nor the chemical stability of the combination of all ingredients in the sterile compounded drug preparation, and that, in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia – National Formulary (USP37-NF32) Through 2nd Supplement (37th Revision, Effective December 1, 2014), hereby incorporated by reference, that would justify an extended beyond use date, conforms to the following limitations:

(a) The beyond use date shall specify that storage and exposure periods cannot exceed 48 hours at controlled room temperature, 14 days at controlled cold temperature, and 45 days in solid frozen state, where the sterile compounded drug preparation is compounded solely with aseptic manipulations and all of the following apply:

(1) The preparation is compounded entirely within an ISO Class 5 PEC located in an ISO Class 7 cleanroom with an ante-area or compounded entirely within a CAI which meets the requirements in 1751.4(f)(1)-(3), using only sterile ingredients, products, components, and devices; and

(2) The compounding process involves transferring, measuring, and mixing manipulations using not more than three commercially manufactured packages of sterile preparations and not more than two entries into any one sterile container or package of sterile preparations or administration containers/devices to prepare the drug preparation; and

(3) Compounding manipulations are limited to aseptically opening ampules, penetrating disinfected stoppers on vials with sterile needles and syringes or spiked transfer devices, and transferring sterile liquids in sterile syringes to sterile administration devices, package

containers of other sterile preparations, and containers for storage dispensing.

(b) The beyond use date shall specify that storage and exposure periods cannot exceed 30 hours at controlled room temperature, 9 days at controlled cold temperature, and 45 days in solid frozen state, where the sterile compounded drug preparation is compounded solely with aseptic manipulations and all of the following apply:

(1) The preparation is compounded entirely within an ISO Class 5 PEC located in an ISO Class 7 cleanroom with an ante-area or compounded entirely within a CAI which meets the requirements in 1751.4(f)(1)-(3), using multiple individual or small doses of sterile preparations combined or pooled to prepare a compounded sterile preparation that will be administered either to multiple patients or to one patient on multiple occasions; and

(2) The compounding process involves complex aseptic manipulations other than the single-volume transfer; and

(3) The compounding process requires unusually long duration such as that required to complete dissolution or homogenous mixing.

(c) The beyond use date shall specify that storage and exposure periods cannot exceed 24 hours at controlled room temperature, 3 days at controlled cold temperature, and 45 days in solid frozen state, where the sterile compounded drug preparation is compounded solely with aseptic manipulations using non-sterile ingredients, regardless of intervening sterilization of that ingredient and the following applies:

(1) The preparation is compounded entirely within an ISO Class 5 PEC located in an ISO Class 7 cleanroom with an ante-area or compounded entirely within a CAI which meets the requirements in 1751.4(f)(1)-(3).

(d) The beyond use date shall specify that storage and exposure periods cannot exceed 12 hours where the sterile compounded drug preparation is compounded solely with aseptic manipulations and all of the following apply:

(1) The preparation was compounded entirely within an ISO Class 5 PEC that is located in a segregated sterile compounding area and restricted to sterile compounding activities, using only sterile ingredients, components, and devices, by personnel properly cleansed and garbed; and

(2) The compounding process involves simple transfer of not more than three commercially manufactured packages of sterile nonhazardous preparations or diagnostic radiopharmaceutical preparations from the manufacturer's original containers; and

(3) The compounding process involves not more than two entries into any one container or package (e.g., bag, vial) of sterile infusion solution or administration container/device.

(e) Where any sterile compounded drug preparation was compounded either outside of an ISO class 5 PEC or under conditions that do not meet all of the requirements for any of subdivisions (a) through (d), the sterile compounded drug preparation shall be labeled "for immediate use only" and administration shall begin no later than one hour following the start of the compounding process. Unless the "immediate use" preparation is immediately and completely administered by the person who prepared it or immediate and complete administration is witnessed by the preparer, the preparation 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 compounded sterile preparation, and the exact one-hour beyond use date and time. If administration has not begun within one hour following the start of the compounding process, the compounded sterile preparation shall be promptly, properly, entirely, and safely discarded. This provision does not preclude the use of a PEC to compound an "immediate use" preparation. A PEC used solely to compound 'immediate use' preparations need not be placed within an ISO Class 7 cleanroom, with an ante-area. Such "immediate use" preparations shall be compounded only in those limited situations where there is a need for immediate administration of a sterile preparation compounded outside of an ISO class 5 environment and where failure to administer could result in loss of life or intense suffering. Any such compounding shall be only in such quantity as is necessary to meet the immediate need and the circumstance causing the immediate need shall be documented in accordance with policies and procedures.

(f) The beyond use date for any compounded allergen extracts shall be the earliest manufacturer expiration date of the individual allergen extracts.

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

To Add § 1751.9 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

1751.9 Single-Dose and Multi-Dose Containers; Limitations on Use

(a) Single-dose ampules are for immediate use only, and once opened shall not be stored for any time period.

(b) Unless otherwise specified by the manufacturer, any single-dose container of a compounded sterile drug preparation other than an ampule, such as a bag, bottle, syringe or vial, shall be used in its entirety or its remaining contents shall be labeled with a beyond use date and discarded within the following time limit, depending on the environment:

(1) When needle-punctured in an environment with air quality worse than ISO Class 5, within one (1) hour;

(2) When needle-punctured in an environment with ISO Class 5 or better air quality, within six (6) hours. A container must remain within the ISO Class 5 or better air quality to be used for the full six hours, unless otherwise specified by the manufacturer.

(3) If the puncture time is not noted on the container, the container must immediately be discarded.

(c) Unless otherwise specified by the manufacturer, a multi-dose container stored according to the manufacturer's specifications shall be used in its entirety or its remaining contents shall be labeled with a beyond use date and discarded within twenty eight (28) days from initial opening or puncture. Any multi-dose container not stored according to the manufacturer's specifications shall be discarded immediately upon identification of such storage circumstance.

If any open container is not labeled with a beyond use date or the beyond use date is not correct, the container must immediately be discarded.

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

To Amend § 1751.10 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

~~1751.8.~~ 1751.10. Sterile ~~Injectable~~ Compounding Reference Materials.

In any pharmacy engaged in compounding sterile ~~injectable drug products~~ preparations, there shall be current and appropriate reference materials regarding the compounding of sterile ~~injectable drug products~~ preparations located in or immediately available to the pharmacy.

Authority cited: Sections 4005 and 4127, Business and Professions Code. Reference: Sections 4005, 4036, 4037, 4051, 4052, and 4127, Business and Professions Code.

To Add Article 7.5 of Division 17 of Title 16 of the California Code of Regulations to read as follow

Article 7.5 Furnishing for Home Administration

To Amend § 1751.10 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

~~1751.10.~~ 1752. Furnishing to Parenteral Patient at Home.

Subject to all provisions of this article, a pharmacist may carry and furnish to a patient at home dangerous drugs, other than controlled substances, and devices for parenteral therapy when the dangerous drug or device is one currently prescribed for the patient.

Authority cited: Section 4005, Business and Professions Code. Reference: Section 4005, Business and Professions Code.

To Amend § 1751.11 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

~~1751.11.~~ 1753. Furnishing to Home Health Agencies and Licensed Hospices.

Subject to the following conditions, a licensed pharmacy may furnish to a home health agency licensed under provisions of Chapter 8 (commencing with section 1725 of Division 2 of the Health and Safety Code) or to a hospice licensed under provisions of Chapter 8.5 (commencing with section 1745 of Division 2 of the Health and Safety Code) dangerous drugs for parenteral therapy other than controlled substances, in a portable container for furnishing to patients at home for emergency treatment or adjustment of parenteral drug therapy by the home health agency or licensed hospice.

(a) The pharmacy, having ownership and responsibility for the portable containers, shall ensure that each portable container is:

- (1) furnished by a registered pharmacist;
- (2) sealed in such a manner that a tamper-proof seal must be broken to gain access to the drugs;
- (3) under the effective control of a registered nurse, pharmacist or delivery person at all times when not in the pharmacy;
- (4) labeled on the outside of the container with a list of the contents;
- (5) maintained at an appropriate temperature according to United States Pharmacopeia Standards (1995, 23rd Revision), and protected at all times from extreme temperatures that could damage the contents.

(b) The portable container may contain up to:

- (1) 1000mL of 0.9% sodium chloride intravenous infusion in containers of a size determined by the pharmacy;
- (2) 1000mL of 5% dextrose in water injection in containers of a size determined by the

pharmacy;

(3) two vials of urokinase 5000 units;

(4) Each of the following items shall be in sealed, unused containers; the furnishing pharmacy may select any or all of these dangerous drugs in up to five dosage units for inclusion in the sealed, portable container:

(A) heparin sodium lock flush 100 units/mL;

(B) heparin sodium lock flush 10 units/mL;

(C) epinephrine HCl solution 1:1,000;

(D) epinephrine HCl solution 1:10,000;

(E) diphenhydramine HCl 50mg/mL;

(F) methylprednisolone 125mg/2mL;

(G) normal saline, preserved, up to 30 mL vials;

(H) naloxone 1mg/mL 2 mL;

(I) droperidol 5mg/2mL;

(J) prochlorperazine 10mg/2mL;

(K) promethazine 25mg/mL;

(L) dextrose 25gms/50mL;

(M) glucagon 1mg/mL;

(N) insulin (human) 100 units/mL;

(O) bumetamide 0.5mg/2mL;

(P) furosemide 10mg/mL;

(Q) EMLA Cream 5 gm tube;

(R) Lidocaine 1 percent 30mL vials.

(5) The pharmacy shall ensure that the specific dangerous drugs and quantities to be included in the portable container are listed in the home health agency's or licensed hospice's policies and procedures.

(c) The pharmacy shall not supply a portable container to a home health agency or licensed hospice which does not:

(1) implement and maintain policies and procedures for:

- (A) the storage, temperature stability and transportation of the portable container;
 - (B) the furnishing of dangerous drugs from the portable container upon the written or oral authorization of a prescriber; and
 - (C) a specific treatment protocol for the administration of each medication contained in the portable container.
- (2) have the policies, procedures and protocols reviewed and revised (as needed) annually by a group of professional personnel including a physician and surgeon, a pharmacist and a registered nurse.
- (d) A copy of these policies, procedures and protocols shall be maintained by the furnishing pharmacy from each home health agency or licensed hospice for which the pharmacy furnishes portable containers.
 - (e) In cases where a drug has been administered to a patient pursuant to the oral order of a licensed prescriber, the pharmacy shall ensure that the oral order is immediately written down by the registered nurse or pharmacist and communicated by copy or fax within 24 hours to the furnishing pharmacy, with a copy of the prescriber-signed document forwarded to the dispensing pharmacy within 20 days.
 - (f) The pharmacy shall ensure that within seven days (168 hours) after the seal has been broken on the portable container, the home health agency's director of nursing service or a registered nurse employed by the home health agency or licensed hospice returns the container to the furnishing pharmacy. The furnishing pharmacy shall then perform an inventory of the drugs used from the container, and if the container will be reused, must restock and reseal the container before it is again furnished to the home health agency or licensed hospice.
 - (g) The furnishing pharmacy shall have written policies and procedures for the contents, packaging, inventory monitoring, labeling and storage instructions of the portable container.
 - (h) The furnishing pharmacy shall ensure that the home health agency or licensed hospice returns the portable containers to the furnishing pharmacy at least every 60 days for verification of product quality, quantity, integrity and expiration dates, or within seven days (168 hours) after the seal has been broken.

(i) The furnishing pharmacy shall maintain a current inventory and record of all items placed into and furnished from the portable container.

Note: Authority cited: Sections 4005 and ~~and~~ 4057, Business and Professions Code. Reference: Sections 4040, 4057, 4081 and 4332, Business and Professions Code.

To Amend § 1751.12 in Article 7 of Division 17 of Title 16 of the California Code of Regulations to read as follows:

~~1751.12~~ 1754. Obligations of a Pharmacy Furnishing Portable Containers.

(a) A licensed pharmacy shall not issue portable containers to any home health agency or licensed hospice unless the home health agency or licensed hospice complies with provisions of section ~~1751.11~~ 1753.

(b) A licensed pharmacy shall cease to furnish portable containers to a home health agency or licensed hospice if the home health agency or licensed hospice does not comply with provisions of section ~~1751.11~~ 1753.

Note: Authority cited: Sections 4005 and 4057, Business and Professions Code. Reference: Sections 4040, 4057, 4081 and 4332, Business and Professions Code.

Attachment 7



COMPOUNDING SELF-ASSESSMENT

The California Code of Regulations section 1735.2 requires the pharmacist-in-charge of each pharmacy licensed under section 4037 or 4029 of the Business and Professions Code that compounds drug products to complete a self-assessment of the pharmacy's compliance with federal and state pharmacy law. **The assessment shall be performed before July 1 of every odd-numbered year. The pharmacist-in-charge must also complete a self-assessment within 30 days whenever; (1) a new pharmacy permit has been issued, or (2) there is a change in the pharmacist-in-charge; or (3) there is a change in the licensed location of the pharmacy. The primary purpose of the self-assessment is to promote compliance through self-examination and education.**

The self-assessment must be completed in its entirety and may be completed online, printed and retained in the pharmacy. Do not copy a previous assessment.

Each self-assessment must be kept on file in the pharmacy for three years after it is performed.

Pharmacy Name: _____

Address: _____ Phone: _____

Fax: _____

Ownership: Sole Owner Partnership Corporation LLC
 Non-Licensed Owner Other (please specify) _____

Permit #: _____ Exp. Date: _____ Other Permit #: _____ Exp. Date: _____

Licensed Sterile Compounding Permit # _____ Expiration: _____

Accredited by: _____ From: _____ To: _____

Centralized Hospital Packaging Permit #: _____ Exp. Date: _____

DEA Registration #: _____ Exp. Date: _____ Date of DEA Inventory: _____

Hours: Weekdays _____ Sat _____ Sun. _____ 24 Hours _____

PIC: _____ RPH # _____ Exp. Date: _____

Website address (optional): _____

Pharmacy Staff (pharmacists, intern pharmacists, pharmacy technicians assigned to compounding duties):
 (Please use an additional sheet if necessary)

1. _____	RPH # _____ APP # _____ DEA # _____	Exp. Date: _____ Exp. Date: _____ Exp. Date: _____
2. _____	RPH # _____ APP # _____ DEA # _____	Exp. Date: _____ Exp. Date: _____ Exp. Date: _____
3. _____	RPH # _____ APP # _____ DEA # _____	Exp. Date: _____ Exp. Date: _____ Exp. Date: _____
4. _____	RPH # _____ APP # _____ DEA # _____	Exp. Date: _____ Exp. Date: _____ Exp. Date: _____
5. _____	RPH # _____ APP # _____ DEA # _____	Exp. Date: _____ Exp. Date: _____ Exp. Date: _____
6. _____	RPH # _____ APP # _____ DEA # _____	Exp. Date: _____ Exp. Date: _____ Exp. Date: _____
7. _____	RPH # _____ APP # _____ DEA # _____	Exp. Date: _____ Exp. Date: _____ Exp. Date: _____
8. _____	INT # _____	Exp. Date: _____
9. _____	INT # _____	Exp. Date: _____
10. _____	INT # _____	Exp. Date: _____
11. _____	TCH # _____	Exp. Date: _____
12. _____	TCH # _____	Exp. Date: _____
13. _____	TCH # _____	Exp. Date: _____
14. _____	TCH # _____	Exp. Date: _____
15. _____	TCH # _____	Exp. Date: _____

COMPOUNDING SELF-ASSESSMENT

All references to the California Code of Regulations (CCR) are to Title 16 unless otherwise noted. Please mark the appropriate box for each question. If "NO", enter an explanation on "CORRECTIVE ACTION OR ACTION PLAN" lines at the end of the section. If more space is needed, you may add additional sheets.

ALL COMPOUNDING Complete Sections 1 through 8.

1. Definitions (CCR 1735 and 1735.1)

Yes No N/A

1.1 The pharmacy compounds as defined in CCR 1735(a).

1.2 Each pharmacist involved with compounding understands the definitions in CCR 1735.1.

2. Compounded Limitations and Requirements (CCR 1735.2)

Yes No N/A

2.1 The pharmacy does not compounded drug preparations prior to receipt of a valid prescription unless under the following conditions as allowed in CCR 1735.2(a).

2.2 The pharmacy prepares and stores a limited quantity of a compounded drug preparation in advance of receipt of a patient specific prescription solely in such quantity as is necessary to ensure continuity of care of an identified population as defined in CCR 1735.2(b).

2.3 The pharmacy compounds a reasonable quantity of drug preparation which is furnished to a prescriber for office use upon prescriber order as allowed in CCR 1735.2(c) and under all of the following requirements:

2.3.1 Is ordered by the prescriber or the prescribers' agent on a purchase order or other documentation received by the pharmacy prior to furnishing that lists the number of patients seen or to be seen in the prescriber's office for whom the drug is needed or anticipated, and the quantity for each patient sufficient for office administration; (CCR 1735.2[c][1]) **AND**

2.3.2 Is delivered to the prescriber's office and signed for by the prescriber or the prescriber's agent; (CCR 1735.2[c][2]) **AND**

2.3.3 Is sufficient for administration or application to patients in the prescriber's office or for distribution of not more than a 120-hour supply for veterinary medical practices; (CCR 1735.2[c][3]) **AND**

2.3.4 The pharmacist has a credible basis for concluding it is a reasonable quantity for office use considering the intended use of the compounded preparation and the nature of the prescriber's practice; (CCR 1735.2[c][4]) **AND**

2.3.5 Is an amount which the pharmacy is capable of compounding in compliance with pharmaceutical standards for integrity, potency, quality and strength of the compounded drug preparation; (CCR 1735.2[c][5]) **AND**

2.3.6 Does not exceed an amount the pharmacy can reasonably and safely compound. (CCR 1735.2[c][6])

2.4. The pharmacy does NOT compound drug preparations that: (CCR 1735.2[d])

2.4.1 Are classified by the FDA as demonstrably difficult to compound; (CCR 1735.2[d][1])

2.4.2 Appear on an FDA list of drugs that have been withdrawn or removed from the market; (CCR 1735.2[d][2]) or

2.4.3 Are copies or essentially copies of one or more commercially available drug products.
(CCR 1735.2[d][3])

Yes No N/A

2.5 The pharmacy does not compound drug preparations until it has prepared a written master formula document that includes the following elements: (CCR 1735.2[e][1-8])

- 2.5.1 Active ingredients used.
- 2.5.2 Equipment to be used.
- 2.5.3 Beyond use date (BUD).
- 2.5.4 Inactive ingredients used.
- 2.5.5 Specific and essential compounding steps.
- 2.5.6 Quality reviews required at each step.
- 2.5.7 Post-compounding process or procedures, if required.
- 2.5.8 Instructions for storage and handling.

2.6 The master formula for a drug preparation that is not routinely compounded by the pharmacy may be recorded on the prescription document itself. (CCR 1735.2[f])

2.7 The pharmacists performing or supervising compounding understand they are responsible for the integrity, potency, quality, and labeled strength of a compounded drug preparation until the beyond use date indicated on the label, so long as label instructions for storage and handling are followed after the preparation is dispensed. (CCR 1735.2[g])

2.8 All chemicals, bulk drug substances, drug preparations and other components used for drug compounding are stored and used according to compendia and other applicable requirements to maintain their integrity, potency, quality and labeled strength. (CCR 1735.2[h])

2.9 Every compounded drug preparation is given a beyond use date representing the date or date and time beyond which the compounded drug preparation should not be used, stored, transported or administered, and is determined based on the professional judgment of the pharmacist performing or supervising the compounding. (CCR 1735.2[i])

2.9.1 For non-sterile compounded drug preparations, the beyond use date does not exceed any of the following: (CCR 1735.2[i][1][A-F])

- 2.9.1.1 The shortest expiration date or beyond use date of any ingredient in the compounded drug preparation,
- 2.9.1.2 The chemical stability of any one ingredient in the compounded drug preparation;
- 2.9.1.3 The chemical stability of the combination of all ingredients in the compounded drug preparation,
- 2.9.1.4 180 days for non-aqueous formulations,
- 2.9.1.5 14 days for water-containing oral formulations, and
- 2.9.1.6 30 days for water-containing topical/dermal and mucosal liquid and semisolid formulations.

2.9.2 For sterile compounded drug preparations, the beyond use date does not exceed any of the following: (CCR 1735.2[i][2][A-D])

- 2.9.2.1 The shortest expiration date or beyond use date of any ingredient in the sterile compounded drug preparation,
- 2.9.2.2 The chemical stability of any one ingredient in the sterile compounded drug preparation,
- 2.9.2.3 The chemical stability of the combination of all ingredients in the sterile compounded drug preparation, and
- 2.9.2.4 The beyond use date assigned for sterility in CCR 1751.8.

2.9.3 Extension of a beyond use date is supported by the following: (CCR 1735.2[i][3][A-C])

- 2.9.3.1 Method Suitability Test,
- 2.9.3.2 Container Closure Integrity Test, and
- 2.9.3.3 Stability Studies.

- 2.9.4 The finished drugs or compounded drug preparations tested and studied are compounded using the same identical components or ingredients, specific and essential compounding steps, quality reviews, and packaging as the finished drug or compounded drug preparation. (CCR 1735.2[i][4])
- 2.9.5 Shorter dating is used if it is deemed appropriate in the professional judgment of the responsible pharmacist. (CCR 1735.2[i][5])

2.10 Self-assessment is completed, as required, prior to compounding a drug preparation. (CCR 1735.2[k])

- 2.11 Packages of ingredients, both active and inactive, which lack a supplier's expiration date are subject to the following limitations: (CCR 1735.2[l])
- 2.11.1 Ingredients are not used for any non-sterile compounded drug preparation more than three (3) years after the date of receipt by the pharmacy.
 - 2.11.2 Ingredients are not used for any sterile compounded drug preparation more than one (1) year after the date of receipt by the pharmacy.

CORRECTIVE ACTION OR ACTION PLAN: _____

3. Recordkeeping for Compounded Drug Preparation (CCR 1735.3)

Yes No N/A

- 3.1 The pharmacy makes and retains a record for each compounded drug preparation which includes, at least, the following: (CCR 1735.3[a][1-2])
- 3.1.1 The master formula document.
 - 3.1.2 A compounding log consisting of a single document containing all of the following:
 - 3.1.2.1 The name and strength of the compounded drug preparation.
 - 3.1.2.2 The date the drug preparation was compounded.
 - 3.1.2.3 The identity of the pharmacy personnel who compounded the drug preparation.
 - 3.1.2.4 The identity of the pharmacist reviewing the final drug preparation.
 - 3.1.2.5 The quantity of each component used in compounding the drug preparation.
 - 3.1.2.6 The manufacturer or supplier, expiration date and lot number of each component.
 - 3.1.2.7 The pharmacy assigned reference or lot number for the compounded drug preparation.
 - 3.1.2.8 The beyond use date or beyond use date and time of the final compounded drug preparation.
 - 3.1.2.9 The final quantity or amount of drug preparation compounded.
 - 3.1.2.10 Documentation of quality reviews and required post-compounding process and procedures.
- 3.2 The pharmacy maintains records of the proper acquisition, storage, and destruction of chemicals, bulk drug substances, components and drug preparations used in compounding. (CCR 1735.3[b])
- 3.3 Active ingredients are obtained from a supplier registered with the Food and Drug Administration (FDA). All other chemicals, bulk drug substances, and drug components used to compound drug preparations are to be obtained, whenever possible, from FDA-registered suppliers. The pharmacy acquires and retains certificates of purity or analysis, either written in English or translated into English, for chemicals, bulk drug substances, and drug products used in compounding. (CCR 1735.3[c])
- 3.5 The pharmacy maintains and retains all records required in the pharmacy in a readily retrievable form for at least three years (CCR 1735.3[d]).

4. Labeling of Compounded Drug Preparation (CCR 1735.4)

Yes No N/A

- 4.1 Each compounded drug preparation has at least the following affixed to the container on a label prior to dispensing: (CCR 1735.4[a][1-6])
 - 4.1.1 Name of the compounding pharmacy and dispensing pharmacy (if different);
 - 4.1.2 Name (brand or generic) and strength, volume, or weight of each active ingredient. For admixed intravenous (IV) solutions, the IV solution utilized shall be included;
 - 4.1.3 Instructions for storage, handling, and administration. For admixed IV solutions, the rate of infusion shall be included;
 - 4.1.4 The beyond use date for the drug preparation;
 - 4.1.5 The date compounded; and
 - 4.1.6 The lot number or pharmacy reference number.
- 4.2 Any compounded drug preparation dispensed to a patient or readied for dispensing to a patient is labeled with the information required under Business and Professions Code section 4076 and California Code of Regulations, title 16, section 1707.5. (CCR 1735.4[b])
- 4.3 Any compounded drug preparation dispensed to a patient or readied for dispensing to a patient also includes, on the container label or on a receipt provided to the patient, a statement the drug preparation has been compounded by the pharmacy. (CCR 1735.4[c])
- 4.4 Drug preparations compounded into unit-dose containers that are too small or otherwise impractical for full compliance with the requirements of CCR 1735.4(a), (b), and (c) are labeled with at least the name(s) of the active ingredient(s), concentration of strength, volume or weight, pharmacy reference or lot number, and beyond use date. (CCR 1735.4[d])
- 4.5 All hazardous agents bear a special label which states "Chemotherapy - Dispose of Properly" or "Hazardous – Dispose of Properly. (CCR 1735.4[e])

CORRECTIVE ACTION OR ACTION PLAN: _____

5. Compounding Policies and Procedures (CCR 1735.5)

Yes No N/A

- 5.1 The pharmacy maintains written policies and procedure for compounding which 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. (CCR 1735.5[a])
- 5.2 The policy and procedures are reviewed on an annual basis by the pharmacist-in-charge and are updated whenever changes are implemented. (CCR 1735.5[b])
- 5.3 The policies and procedures include at least the following: (CCR 1735.5[c][1-11])
 - 5.3.1 Procedures for notifying staff assigned to compounding duties of any changes in policies or procedures.
 - 5.3.2 A written plan for recall of a dispensed compounded drug preparation where subsequent information demonstrates the potential for adverse effects with continued use. The plan ensures all affected doses can be accounted for during the recall and shall provide steps to identify which patients received the affected lot or compounded drug preparation(s).

- 5.3.3 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.
- 5.3.4 Procedures for evaluating, maintaining, certifying, cleaning, and disinfecting the facility (physical plant) used for compounding, and for training on these procedures as part of the staff training and competency evaluation process.
- 5.3.5 Documentation of the methodology used to validate integrity, potency, quality, and labeled strength of compounded drug preparations. The methodology must be appropriate to compounded drug preparations.
- 5.3.6 Documentation of the methodology and rationale or reference source used to determine appropriate beyond use dates for compounded drug preparations.
- 5.3.7 Dates and signatures reflecting all annual reviews of the policies and procedures by the pharmacist-in-charge.
- 5.3.8 Dates and signatures accompanying any revisions to the policies and procedures approved by the pharmacist-in-charge.
- 5.3.9 Policies and procedures for storage of compounded drug preparations in the pharmacy and daily documentation of all room, refrigerator, and freezer temperatures within the pharmacy.
- 5.3.10 Policies and procedures for ensuring appropriate functioning of refrigeration devices, monitoring refrigeration device temperatures, and actions to take regarding any out of range temperature variations within the pharmacy.
- 5.3.11 Policies and procedures for proper garbing when compounding with hazardous products; including when to utilize double shoe covers.

CORRECTIVE ACTION OR ACTION PLAN: _____

6. Compounding Facilities and Equipment (CCR 1735.6)

Yes No N/A

- 6.1 The pharmacy maintains written documentation regarding the facilities and equipment necessary for safe and accurate compounding of compounded drug preparations which includes records of certification of facilities or equipment, if applicable. (CCR 1735.6[a])
- 6.2 All equipment used to compound a drug preparation is stored, used and maintained in accordance with manufacturers' specifications. (CCR 1735.6[b])
- 6.3 All equipment used to compound a drug preparation is calibrated prior to use to ensure accuracy. (CCR 1735.6[c])
 - 6.3.1 Documentation of each calibration is recorded in a form which is not alterable and is maintained and retained in the pharmacy.
- 6.4 When engaged in hazardous drug compounding, the pharmacy maintains written documentation regarding appropriate cleaning of facilities and equipment to prevent cross-contamination with non-hazardous drugs. (CCR 1735.6[d])
- 6.5 Hazardous drug compounding is completed in an externally vented physically separate room with the following requirements: (CCR 1735.6[e])
 - 6.5.1 Minimum of 30 air changes per hour except that 12 air changes per hour are acceptable for segregated compounding areas with a BSC or CACI when products are assigned a BUD of 12 hrs or less or when nonsterile products are compounded; and

- 6.5.2 Maintained at a negative pressure of 0.01 to 0.03 inches of water column relative to all adjacent spaces (rooms, above ceiling, and corridors); and
- 6.5.3 Each PEC in the room is externally vented; and
- 6.5.4 All surfaces within the room are smooth, seamless, impervious, and non-shedding.

6.6 This pharmacy has applied and was granted a waiver for the following physical construction or alteration to a facility or physical environment. (CCR 1735.6[f])

Code waiver was granted for:

Expiration of waiver:

CORRECTIVE ACTION OR ACTION PLAN: _____

7. Training of Compounding Staff (CCR 1735.7)

Yes No N/A

- 7.1 The pharmacy maintains documentation demonstrating personnel involved in compounding have the skills and training required to properly and accurately perform their assigned responsibilities and documentation demonstrating all personnel involved in compounding are trained in all aspects of policies and procedures. This training includes, but is not limited to, support personnel (e.g. institutional environmental services, housekeeping), maintenance staff, supervising pharmacists and all others whose jobs are related to the compounding process. (CCR 1735.7[a])
- 7.2 The pharmacy has developed and maintains an ongoing 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. (CCR 1735.7[b])
- 7.3 Pharmacy personnel assigned to compounding duties demonstrate knowledge about processes and procedures used in compounding prior to compounding any drug preparation. (CCR 1735.7[c])

CORRECTIVE ACTION OR ACTION PLAN: _____

8. Compounding Quality Assurance (CCR 1735.8)

Yes No N/A

- 8.1 The pharmacy maintains, as part of its written policies and procedures, a written quality assurance plan to monitor and ensure the integrity, potency, quality and labeled strength of compounded drug preparation. (CCR 1735.8[a])
- 8.2 The pharmacy's quality assurance plan includes the written procedures and standards for at least the following:
 - 8.2.1 Verification, monitoring and review of the adequacy of the compounding processes as well as documentation of review of those processes by qualified pharmacy personnel. (CCR 1735.8[b])

- 8.2.2 Qualitative and quantitative analysis of compounded drug preparations to ensure integrity, potency, quality and labeled strength, including the frequency of testing. Frequency of routine testing and analysis is done on an annual basis. (CCR 1735.8[c])
- 8.2.3 Such reports are retained by the pharmacy and collated with the compounding record and master formula document. (CCR 1735.8[c])
- 8.2.4 Scheduled action in the event any compounded drug preparation is ever discovered to be below minimum standards for integrity, potency, quality or labeled strength. (CCR 1735.8[d])
- 8.2.5 Response to out-of-range temperature variations within the pharmacy and within patient care areas of a hospital where furnished drug is returned for redispensing. (CCR 1735.8[e])

COMPOUNDING STERILE DRUGS

Does the pharmacy compound sterile drug preparation for injection, administration into the eye, or for inhalation? (B&PC 4127)

Yes No

If yes, complete Sections 9 through 25.

FOR PHARMACIES THAT COMPOUND STERILE DRUG preparation:

9. Compounding Drug for Other Pharmacy for Parenteral Therapy

Yes No N/A

9.1 Any pharmacy that contracts to compound a drug for parenteral therapy, pursuant to a prescription, for delivery to another pharmacy shall report that contractual arrangement to the board. (B&PC 4123)

9.1.1 The contractual arrangement is reported to the board within 30 days of commencing that compounding.

10. Compounding Sterile Injectables from Nonsterile Ingredients; Requirements

Yes No N/A

10.1 The pharmacy compounds sterile injectable products from one or more nonsterile ingredients in one of the following environments: (B&PC 4127.7)

10.1.1. An ISO Class 5 laminar airflow hood within an ISO Class 7 cleanroom. A positive air pressure differential in the cleanroom that is relative to adjacent areas. (B&PC 4127.7[a])

10.1.2 An ISO Class 5 cleanroom. (B&PC 4127.7[b])

10.1.3 A barrier isolator that provides an ISO Class 5 environment for compounding. (B&PC 4127.7[c])

11. Sterile Injectable Compounding; Compounding Area (CCR 1751)

Yes No N/A

11.1 The pharmacy conforms 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 compounding. (CCR 1751[a])

Yes No N/A

- 11.2 The pharmacy has a compounding area designated for the preparation of sterile drug preparations ~~that is~~ in a restricted location where traffic has no impact on the performance of the Primary Engineering Control(s) (PEC). (CCR 1751[b])
 - 11.2.1 The cleanroom, including the walls, ceilings, and floors, are constructed in accordance with Section 1250.4 of Title 24, Part 2, Chapter 12, of the California Code of Regulations.
 - 11.2.2 The pharmacy is ventilated in a manner in accordance with Section 505.5 of Title 24, Part 4, Chapter 5 of the California Code of Regulations.
 - 11.2.3 The environments within the pharmacy meet at least the following standards: (CCR 1751[b])
 - 11.3.1 Each ISO environment is certified at least every six months by a qualified technician in accordance with Section 1751.4.
 - 11.3.1.1 Certification records must be retained in the pharmacy.
 - 11.3.2 Items related to the compounding of sterile drug preparations within the compounding area are stored in such a way as to maintain the integrity of an aseptic environment.
 - 11.3.3 A sink is included in accordance with Section 1250.4 of Title 24, Part 2, Chapter 12, of the California Code of Regulations. Sinks and drains are not present in any ISO Class 7 or better cleanroom, nor in a segregated sterile compounding area within three feet of an ISO Class 5 or better PEC, with the exception of emergency eye-rinsing stations. A sink may be located in an ante-area.
 - 11.3.4 There is a refrigerator and where appropriate, a freezer, of sufficient capacity to meet the storage requirements for all material requiring refrigeration or freezing, and a backup plan is in place to ensure continuity of available compounded drug preparations in the event of a power outage.

12. Sterile Injectable Compounding; Compounding Area (CCR 1250.4, 505.5 and 505.5.1)
 TITLE 24, PART 2, CHAPTER 12, REGULATIONS

Yes No N/A

- 12.1 The pharmacy has designated area for the preparation of sterile products for dispensing which meets at least the following: (24 CCR 1250.4)
 - 12.1.1 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. (24 CCR 1250.4[1])
 - 12.1.2 Has non-porous and cleanable surfaces, walls, floors, ceilings and floor coverings. (24 CCR 1250.4[2])
 - 12.1.3 The pharmacy is arranged in such a manner that the laminar-flow hood (PEC) 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 preparations. There is sufficient space, well separated from the laminar-flow hood area, for the storage of bulk materials, equipment and waste materials. (24 CCR 1250.4[3])
 - 12.1.4 A sink with hot and cold running water is within the parenteral preparation compounding area or adjacent to it. (24 CCR 1250.4[4])
 - 12.1.5 The pharmacy compounding sterile injectable preparations from one or more nonsterile ingredients, compounds the preparations in one of the following environments: (24 CCR 1250.4[5])
 - 12.1.5.1 An ISO Class 5 laminar airflow hood within an ISO Class 7 cleanroom. The cleanroom must have a positive air pressure differential relative to adjacent areas.
 - 12.1.5.2 An ISO Class 5 cleanroom.
 - 12.1.5.3 A barrier isolator that provides an ISO Class 5 environment for compounding.

Yes No N/A

- 12.2 The pharmacy has a designated area for the compounding of sterile preparations for dispensing which shall: (24 CCR 505.5)
12.2.1 Be ventilated in a manner not interfering with laminar air flow.

Yes No N/A

- 12.3 Pharmacies preparing parenteral cytotoxic agents, all compounding is conducted within a certified Class II Type A or Class II Type B vertical laminar air flow hood with bag in-bag out design. The pharmacy ensures that contaminated air plenums under positive air pressure are leak tight. (24 CCR 505.5.1)

CORRECTIVE ACTION OR ACTION PLAN: _____

13. Sterile Compounding Recordkeeping Requirements. (CCR 1751.1)

Yes No N/A

- 13.1 In addition to the records required by section 1735.3 the pharmacy maintains at least the following records, which are in a readily retrievable, within the pharmacy: (CCR 1751.1[a][1-11])
- 13.1.1 Documents evidencing training and competency evaluations of employees in sterile drug preparation policies and procedures.
 - 13.1.2 Results of hand hygiene and garbing assessments with integrated gloved fingertip testing.
 - 13.1.3 Results of assessments of personnel for aseptic techniques including results of media-fill tests and gloved fingertip testing performed in association with media-fill tests.
 - 13.1.4 Results of viable air and surface sampling.
 - 13.1.5 Video of smoke studies in all ISO certified spaces.
 - 13.1.6 Documents indicating daily documentation of room, refrigerator, and freezer temperatures appropriate for sterile compounded drug preparations consistent with the temperatures listed in section 1735.1 for:
 - 13.1.6.1 Controlled room temperature.
 - 13.1.6.2 Controlled cold temperature.
 - 13.1.6.3 Controlled freezer temperature.
 - 13.1.7 Certification(s) of the sterile compounding environment(s).
 - 13.1.8 Documents indicating daily documentation of air pressure differentials or air velocity measurements between all adjoining ISO rooms or areas, including those associated with compounding aseptic (containment) isolators, and air pressure differentials or air velocity measurements between all rooms or spaces with an immediate entry or opening to ISO rooms or areas.
 - 13.1.9 Other facility quality control records specific to the pharmacy's policies and procedures (e.g., cleaning logs for facilities and equipment, incubator temperatures).
 - 13.1.10 Logs or other documentation of inspections for expired or recalled chemicals, bulk drug substances, drug products, or other ingredients.
 - 13.1.11 Preparation records including the master formula document, the preparation compounding log, and records of end-product evaluation testing and results.
- 13.2 The pharmacy compounds for future use pursuant to section 1735.2, and in addition to those records required by section 1735.3, the pharmacy makes and keeps records indicating the name, lot number, and

amount of any drug preparation compounded for future use, the date on which any preparation was provided to a prescriber, and the name, address, license type and number of the prescriber. (CCR 1751.1[b])

- 13.3 The pharmacy maintains and retains 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. If only recorded and stored electronically, on magnetic media, or in any other computerized form, the records are maintained as specified by Business and Professions Code section 4070 subsection (c). (CCR 1751.1[c])

CORRECTIVE ACTION OR ACTION PLAN: _____

14. Sterile Labeling Requirements (CCR 1751.2)

Yes No N/A

- 14.1 In addition to the labeling information required under Business and Professions Code section 4076 and California Code of Regulations, title 16, sections 1707.5 and 1735.4, the pharmacy labels each compounded sterile drug preparations with at least the following information: (CCR 1751.2[a-c])
- 14.1.1 The telephone number of the pharmacy.
 - 14.1.2 Instructions for storage, handling, and administration.
 - 14.1.3 All hazardous agents shall bear a special label which states "Chemotherapy - Dispose of Properly" or "Hazardous – Dispose of Properly.":

CORRECTIVE ACTION OR ACTION PLAN: _____

15. Sterile Policies and Procedures (CCR 1751.3)

Yes No N/A

- 15.1 The pharmacy maintains written policies and procedures for compounding and understands any material failure to follow the pharmacy's written policies and procedures shall constitute a basis for disciplinary action. CCR 1751.3[a])
- 15.2 In addition to the elements required by section 1735.5, there are written policies and procedures regarding at least the following: (CCR 1751.3[a][1-24])
- 15.2.1 Action levels for colony-forming units (CFUs) detected during viable surface sampling, glove fingertip, and viable air sampling and actions to be taken when the levels are exceeded.
 - 15.2.2 Airflow considerations and pressure differential monitoring.
 - 15.2.3 An environmental sampling plan and procedures specific to viable air, surface and gloved fingertip sampling as well as nonviable particle sampling.
 - 15.2.4 Cleaning and maintenance of ISO environments and segregated compounding areas.
 - 15.2.5 Compounded sterile drug preparation stability and beyond use dating.
 - 15.2.6 Compounding, filling, and labeling of sterile drug preparations.
 - 15.2.7 Daily and monthly cleaning and disinfection schedule for the controlled areas and any equipment in the controlled area as specified in section 1751.4.
 - 15.2.8 Depyrogenation of glassware (if applicable)
 - 15.2.9 Facility management including certification and maintenance of controlled environments and related equipment.

- 15.2.10 For compounding aseptic isolators and compounding aseptic containment isolators, documentation of the manufacturer's recommended purge time.
- 15.2.11 Hand hygiene and garbing.
- 15.2.12 Labeling of the sterile compounded drug preparations based on the intended route of administration and recommended rate of administration.
- 15.2.13 Methods by which the supervising pharmacist will fulfill his or her responsibility to ensure the quality of compounded drug preparations.
- 15.2.14 Orientation, training, and competency evaluation of staff in all aspects of the preparation of sterile drug preparations including didactic training and knowledge/competency assessments which include at minimum: hand hygiene and garbing; decontamination (where applicable); cleaning and disinfection of controlled compounding areas; and proper aseptic technique demonstrated through the use of a media-fill test performed by applicable personnel; and aseptic area practices.
- 15.2.15 Preparing sterile compounded drug preparations from non-sterile components (if applicable). This shall include sterilization method suitability testing for each master formula document.
- 15.2.16 Procedures for handling, compounding and disposal of hazardous agents. The written policies and procedures shall describe the pharmacy protocols for cleanups and spills in conformity with local health jurisdiction standards.
- 15.2.17 Procedures for handling, compounding and disposal of infectious materials. The written policies and procedures shall describe the pharmacy protocols for cleanups and spills in conformity with local health jurisdiction standards.
- 15.2.18 Proper use of equipment and supplies.
- 15.2.19 Quality assurance program compliant with sections 1711, 1735.8, and 1751.7.
- 15.2.20 Record keeping requirements.
- 15.2.21 Temperature monitoring in compounding and controlled storage areas.
- 15.2.22 The determination and approval by a pharmacist of ingredients and the compounding process for each preparation before compounding begins.
- 15.2.23 Use of automated compounding devices (if applicable).
- 15.2.24 Visual inspection and other final quality checks of sterile drug preparations.

- 15.3 For lot compounding, the pharmacy maintains a written policies and procedures which includes at least the following: (CCR 1751.3[b][1-3])
 - 15.3.1 Use of master formula documents and compounding logs.
 - 15.3.2 Appropriate documentation.
 - 15.3.3 Appropriate sterility and potency testing.

- 15.3. For non-sterile-to-sterile batch compounding, the pharmacy maintains a written policies and procedures for compounding which included at least the following. (CCR 1751.2[c][1-2])
 - 15.3.1 Process validation for chosen sterilization methods.
 - 15.3.2 End-product evaluation, quantitative, and qualitative testing.

- 15.4. All personnel involved have read the policies and procedures before compounding sterile drug preparations. All personnel involved have read all additions, revisions, and deletions to the written policies and procedures. Each review is documented by a signature and date. (CCR 1751.3[e])

CORRECTIVE ACTION OR ACTION PLAN: _____

16. Facility & Equipment Standards for Sterile Compounding (CCR 1751.4)

Yes No N/A

- 16.1 No sterile drug preparation is compounded if it is known, or reasonably should be known, that the compounding environment fails to meet criteria specified in the pharmacy's written policies and procedures for the safe compounding of sterile drug preparations (CCR 1751.4[a])
- 16.2 During the compounding of sterile drug preparations, access to the areas designated for compounding is limited to those individuals who are properly attired (CCR 1751.4[b])
- 16.3 All equipment used in the areas designated for compounding is made of a material that can be easily cleaned and disinfected. (CCR 1751.4[c])
- 16.4 Cleaning is done using a germicidal detergent and sterile water. A sporicidal agent is used at least monthly (CCR 1751.4[d][1-4])
 - 16.4.1 All ISO Class 5 surfaces, work table surfaces, carts, counters, and the cleanroom floor are cleaned at least daily. After each cleaning, disinfection using a suitable sterile agent occurs on all ISO Class 5 surfaces, work table surfaces, carts, and counters.
 - 16.4.2 Walls, ceilings, storage shelving, tables, stools, and all other items in the ISO Class 7 or ISO Class 8 environment are cleaned at least monthly.
 - 16.4.3 Cleaning shall also occur after any unanticipated event that could increase the risk of contamination.
 - 16.4.4 All cleaning materials, such as wipers, sponges, and mops, shall be non-shedding and dedicated to use in the cleanroom, or ante-area, and segregated sterile compounding areas and shall not be removed from these areas except for disposal.
- 16.5 Disinfection, using a suitable sterile agent, occurs on all surfaces in the ISO Class 5 PEC frequently, including: (CCR 1751.4[e])
 - 16.5.1 At the beginning of each shift;
 - 16.5.2 At least every 30 minutes when compounding involving human staff is occurring or before each lot;
 - 16.5.3 After each spill; and
 - 16.5.4 When surface contamination is known or suspected.
- 16.6 Pharmacies preparing sterile compounded preparations are using a PEC that provides ISO Class 5 air or better air quality (CCR 1751.4[f])
 - 16.6.1 Certification and testing of primary and secondary engineering controls are performed no less than every six months and whenever the device or area designated for compounding is relocated, altered or a service to the facility is performed which would impact the device or area.
 - 16.6.2 Certification is completed by a qualified technician who is familiar with certification methods and procedures in accordance with CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2006-13, Revised May 20, 2015).
 - 16.6.2.1 Certification records are retained for at least 3 years.
 - 16.6.3 Unidirectional compounding aseptic isolators or compounding aseptic containment isolators used outside of an ISO Class 7 cleanroom if the isolators are certified to meet the following criteria: (CCR 1751.4[f][1-3])
 - 16.6.3.1 Particle counts sampled approximately 6-12 inches upstream of the critical exposure site shall maintain ISO Class 5 levels during compounding operations.
 - 16.6.3.2 Not more than 3520 particles (0.5 um and larger) per cubic meter shall be counted during material transfer, with the particle counter probe located as near to the transfer door as possible without obstructing transfer.
 - 16.6.3.3 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.
 - 16.6.4 Compounding aseptic isolators that do not meet the requirements as outlined in this subdivision or are not located within an ISO Class 7 cleanroom are only be used to compound preparations that

meet the criteria specified in accordance with subdivision (d) of Section 1751.8 of Title 16, Division 17, of the California Code of Regulations.

- 16.7 Pharmacies preparing sterile hazardous agents shall do so in accordance with Section 505.5.1 of Title 24, Chapter 5, of the California Code of Regulations, requiring a negative pressure PEC.
 - 16.7.1 Additionally, each PEC used to compound hazardous agents shall be externally vented.
 - 16.7.2 The negative pressure PEC is certified every six months by a qualified technician who is familiar with CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2006-13, Revised May 20, 2015).
 - 16.7.3 Any drug preparation compounded in a PEC where hazardous drugs are prepared are labeled as hazardous, regardless of whether the drug ingredients are considered hazardous. (CCR 1751.4[g])
 - 16.7.4 During hazardous drug compounding performed in a compounding aseptic containment isolator, full hand hygiene and garbing occurs. Garbing shall include hair cover, facemask, beard cover (if applicable), polypropylene or low shedding gown that closes in the back, shoe covers, and two pairs of sterile ASTM D6978-05 standard gloves. (CCR 1751.4[g][1])

- 16.8 If a compounding aseptic isolator is certified by the manufacturer to maintain ISO Class 5 air quality during dynamic operation conditions during compounding as well as during the transfer of ingredients into and out of the compounding aseptic isolator, then it may be placed into a non-ISO classified room. Individuals who use compounding aseptic isolators in this manner must ensure appropriate garbing, which consists of donning sterile gloves over the isolator gloves immediately before non-hazardous compounding. These sterile gloves must be changed by each individual whenever continuous compounding is ceased and before compounding starts again. (CCR 1751.4[h])

- 16.9 Compounding aseptic isolators and compounding aseptic containment isolators used in the compounding of sterile drug preparations shall use non-turbulent unidirectional air flow patterns. A smoke patterned test shall be used to determine air flow patterns. (CCR 1751.4[i])

- 16.10 Viable surface sampling is done at least every six months for all sterile-to-sterile compounding and quarterly for all non-sterile-to-sterile compounding. Viable air sampling is be done by volumetric air sampling procedures which test a sufficient volume of air (400 to 1,000 liters) at each location and shall be done at least once every six months. Viable surface and viable air sampling are performed by a qualified individual who is familiar with the methods and procedures for surface testing and air sampling. Viable air sampling is performed under dynamic conditions which simulate actual production. Viable surface sampling is performed under dynamic conditions of actual compounding. When the environmental monitoring action levels are exceeded, the pharmacy identifies the CFUs at least to the genus level in addition to conducting an investigation pursuant to its policies and procedures. Remediation shall include, at minimum, an immediate investigation of cleaning and compounding operations and facility management. (CCR 1751.4[j])

- 16.11 The sterile compounding area in the pharmacy has a comfortable and well-lighted working environment, which includes a room temperature of 20-24 degrees Celsius (68-75 degrees Fahrenheit) or cooler to maintain comfortable conditions for compounding personnel when attired in the required compounding garb. (CCR 1751.4[k])

CORRECTIVE ACTION OR ACTION PLAN: _____

17. Sterile Compounding Attire (CCR 1751.5)

Yes No N/A

- 17.1. When compounding sterile drug products preparations the following standards are met: (CCR 1751.5[a][1-6])
- 17.1.1 Personal protective equipment consisting of a low non-shedding coverall gown, head cover, face mask, facial hair covers (if applicable), and shoe covers are worn inside the designated area at all times. For hazardous compounding, double shoe covers are worn.
 - 17.1.2 Personal protective equipment is donned and removed in an ante-area or immediately outside the segregated compounding area.
 - 17.1.3 Personnel dons personal protective equipment in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. The following order is to be followed unless the pharmacy has a procedure in place which documents a method equivalent to or superior to the method described here: The donning of shoe covers or dedicated shoes, head and facial hair covers and face masks shall be followed by the washing of hands and forearms up to the elbows for 30 seconds with soap and water, drying hands, and then the donning of a non-shedding gown.
 - 17.1.4 Compounding personnel does not wear any wrist, hand, finger, or other visible jewelry, piercing, headphones, earbuds, or personal electronic device.
 - 17.1.5 Sterile gloves that have been tested for compatibility with disinfection by isopropyl alcohol are worn. Hand cleansing with a persistently active alcohol-based product followed by the donning of sterile gloves may occur within the ante or cleanroom. Gloves are routinely disinfected with sterile 70 percent isopropyl alcohol before entering or re-entering the PEC and after contact with non-sterile objects. Gloves are routinely inspected for holes, punctures, or tears and replaced immediately if such are detected.
 - 17.1.6 Individuals experiencing exposed rashes, sunburn, weeping sores, conjunctivitis, active respiratory infections or other communicable disease, or those wearing cosmetics, nail polish, or artificial nails are excluded from the ISO Class 5 and ISO Class 7 compounding areas until their conditions are remedied.
- 17.2. When preparing hazardous agents, appropriate gowns and personal protective equipment are worn regardless of the PECs used (e.g., biological safety cabinet and compounding aseptic containment isolator). (CCR 1751.5[b])

CORRECTIVE ACTION OR ACTION PLAN: _____

18. Sterile Compounding Consultation; Training of Sterile Compounding Staff. (CCR 1751.6)

Yes No N/A

- 18.1 Consultation is available to the patient and/or primary caregiver concerning proper use, storage, handling, and disposal of sterile drug preparations and related supplies furnished by the pharmacy. (CCR 1751.6[a])
- 18.2 The pharmacist-in-charge ensures all pharmacy personnel engaging in compounding sterile drug preparations have training and demonstrated competence in the safe handling and compounding of sterile drug preparations, including hazardous agents if the pharmacy compounds products with hazardous agents. (CCR 1751.6[b])
- 18.3 Records of training and demonstrated competence are available for each individual and shall be retained for three years beyond the period of employment (CCR 1751.6[c])

- 18.4 The pharmacist-in-charge is responsible to ensure the continuing competence of pharmacy personnel engaged in compounding sterile drug preparations (CCR 1751.6[d])
- 18.5 The pharmacy complies with at least the following training requirements: (CCR 1751.6[e])
 - 18.5.1 The pharmacy establishes and follows a written program of training and performance evaluation designed to ensure 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: (CCR 1751.6[e][1][A-J])
 - 18.5.1.1 Aseptic technique.
 - 18.5.1.2 Pharmaceutical calculations and terminology.
 - 18.5.1.3 Sterile preparation compounding documentation.
 - 18.5.1.4 Quality assurance procedures.
 - 18.5.1.5 Aseptic preparation procedures.
 - 18.5.1.6 Proper hand hygiene, gowning and gloving technique.
 - 18.5.1.7 General conduct in the controlled area (aseptic area practices).
 - 18.5.1.8 Cleaning, sanitizing, and maintaining of the equipment and the controlled area.
 - 18.5.1.9 Sterilization techniques for compounding sterile drug preparations from one or more non-sterile ingredients.
 - 18.5.1.10 Container, equipment, and closure system selection.
 - 18.5.2 Each person engaged in sterile compounding has successfully completed practical skills training in aseptic technique and aseptic area practices using models that are comparable to the most complex manipulations to be performed by the individual. Each pharmacist responsible for, or directly supervising and controlling, aseptic techniques or practices, must demonstrate the skills needed to ensure the sterility of compounded drug preparations. 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 at least every 12 months. Results of these assessments must be documented and retained in the pharmacy for three years. (CCR 1751.6[e][2])

CORRECTIVE ACTION OR ACTION PLAN: _____

19. Sterile Injectable Compounding Quality Assurance and Process Validation (CCR 1751.7)

Yes No N/A

- 19.1 There is a written, documented, ongoing quality assurance program maintained by the pharmacy that monitors personnel performance, equipment, and facilities, and the pharmacist-in-charge assures the end-product meets the required specifications by periodic sampling. (CCR 1751.7[a])
 - 19.1.1 The quality assurance program shall include at least the following (CCR 1751.7[a][1-3])
 - 19.1.1.1 Procedures for cleaning and sanitization of the sterile preparation area.
 - 19.1.1.2 Actions to be taken in the event of a drug recall.
 - 19.1.1.3 Documentation justifying the chosen beyond use dates for compounded sterile drug preparations.
- 19.2.1 The pharmacy and each individual involved in the compounding of sterile drug preparations successfully demonstrate competency on aseptic technique and aseptic area practices before being allowed to prepare sterile drug preparations. (CCR 1751.7[b][1])
- 19.2.2 Each individual's competency is revalidated at least every twelve months for sterile to sterile compounding and at least every six months for individuals compounding sterile preparations from non-sterile ingredients. (CCR 1751.7[b][2])
- 19.2.3 The pharmacy's validation process on aseptic technique and aseptic area practices is to be revalidated whenever: (CCR 1751.7[b][3][A-B])
 - 19.2.3.1 The quality assurance program yields an unacceptable result.

19.2.3.2 There is any change in the compounding process, the Primary Engineering Control (PEC), or the compounding environment. For purposes of this subsection, a change includes, but is not limited to, when the PEC is moved, repaired or replaced, when the facility is modified in a manner affecting airflow or traffic patterns, or when improper aseptic techniques are observed.

19.2.4 The pharmacy must document the validation and revalidation process (CCR 1751.7[b][4]).

- 19.3 All sterile compounding personnel have successfully completed an initial competency evaluation. In addition, immediately following the initial hand hygiene and garbing procedure, each individual who may be required to do so in practice has successfully completed a gloved fingertip (all fingers on both hands) sampling procedure (zero colony forming units for both hands) at least three times before initially being allowed to compound sterile drug preparations. (CCR 1751.7[c])
- 19.4 Re-evaluation of garbing and gloving competency occurs at least every 12 months for personnel compounding products made from sterile ingredients and at least every six months for personnel compounding products from non-sterile ingredients. (CCR 1751.7[d])
- 19.5 Batch-produced sterile drug preparations compounded from one or more non-sterile ingredients, except as provided in paragraph (2), are subject to documented end product testing for sterility and pyrogens and are quarantined until the end product testing confirms sterility and acceptable levels of pyrogens. Sterility testing is performed per USP chapter 71 and pyrogen testing confirms acceptable levels of pyrogen per USP chapter 85 limits before dispensing. This requirement of end product testing confirming sterility and acceptable levels of pyrogens prior to dispensing applies regardless of any sterility or pyrogen testing that may have been conducted on any ingredient or combination of ingredients which were previously non-sterile. Exempt from pyrogen testing are topical ophthalmic and inhalation preparation. (CCR 1751.7[e][1])
- 19.5.1 The following non-sterile-to-sterile batch drug preparations do not require end product testing for sterility and pyrogens: (CCR 1751.7[e][2][A-B])
- 19.5.1.1 Preparations for self-administered ophthalmic drops in a quantity sufficient for administration to a single patient for 30 days or less pursuant to a prescription.
- 19.5.1.2 Preparations for self-administered inhalation in a quantity sufficient for administration to a single patient for 5 days or less pursuant to a prescription.

CORRECTIVE ACTION OR ACTION PLAN: _____

20. Beyond Use Dating for Sterile Compounded Drug Preparations (CCR 1751.8)

Yes No N/A

- 20.1 Every sterile compounded drug preparation is given and labeled with a beyond use date in compliance with 1735.2 and does not exceed the shortest expiration date or beyond use date of any ingredient in sterile the compounded drug preparation, nor the chemical stability of any one ingredient in the sterile compounded drug preparation, nor the chemical stability of the combination of all ingredients in the sterile compounded drug preparation, and , in the absence of passing a sterility test in accordance with standards for sterility testing found in Chapter 797 of the United States Pharmacopeia would justify an extended beyond use date, conforms to the following limitations:
- 20.2 The beyond use date states storage and exposure periods cannot exceed 48 hours at controlled room temperature, 14 days at controlled cold temperature, and 45 days in solid frozen state, where the sterile compounded drug preparation is compounded solely with aseptic manipulations and all of the following apply: (CCR 1751.8[a])

- 20.2.1 The preparation is compounded entirely within an ISO Class 5 PEC located in an ISO Class 7 cleanroom with an ante-area or compounded entirely within a CAI which meets the requirements in 1751.4(f)(1)-(3), using only sterile ingredients, products, components, and devices; **and**
- 20.2.2 The compounding process involves transferring, measuring, and mixing manipulations using not more than three commercially manufactured packages of sterile preparations and not more than two entries into any one sterile container or package of sterile preparations or administration containers/devices to prepare the drug preparation; **and**
- 20.2.3 Compounding manipulations are limited to aseptically opening ampules, penetrating disinfected stoppers on vials with sterile needles and syringes or spiked transfer devices, and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile preparations, and containers for storage dispensing.

- 20.3 The beyond use date states storage and exposure periods cannot exceed 30 hours at controlled room temperature, 9 days at controlled cold temperature, and 45 days in solid frozen state, where the sterile compounded drug preparation is compounded solely with aseptic manipulations and all of the following apply: (CCR 1751.8[b])
 - 20.3.1 The preparation is compounded entirely within an ISO Class 5 PEC located in an ISO Class 7 cleanroom with an ante-area or compounded entirely within a CAI which meets the requirements in 1751.4(f)(1)-(3), using multiple individual or small doses of sterile preparations combined or pooled to prepare a compounded sterile preparation that will be administered either to multiple patients or to one patient on multiple occasions; and
 - 20.3.2 The compounding process involves complex aseptic manipulations other than the single-volume transfer; and
 - 20.3.3 The compounding process requires unusually long duration such as that required to complete dissolution or homogenous mixing.

- 20.4 The beyond use date states storage and exposure periods cannot exceed 24 hours at controlled room temperature, 3 days at controlled cold temperature, and 45 days in solid frozen state, where the sterile compounded drug preparation is compounded solely with aseptic manipulations using non-sterile ingredients, regardless of intervening sterilization of that ingredient and the following applies: (CCR 1751.8[c])
 - 20.4.1 The preparation is compounded entirely within an ISO Class 5 PEC located in an ISO Class 7 cleanroom with an ante-area or compounded entirely within a CAI which meets the requirements in 1751.4(f)(1)-(3).

- 20.5 The beyond use date states storage and exposure periods cannot exceed 12 hours where the sterile compounded drug preparation is compounded solely with aseptic manipulations and all of the following apply: (CCR 1751.8[d])
 - 20.5.1 The preparation was compounded entirely within an ISO Class 5 PEC that is located in a segregated sterile compounding area and restricted to sterile compounding activities, using only sterile ingredients, components, and devices, by personnel properly cleansed and garbed; and
 - 20.5.2 The compounding process involves simple transfer of not more than three commercially manufactured packages of sterile nonhazardous preparations or diagnostic radiopharmaceutical preparations from the manufacturer's original containers; and
 - 20.5.3 The compounding process involves not more than two entries into any one container or package (e.g., bag, vial) of sterile infusion solution or administration container/device.

- 20.6 Any sterile compounded drug preparation which was compounded either outside of an ISO class 5 PEC or under conditions that do not meet all of the requirements for any of subdivisions (a) through (e), the sterile

compounded drug preparation is be labeled “for immediate use only” and administration shall begin no later than one hour following the start of the compounding process.

- 20.6.1 Unless the “immediate use” preparation is immediately and completely administered by the person who prepared it or immediate and complete administration is witnessed by the preparer, the preparation 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 compounded sterile preparation, and the exact one-hour beyond use date and time.
- 20.6.2 If administration has not begun within one hour following the start of the compounding process, the compounded sterile preparation shall be promptly, properly, entirely, and safely discarded.
- 20.6.3 “Immediate use” preparations are only compounded in those limited situations where there is a need for immediate administration of a sterile preparation compounded outside of an ISO Class 5 environment and where failure to administer could result in loss of life or intense suffering.
- 20.6.4 Any such compounding shall be only in such quantity as is necessary to meet the immediate need and the circumstance causing the immediate need shall be documented in accordance with policies and procedures. (CCR 1751.8[e])

- 20.7 The beyond use date for any compounded allergen extracts is the earliest manufacturer expiration date of the individual allergen extracts. (CCR 1751.8[f])

CORRECTIVE ACTION OR ACTION PLAN: _____

21. Single-Dose and Multi-Dose Containers; Limitations on Use (CCR 1751.9)

Yes No N/A

- 21.1 Single-dose ampules are for immediate use only, and once opened are not stored for any time period. (CCR 1751.9[a])
- 21.2 Unless otherwise specified by the manufacturer, any single-dose container of a compounded sterile drug preparation other than an ampule, such as a bag, bottle, syringe or vial, is used in its entirety or its remaining contents are be labeled with a beyond use date and discarded within the following time limit, depending on the environment: (CCR 1751.9[b])
 - 12.2.1 When needle-punctured in an environment with air quality worse than ISO Class 5, within one (1) hour.
 - 12.2.2 When needle-punctured in an environment with ISO Class 5 or better air quality, within six (6) hours. A container remains within the ISO Class 5 or better air quality to be used for the full six hours, unless otherwise specified by the manufacturer.
 - 12.2.3 If the puncture time is not noted on the container, the container is immediately discarded.
- 21.3 Unless otherwise specified by the manufacturer, a multi-dose container stored according to the manufacturer’s specifications is used in its entirety or its remaining contents are be labeled with a beyond use date and discarded within twenty eight (28) days from initial opening or puncture. Any multi-dose container not stored according to the manufacturer’s specifications is discarded immediately upon identification of such storage circumstance. If any open container is not labeled with a beyond use date or the beyond use date is not correct, the container is immediately be discarded. (CCR 1751.9[c])

22. Sterile Compounding Reference Materials (CCR 1751.10)

- 22.1 The pharmacy has current and appropriate reference materials regarding the compounding of sterile drug preparations located in or immediately available to the pharmacy. (CCR 1751.10)

23. Sterile Compounding License Renewal (B&PC 4127.1, 4127.2)

A license to compound sterile drug preparation will not be renewed until the following is met: (B&PC 4127.1, 4127.2)

Yes No N/A

- 23.1 The pharmacy has been inspected by the board and is in compliance with applicable laws and regulations.
- 23.2 The board reviews a current copy of the pharmacy's policies and procedures for sterile compounding.
- 23.3 The board is provided with copies of all inspection reports conducted of the pharmacy's premises in the prior 12 months documenting the pharmacy's operation.
- 23.4 The board is provided with copies of any reports from a private accrediting agency conducted in the prior 12 months documenting the pharmacy's operation.
- 23.5 The board receives a list of all sterile medications compounded by the pharmacy since the last license renewal.
- 23.2 A nonresident pharmacy has reimbursed the board for all actual and necessary costs incurred by the board in conducting an inspection of the pharmacy at least once annually. (B&PC 4127.2[c])

CORRECTIVE ACTION OR ACTION PLAN: _____

24. Duties of a Pharmacy Issuing a Sterile Compounded Drug Recall (B&PC 4127.9)

Yes No N/A

- 24.1 The pharmacy contacts the recipient pharmacy, prescriber or patient of the recalled drug and the board as soon as possible within 12 hours of the recall notice if both (1) the use of or exposure to the recalled drug product may cause serious adverse health consequences or death; and (2) the recalled drug was dispensed or is intended for use in California. (B&PC 4127.9[a] B&PC 4127.1 and 4127.2)
- 24.2 A recall notice is made to the patient if the recalled drug was dispensed directly to the patient. (B&PC 4127.9[b][1])

Yes No N/A

- 24.3 A recall notice is made to the prescriber if the recalled drug was dispensed directly to the prescriber. (B&PC 4127.9[b][2])
- 24.4 A recall notice is made to the recipient pharmacy who shall notify the prescriber or patient if the recalled drug was dispensed thereafter. (B&PC 4127.9[b][3])

PHARMACIST-IN-CHARGE CERTIFICATION:

I, (Please print) _____, RPH # _____ hereby certify that I have completed the self-assessment of this pharmacy of which I am the pharmacist-in-charge. Any deficiency identified herein will be corrected. I understand that all responses are subject to verification by the Board of Pharmacy. I further state under penalty of perjury of the laws of the State of California that the information I have provided in this self-assessment form is true and correct.

Signature _____ Date _____
(Pharmacist-in-Charge)

ACKNOWLEDGEMENT BY OWNER OR HOSPITAL ADMINISTRATOR:

I, (please print) _____, hereby certify under penalty of perjury of the laws of the State of California that I have read and reviewed this completed self-assessment. I understand that failure to correct any deficiency identified in this self-assessment could result in the revocation of the pharmacy's license issued by the California State Board of Pharmacy.

Signature _____ Date _____



Attachment 8

Compounding Regulations Q&A for the pending changes to Title 16 CCR 1735 and CCR 1751

Based on the Second Modified text dated November 17, 2015.

Guidance not meant to be a substitute for legal counsel.

1. When referring to a compounding aseptic isolator, what is meant by “not be recirculated nor turbulent” in CCR 1735.1(f) and CCR 1735.1(g)?

Please see CETA: Compounding Isolator Testing Guide document CAG-002-2006 (revised 12/08/08) for a clearer understanding of certification requirements.

2. When referring to a commercially available product, what is “essentially a copy”?

See CCR 1735.1 (k) for definition.

Please note nothing in this section is intended to limit the compounding or reconstitution of commercially available products per the manufacture’s FDA approved prescribing information.

3. What is meant by a “clinically significant difference” between a compounded preparation and the comparable commercially available drug product?

This is to be determined by a prescribing practitioner; please see CCR 1735.1(k)

4. Where is sterile compounding required to be done?

See CCR 1735.6 for Compounding Facilities and Equipment requirements and CCR 1751.4 for Facility and Equipment Standards for Sterile Compounding. The requirements outlined in CCR 1735.6 and CCR 1751.4 must **BOTH** be met when sterile compounding is done.

5. What does “evaluated for sterility” mean in CCR 1735.1(u) with regards to a “media-fill test?”

“Evaluated for sterility” means the growth-based media is, according to the media’s manufacturer guidelines, correctly stored, monitored, and reviewed for the presence of growth or lack thereof.

6. What is meant by “most complex compounding procedures” in CCR 1735.1(u) ?

Please see CCR 1751.7(b) for the full requirements for process validation.

7. Why do the BOP regulations conflict with the FDA's enforcement and guidance of 503A practice under FD&C act, as related to "office use" of compounded drug products?

The BOP is tasked with protecting of the public of California by enforcing the California regulations and statutes. The FDA does not enforce the same set of regulations or statutes as the BOP and there will be occasional conflicts.

8. Under CCR 1735.2(d) why is the BOP preventing hospitals from compounding and requiring them to use commercially available ready for administration sterile products?

See CCR 1735.1 (k) for definition of "essentially a copy." Please note nothing in this section is intended to limit the compounding or reconstitution of commercially available products per the manufactures FDA approved prescribing information.

9. Do the requirements for the assignment of beyond use dates (BUD) apply to both sterile and non-sterile compounds?

See CCR 1735.2(i)(1) for the requirement of assignment of the BUD of a non-sterile compounded drug product. See CCR 1735.2(i)(2) and CCR 1751.8 for the requirement of assignment of the BUD of a sterile compounded drug product.

10. What is meant by "container closure integrity test" under CCR 1735.2(i)(3)(B)?

Please see USP <1207> STERILE PRODUCT PACKAGING—INTEGRITY EVALUATION.

11. What is meant by "stability studies" under CCR 1735.2(i)(3)(C)?

Please see USP <1150> PHARMACEUTICAL STABILITY.

12. Do you really expect a master formula, as defined in CCR 1735.2(e), for all compounded products made for an inpatient in a licensed health care facility?

Yes, a compliant master formula shall be prepared prior to the compounding of any product with the exception as defined in CCR 1735.2(f). Nothing in this regulation is meant to require a paper or printed version of a master formula, as long as the compliant electronic master formula is readily retrievable.

13. Do you really expect the compounding log to be a single document as defined in 1735.3(a)(2)

Yes, the compounding log shall be a single document which may be more than one page. Nothing in this regulation is meant to require a paper or printed version of a compounding log, as long as the compliant electronic compounding log document is readily retrievable.

14. What are the expectations of the BOP with regards to the training of environmental services staff (i.e. EVS)?

As required by CCR 1735.7(a), the EVS or any staff cleaning the compounding area must have the skills and training required to properly and accurately perform their assigned responsibility and there must be documentation demonstrating this training.

15. What is the value to randomly testing one product per year for qualitative and quantitative analysis as required by CCR 1735.8(c)?

The testing of one product per year for qualitative and quantitative analysis, as required by CCR 1735.8(c), is the minimum requirement set forth to validate the internal processes of a facility. The BOP allows discretion by the pharmacist-in-charge in determining if a greater quantity or a more frequent sampling of preparations is more representative of the actual practice setting and, therefore, of more value to the evaluation of the internal processes of a facility.

16. Why are continuous monitoring or recording devices not allowed for air pressure differentials under CCR 1751.1(a)(8) ?

Nothing in this section disallows the use of continuous monitoring or recording devices for the measuring of air pressure differentials. California Code of Regulations 1751.8(a)(8) requires the air pressure differentials to be documented daily but does not state how that document is to be made or kept.

17. Why is the BOP requiring me to stop compounding my lot of drugs to disinfect per 1751.4(e)?

Nothing in the regulations requires the compounder to stop compounding to disinfect.

18. Why is the BOP requiring the use of a sterile agent to disinfect in CCR 1751.4(e)?

The EPA defines disinfection and sterilization to have two distinct meanings. The regulation is requiring disinfection with an agent that is sterile. CCR 1751.4(e) only addresses disinfection.

19. Why is the BOP not allowing my CACI to be used outside an ISO Class 7 environment?

California Code of Regulations 1751.4(f) provides for the use of properly certified isolators outside the ISO Class 7 environment.

20. Can you please tell me what type of make-up is allowed in the clean room under the pending regulations?

California Code of Regulations 1751.5(a)(6) disallows all cosmetics in the ISO Class 5 and ISO Class 7 compounding areas.

21. What training is required for a pharmacist who is overseeing compounding?

California Code of Regulations 1751.6(e) defines the training requirement for all pharmacies which compound sterile drug preparations. The pharmacist's requirements is specifically addressed in CCR 1751.6(e)(2).

22. Who does the CCR 1751.8(e) labeling requirement apply to? How can the BOP require a registered nurse or medical doctor to label an immediate use IV preparation?

Under CCR 1735, compounding is defined as occurring in a licensed pharmacy, by or under the supervision of a licensed pharmacist. The BOP has no jurisdiction over nursing or medical practice. CCR 1751.8(e) is related only to immediate use compounds made by pharmacy staff in a licensed pharmacy.

23. What specific areas do compounders (sterile and non-sterile) need to prepare for once the compounding regulations are finalized/implemented?

There are many areas in the pending regulations which have changes compared to the current regulations. The BOP would suggest each PIC read the pending regulations and complete the new self-assessment and then make the determination as to what the most critical changes are for their practice.

24. What does the BOP plan to do after the new revised USP <797> publishes?

The BOP has plans to readdress our regulations once the USP committee has completed their revisions.

25. Why is the BOP planning to enforce USP <800> before the USP implementation date of mid-2018?

The BOP is tasked with protecting of the public of California by enforcing California regulations and statutes. The BOP does not enforce the minimum practice standards set forth by the USP committee. However, the BOP does understand the cost and time associated with a remodel and/or construction can be significant. Therefore, we have a system in place to allow for facilities to apply for a waiver to allow a defined amount of time to become compliant. See CCR 1735.6(f) for full details.

26. Can our inpatient pharmacy make IV's for our outpatient pharmacy to use for our subacute unit?

Under B&PC 4123 one licensed pharmacy can compound patient specific sterile preparation for a second licensed pharmacy after notification to the BOP. Also, please refer to B&PC 4029, B&PC 4380 and CCR 1710 for the allowance of such activity.

27. Would an inspector expect the walls behind the hood to be cleaned even though hoods are hard to move or cannot be moved due to earthquake brackets?

California Code of Regulations 1751.4(d)(2) specifically addresses the cleaning of the walls within a cleanroom.

28. Why would only a resident pharmacy be required under BPC 4127.9(a)(2) to report a recalled sterile compounded preparation to the BOP within 12 hours. Why is a non-resident pharmacy not held to the same standard?

Under BPC 4127.2(e)(3), all nonresident sterile compounding have the same reporting requirement.

29. Can I use the stability study done by a third party to establish the BUD of my compounded preparation?

See CCR 1735.2(i) for the requirements of assigning a BUD for a compounded drug preparation. Specifically, review CCR 1735.2(i)(2) and (3) for the requirements of extending of a BUD.

30. Does PATT2™ testing (media fill testing for training and competency) need to be done per licensed LSC location?

Per CCR 1751.7(b)(1), the same personnel, procedures, equipment, and materials are part of the process to demonstrate competency on aseptic technique and aseptic area practices.

31. In CCR 1735.1(a) what does “high-particulate-generating activities” mean? Specifically, how does it relate to B&PC 4127.7 and USP <797> requirements for presterilization of non-sterile to sterile compounding?

There is no formal definition of high-particulate-generating activities as this is very dependent on the pharmacy’s specific practice.

There is no specific relationship between high-particulate-generating activities and the requirements of B&PC section 4127.7 and Title 24 CCR section 1250.4(5): both of which require all compounding of non-sterile to sterile injectables to be conducted in one of the following environments: 1) An ISO class 5 laminar airflow hood within an ISO class 7 cleanroom. The cleanroom must have a positive air pressure differential relative to adjacent areas. 2) An ISO class 5 cleanroom. 3) A barrier isolator that provides an ISO class 5 environment for compounding.

The 2014 version of USP <797> states in Appendix 1 that “presterilization procedures for high-risk level CSP, such as weighting and mixing, shall be completed in no worse than an ISO Class 8 environment” again there is no relationship specific requirement.

32. Can a Pharmacy Technician, Registered Nurse (RN), Physician (MD/DO), medical assistant (MA) compound in a medical office?

Compounding is defined in CCR 1735(a) as any of the following activities occurring in a licensed pharmacy, by or under the supervision of a licensed pharmacist, pursuant to a prescription: (1) Altering the dosage form or delivery system of a drug (2) Altering the strength of a drug (3) Combining components or active ingredients (4) Preparing a compounded drug preparation from chemicals or bulk drug substances. There is currently no allowance for compounding outside a licensed pharmacy under the supervision of a licensed pharmacist.

33. When labeling a large volume IV solution do I need to have the exact volume label or does the 10% rule apply. (Example: D5W 1000 ml with 20ml of drug added can it be labeled 1,000mls or must it be labeled 1,020ml?)

All IV solutions need to be labeled compliant with at least CCR 1751.2, CCR 1735.4 and B&PC 4076. Please keep in mind there is overfill in each premade manufactured bag so even if you labeled the example bag from above with 1,020ml it would likely be incorrect unless the bag was compounded into an empty sterile bag.

34. I do not understand the exemption under CCR 1735.3(a)(1)(F)(i). What do I not need to log and under what instances? Please explain.

The exemption is for a single lot (see definitions in 1735.1(t)) which will be administered within 72hrs in an appropriately licensed facility. These products do not require the logging of the manufacturer, expiration date and lot number of each component; however, all other requirements in CCR 1735.3(a) must be documented.

35. How long will we have to get in compliance with the new building requirements for hazardous compounding?

The current draft of the regulation will go into effect 1/1/2017.

36. If the new regulations are going to require monthly (instead of the current weekly) cleaning in compounding area, can we start that practice now?

California Code of Regulations 1751.4(d) requires 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. This will be the active and enforceable regulation until 1/1/17.

37. My hospital pharmacy is in the basement and there are challenges to venting hoods to outside and ceiling air filter/exchanges. What exemptions are available?

There are no exemptions available. If a facility anticipates they will not be compliant with the physical requirements by the effective of 1/1/17, a waiver may be requested to allow additional time for the necessary structural changes to be made (see CCR 1735.6(f)).

38. Is the Board going to adopt USP <800>?

No.

39. If the FDA is inspecting 503B facilities, why does the BOP need to?

The BOP is mandated to protect the public of California and, under BPC 4127.1(c) and 4127.2(c), the BOP cannot issue or review a license to compound sterile drug products until the facility has been inspected and found in compliance with regulations adopted by the BOP.

40. Can you look at the architect's plans and provide comments? Can the BOP?

Neither the BOP's inspectors nor the BOP will review or approve any construction projects.

41. Why do I need to label my hormones as "hazardous" when the manufactured products do not require this type of labeling?

All compounded hazardous drugs as defined by CCR 1735.1(r) need to be labeled compliant with at least CCR 1751.2, CCR 1735.4 and B&PC 4076. You may want to consider reviewing USP <800> for the difference in types of exposure, dosage forms, and the assessment of risk that is required while compiling your facility's list of hazardous drugs.

42. Under CCR 1735.1(l), "daily" is defined as "occurring every day the pharmacy is operating." What happens when the compounding area is not open on a day the retail area of the pharmacy is open?

If the pharmacy is open, then activities requiring daily monitoring or maintenance are required. There are no exemptions for any activity if the compounding area(s) is/are not in use but the pharmacy is open. A refrigerator and freezer need to be monitored at least every 24hrs to ensure they are storing the dangerous drugs at the correct temperature. Please see required policies and procedures under CCR 1735.5(c)(9).

43. What drugs does the BOP require to be treated as "hazardous drugs"?

As defined in CCR 1735.1(r), all anti-neoplastic agents identified by NIOSH as meeting the criteria for a hazardous drug and any other drugs, compounds, or materials identified as hazardous by the pharmacist-in-charge. As also required in USP <800>, each entity or each PIC must create and maintain a list of hazardous drug that the entity handles. The BOP is asking the PIC to determine what drugs and dosage forms are handled or manipulated in their facility and to define and document the selected drugs and dosage forms as "hazardous."

44. Our scales are brand new and have internal calibration. We record performance of the daily calibration by recording our initials on an online form. Is this acceptable under CCR 1735.6(c)?

If the calibration is done prior to use, per manufacturer's specification and the documentation online is retrievable and not alterable for 3 years, there is nothing to prevent this type of calibration.

45. California Code of Regulations 1735.6(e) is conflicting with USP <800> when it comes to the ACPH required for non-sterile compounding. Which do we follow?

Currently, CCR 1735.6(e)(1) requires 30 ACPH for all rooms where hazardous compounding is done regardless if it is sterile compounding or not and 12 ACPH are allowed for segregated compounding area (CCR 1735.1(af)). USP <800> has an allowance for a non-sterile hazardous compounding room (C-SEC) with only 12ACPH. On 1/1/17, the BOP's regulations will go into effect requiring all rooms where hazardous compounding takes place to have 30 ACPH.

46. I was told I have to keep a copy of my master formula, my compounding log and my potency result stapled all together. May these be immediately available? For example, the master formula document is online (e.g. PK Software), the compounding log is filed, and the potency and sterility results are stored online. Is this acceptable?

The current wording in CCR 1735.8(c) states: "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." However, the pending regulations in CCR 1735.8 (c) states: "All qualitative and quantitative analysis reports for compounded drug preparations shall be retained by the pharmacy and maintained along with the compounding log and master formula document." These records must be kept in a readily retrievable form for at least 3 years as required by CCR 1735.3 (d) and CCR 1751.1(c).

47. Why under CCR 1751.1(a)(5) are smoke studies required for all ISO certified spaces?

Smoke studies are required for all ISO certified spaces. This will be updated in the next revision.

48. Under CCR 1751.3(a)(1), what action levels for levels for colony-forming units (CFUs) should the pharmacy be following? Internal levels or USP <797>?

The action level needs to be defined by the PIC and noted in a P&P as well as what plan of action will be taken if they are exceeded.

49. Under CCR 1751.3(a)(15) what is meant by a “sterilization method suitability test?”

There must be documentation to show the method used to sterilize a preparation is capable of repeatable sterilization of said preparation. For example: it would not be acceptable to use an autoclave as the method of sterilization for a drug in oil or it would not be acceptable to use a filter for sterilization without completing and documenting the filter integrity test (bubble test).

50. Under CCR 1751.4 (j), what does “qualified individual” mean? I’ve have purchased a microbial air sampler and have been trained using the video and instructions from the manufacturer. Is it acceptable?

The PIC will need to deem who is qualified and what training is required to ensure all equipment use is stored, used, maintained and cleaned in accordance with the manufacturer’s specification. Training and qualification documents need to be made and retained (CCR 1735.3 (d) and CCR 1751.1(c)) to show the individual is qualified. See CCR 1735.7 and 1751.6 for training requirements.

51. Under CCR 1751.7(c) for the initial three times gloved fingertip sampling what is the expectation?

For initial gloved fingertip sampling: this should be conducted on three separate entries into the clean room just after sterile gloves are donned but before gloves are sprayed with sterile alcohol. Each of the three separate entries **MUST** yield zero CFUs to be considered passing for the individual to be allowed to compound sterile drug preparations.

52. Is it required to have each Biological Safety Cabinet (BSC) and Compounding Aseptic Containment Isolator (CACI) external vented?

Yes, please see CCR 1735.6(e)

53. Is it required to each Biological Safety Cabinet (BSC) and Compounding Aseptic Containment Isolator (CACI) to have a dedicated external vent?

No, see CCR 1735.1(c) and CCR 1735.1(f) where it states this external venting **should** be dedicated to one BSC or CACI.

Acronyms:

ACPH: air changes per hour

B&PC: Business and Professions Code

BOP: The California State Board of Pharmacy

BUD: beyond use date

CCR: California Code of Regulations.

CETA: Controlled Environment Testing Association

CFUs: colony-forming units

CSP: Compounded Sterile Preparations

EPA: Environmental Protection Agency

FD&C act: Food Drug and Cosmetic act

FDA: Food and Drug Administration

NIOSH: National Institute for Occupational Safety and Health

P&P: policy and procedure

PIC: Pharmacist- in-Charge

USP <1150>: United States Pharmacopeia Chapter 1150

USP <1207>: United States Pharmacopeia Chapter 1207

USP <797>: United States Pharmacopeia Chapter 797

USP <800>: United States Pharmacopeia Chapter 800

Attachment 9

Insanitary Conditions at Compounding Facilities

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Sara Rothman (CDER) at 301-796-3110.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Compliance**

**August 2016
Compounding and Related Documents**

Insanitary Conditions at Compounding Facilities

Guidance for Industry

*Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research*

*Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002*

Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353

Email: 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)
Office of Compliance**

**August 2016
Compounding and Related Documents**

Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

- I. INTRODUCTION..... 1**
- II. BACKGROUND 2**
- III. POLICY 3**
 - A. Examples of Insanitary Conditions 3**
 - B. Identifying Insanitary Conditions 6**
 - C. Corrective Actions 7**
 - D. Regulatory Action 8**

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry¹

Insanitary Conditions at Compounding Facilities

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or the Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Under section 501(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act), a drug is deemed to be adulterated “if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health.”² Drug products prepared, packed, or held under insanitary conditions could become contaminated and cause serious adverse events, including death.

Under sections 503A and 503B of the FD&C Act, compounded human drug products can qualify for exemptions from specified provisions of the FD&C Act if certain conditions are met. However, neither section 503A nor section 503B provides an exemption from section 501(a)(2)(A) of the FD&C Act. Drugs prepared, packed, or held (hereinafter referred to as “produced”) under insanitary conditions are deemed to be adulterated, regardless of whether the drugs qualify for exemptions set forth in sections 503A or 503B of the Act.³ Any drug that is produced under insanitary conditions is adulterated under the Act, including compounded human and animal drugs; repackaged drug products; compounded or repackaged radiopharmaceuticals; and mixed, diluted, or repackaged biological products. The policies described in this guidance document specifically address pharmacies, Federal facilities, physicians’ offices (including veterinarians’ offices), and outsourcing facilities that compound or repackage human or animal drugs (including radiopharmaceuticals); or that mix, dilute, or repackage biological products. For purposes of this guidance, we refer to such entities as “compounding facilities.”

¹ This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research, in consultation with the Office of Regulatory Affairs and the Center for Veterinary Medicine at the Food and Drug Administration.

² Insanitary conditions are conditions that could cause a drug to become contaminated with filth or rendered injurious to health; the drug need not be actually contaminated. A drug that is actually contaminated with any filthy, putrid, or decomposed substance is deemed to be adulterated under section 501(a)(1) of the FD&C Act.

Contains Nonbinding Recommendations

Draft — Not for Implementation

36 FDA is issuing this guidance to assist compounding facilities in identifying insanitary conditions
37 so that they can implement appropriate corrective actions. This guidance is also intended to
38 assist State regulatory agencies in understanding some examples of what FDA considers to be
39 insanitary conditions that could cause a drug to become contaminated or rendered injurious to
40 health.

41
42 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
43 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
44 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
45 the word *should* in Agency guidances means that something is suggested or recommended, but
46 not required.

II. BACKGROUND

A. Public Health Risk of Insanitary Conditions

51
52 FDA has investigated numerous outbreaks of infections and deaths found to be the result of drug
53 products that were contaminated because they were produced under insanitary conditions. Most
54 notably, in 2012, injectable drug products produced by a compounding facility and shipped
55 across the country caused a fungal meningitis outbreak that resulted in more than 60 deaths and
56 750 cases of infection. FDA has investigated numerous other serious adverse events, including
57 deaths, associated with contaminated drug products produced by compounding facilities, and it is
58 likely that such adverse events are underreported.

59
60 Since the 2012 fungal meningitis outbreak, FDA has identified insanitary conditions at many of
61 the compounding facilities that it has inspected, and numerous compounding facilities have
62 voluntarily recalled drug products intended to be sterile and temporarily or permanently ceased
63 sterile operations as a result of those findings. However, FDA does not inspect the vast majority
64 of compounding facilities in the United States because they generally do not register with FDA
65 unless they elect to become outsourcing facilities.⁴ Therefore, FDA is often not aware of these
66 facilities and potential problems with their drug products, or conditions and practices, unless it
67 receives a complaint, such as a report of a serious adverse event or visible contamination. It is
68 critical that compounding facilities avoid the presence of insanitary conditions and identify and
69 remediate any insanitary conditions at their facilities before the conditions result in drug
70 contamination and patient injury.

71
72 In addition, to protect the public health, it is critical that both FDA and State regulatory agencies
73 take appropriate action when compounders produce drugs under insanitary conditions. Based on
74 its inspections, FDA determines whether compounding facilities produce drugs under insanitary
75 conditions in violation of section 501(a)(2)(A) of the FD&C Act, and if so, the Agency may
76 initiate regulatory action. However, compounding facilities that are not registered with FDA as
77 outsourcing facilities are primarily overseen by the States and, as explained above, generally are
78 not routinely inspected by FDA. Therefore, FDA encourages State regulatory agencies to assess
79 during inspections whether compounding facilities that they oversee engage in poor practices,

⁴ See section 503B of the FD&C Act.

Contains Nonbinding Recommendations

Draft — Not for Implementation

80 including those described below, and if so, to take action, as appropriate, consistent with State
81 laws and regulations, and to contact FDA.

82

III. POLICY

84

85 Section III.A of this guidance describes examples of conditions that would be considered
86 insanitary conditions under section 501(a)(2)(A) of the FD&C Act. FDA has observed each of
87 these conditions in one or more of the compounding facilities it has inspected. **These are only**
88 **examples and are not an exhaustive list. Other conditions not described in this guidance**
89 **may be considered insanitary.**

90

91 Section III.B of this guidance describes procedures that compounding facilities should employ to
92 ensure that they do not have insanitary conditions and that they are capable of producing sterile
93 drug products, and section III.C describes actions that compounding facilities should take if they
94 identify insanitary conditions at their facilities. Finally, section III.D of this guidance describes
95 potential FDA regulatory actions if insanitary conditions are not adequately corrected.

96

97 FDA intends to consider the entire set of conditions at the facility, including whether the facility
98 engages in the procedures described in section III.B, when prioritizing regulatory action against a
99 compounding facility for producing drugs under insanitary conditions.

100

A. Examples of Insanitary Conditions⁵

102

1. Insanitary Conditions Applicable to the Production of Sterile and/or Non-Sterile 103 Drugs

104

105

106 Although maintaining sterility is not a requirement for non-sterile drugs, non-sterile drugs can
107 become contaminated with microorganisms of a type or at a level that can cause patient harm.
108 Non-sterile aqueous solutions are particularly susceptible to microbial growth if contaminated.
109 Contamination may also include non-viable filth and the presence of unintended drug
110 components. The following are examples of insanitary conditions that are applicable to both
111 sterile and non-sterile drug production.

112

- 113 • Vermin (e.g., insects, rodents) observed in production areas or areas immediately
114 adjacent to production.
- 115 • Visible microbial contamination (e.g., bacteria, mold) in the production area.
- 116 • Non-microbial contamination in the production area (e.g., rust, glass shavings, hairs).
- 117 • Handling beta-lactam, hazardous, or highly potent drugs (e.g., hormones) without
118 providing adequate containment, segregation, and cleaning of work surfaces, utensils, and
119 personnel to prevent cross-contamination.
- 120 • Production of drugs while construction is underway in an adjacent area without adequate
121 controls to prevent contamination of the production environment and product.

⁵ For definitions of some of the terms used in this section, refer to United States Pharmacopeia (USP) Chapter <797>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162

2. Insanitary Conditions in a Sterile Operation

a. Aseptic Practices

- Putting on gowning apparel improperly, in a way that may cause the gowning apparel to become contaminated. This includes, for example, gowning in non-classified areas, gowning apparel touching the floor, or putting on sterile gloves improperly (e.g., touching the outside of a glove with bare hands).
- Failing to disinfect or change gloves frequently enough given the nature of the operations to prevent contamination.
- Engaging in aseptic processing wearing non-sterile gloves. This could contaminate the critical area.⁶
- Engaging in aseptic manipulations with exposed hands, wrists, legs, hair, or mouth, for example.
- Performing aseptic manipulations outside of an International Organization for Standardization Class 5 (ISO 5) area.
- Exposing unprotected sterile product, including stock solutions, to lower than ISO 5 quality air (e.g., removing it from the ISO 5 area without a robust and intact container closure system).
- Engaging in aseptic processing after leaving the cleanroom and re-entering from a non-classified area without first replacing gowning apparel (e.g., sterile gloves, gowns, mask, foot covers). Movement of personnel in and out of the cleanroom without regowning may bring contaminants from the non-classified areas into the cleanroom.
- Moving quickly in the vicinity of open containers or instruments (e.g., needles). While conducting aseptic manipulations, ISO 5 airflow must be unidirectional to protect the product from contaminating particles. Quick movement of personnel disrupts the airflow and increases the risk of bringing lesser quality air into the ISO 5 area.
- Conducting aseptic manipulations or placing equipment/supplies in an area that blocks the movement of first pass air around an open container, whether before or after it is filled with sterile product. If unidirectional air over the critical surface is blocked, the area is no longer protected. If it is blocked by personnel conducting aseptic manipulations, contamination on personnel, particularly on exposed skin, could be introduced to the critical area.
- Using a non-sterile tool or manually contacting the inner surface of the container or closure. For example, during manual stoppering (e.g., hand stoppering), personnel touching the top of open containers, or the lower side or bottom of closures. This could contaminate the drug in the vials.
- Touching equipment or other surfaces (e.g., walls, telephone, floors) located outside of the ISO 5 area with gloved hands and then proceeding with aseptic manipulations without changing or sanitizing gloves.

⁶ A *critical area* is an area designed to maintain sterility of sterilized materials. Sterilized product, containers or closures, and equipment may be exposed in critical areas. The ISO 5 area is the critical area, and the terms are used interchangeably throughout this guidance.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 163
- 164
- 165
- 166
- 167
- 168
- 169
- 170
- 171
- 172
- 173
- 174
- 175
- 176
- 177
- 178
- 179
- 180
- 181
- 182
- 183
- 184
- 185
- 186
- 187
- 188
- 189
- 190
- 191
- 192
- 193
- 194
- 195
- 196
- 197
- 198
- 199
- 200
- 201
- 202
- 203
- 204
- 205
- 206
- 207
- Storing open sterile vials within the critical area without protective cover longer than needed for the process of filling drug product. The longer a vial is open to the environment, the greater the risk of contamination.
 - Failure to disinfect container closure systems of sterile drug components immediately prior to opening for use.
- b. Equipment/ Facilities
- Actionable microbial contamination of the ISO 5 area or in adjacent areas.
 - Cleanroom with unsealed, loose ceiling tiles.
 - ISO classified areas with difficult to clean (e.g., porous), particle-generating, or visibly dirty (e.g., rusty) equipment or surfaces such as shelving, floors, walls, doors, window sills, and ceilings. For example, wood is both difficult to clean and particle-generating.
 - Classified areas and segregated production areas surrounding the ISO 5 area that contain dust-collecting overhangs (e.g., utility pipes or ledges, such as windowsills).
 - ISO 5 area open to the surrounding cleanroom with minimal or no physical barriers separating it from non-aseptic activities (e.g., non-aseptic weighing materials, gowning, container labeling).
 - ISO 5 area open to non-classified rooms (segregated production area). Lower quality air from the surrounding room entering the ISO 5 area increases the risk of introducing microbial contamination into drug products being manipulated.
 - A facility designed and/or operated in a way that permits poor flow of personnel or materials, or allows the influx of poor quality air into a higher classified area. Examples include:
 - materials flow into the ISO 7 area directly from an unclassified area;
 - air return located next to the high efficiency particulate arrestance (HEPA) filter rather than near the floor;
 - an air vent between classified and unclassified areas;
 - a door opened between the unclassified area and the ISO 8 anteroom while the door between the ISO 7 and ISO 8 areas is also open;
 - inadequate pressure differentials between areas of higher quality air and lower quality air.
 - A lack of HEPA-filtered air, or inadequate HEPA filter coverage or airflow, over the area to which sterile product is exposed.
 - HEPA filters that are not sealed around each perimeter to the support frame. The air entering the cleanroom must be HEPA filtered to remove airborne particles. If HEPA filters are not sealed, air that is not HEPA filtered could enter the cleanroom.
 - The presence of sinks or drains in the cleanroom where the ISO 5 area is located. Sinks and drains are sources of microbial contamination.
 - Use of non-sterilized or non-depyrogenated equipment (e.g., transfer tubing, temporary bulk containers). Use of such equipment can introduce or increase bioburden and endotoxins.
 - Use of non-sterilized or non-depyrogenated final containers/closures. Use of such container/closures could contaminate the drug product after it has been sterilized.

Contains Nonbinding Recommendations

Draft — Not for Implementation

c. Sterilization

- The “sterilizing filter” is not adequate to accomplish sterilization and is not pharmaceutical grade.
- Temperature and time conditions used for heat sterilization are not lethal to heat-resistant microorganisms.

d. Cleaning and Disinfecting

- Non-sterile disinfecting agents and cleaning pads or wipes are used in the aseptic processing areas, especially the ISO 5 area. Non-sterile cleaning and disinfecting items could spread microbial spores.
- No, improper, or infrequent, use of a sporicidal agent in the facility’s cleanrooms and ISO 5 area.
- No disinfection of equipment and/or supplies entering the aseptic processing areas. Disinfection should occur at each transition from areas of lower quality air to areas of higher quality (e.g., from non-classified to first classified room, from anteroom to buffer room, from buffer room to ISO 5 area).
- Disinfectant contact time (also known as “dwell time”) and coverage of the item being disinfected are insufficient to achieve adequate levels of disinfection. The use, including contact time, of commercially-obtained disinfectants should follow the manufacturer’s instructions.

B. Identifying Insanitary Conditions

Certain procedures are critical to ensuring that compounding facilities do not have insanitary conditions that could compromise drug sterility and that they are capable of producing sterile drug products. FDA recommends that compounding facilities that produce drugs that are intended to be sterile routinely employ these procedures to help ensure that they can produce sterile products. A non-exhaustive list of such procedures follows.

1. Conduct routine⁷ environmental monitoring, including a) nonviable airborne particulate sampling; b) viable airborne particulate sampling; c) personnel sampling (including glove fingertip sampling); and d) surface sampling, including but not limited to equipment, work surfaces, and room surfaces. Environmental monitoring provides information on the quality of the aseptic processing environment and, if problematic, the compounding

⁷ For compounding facilities that are not registered with FDA as outsourcing facilities, see USP Chapter <797>. For outsourcing facilities, see FDA’s draft guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (“interim CGMP draft guidance”). Once final, this guidance will represent FDA’s current thinking regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until FDA promulgates CGMP regulations that are more specific to outsourcing facilities.

This interim CGMP draft guidance states that outsourcing facilities should conduct environmental monitoring of the ISO 5 area at least daily. FDA recommends that compounding facilities that are not registered as outsourcing facilities also conduct daily environmental monitoring during operations.

Contains Nonbinding Recommendations

Draft — Not for Implementation

244 facility should promptly identify potential routes of contamination and perform corrective
245 actions.

- 246
- 247 2. Certify the ISO 5 area every six months. If the ISO 5 area is not certified every six
248 months or does not pass all certification requirements, there is no assurance that the ISO
249 5 area is working properly (e.g., generating unidirectional ISO 5 airflow). Smoke studies
250 should be conducted as part of the certification to assess the airflow patterns necessary to
251 maintain unidirectional flow from areas of higher air quality (e.g., ISO 5) to areas of
252 lower air quality (e.g., ISO 7) to prevent microbial contamination of the sterile drug
253 products during processing. Conducting smoke studies under dynamic conditions helps
254 to ensure that unidirectional airflow is maintained while personnel are working in the ISO
255 5 area.
- 256
- 257 3. Measure pressure differentials during operations to help ensure proper airflow (i.e., from
258 areas of higher quality air to adjacent areas with lower quality air).
- 259
- 260 4. Conduct media fill studies to closely simulate aseptic production operations incorporating, as
261 appropriate, worst-case activities and conditions that provide a challenge to aseptic
262 operations.
- 263

C. Corrective Actions

264
265
266 A compounding facility should immediately assess the impact of insanitary conditions on drug
267 products produced, which should include an evaluation of how widespread the insanitary
268 conditions are and over what period of time the conditions existed.

269
270 The compounding facility also should determine whether to cease production of drug products
271 until the conditions have been corrected and initiate a recall of all potentially affected lots on the
272 market.

273
274 For example, FDA considers the following insanitary conditions to be particularly serious, and if
275 any one of these conditions exists, FDA strongly recommends that a compounding facility
276 immediately initiate a recall of purportedly sterile drugs and cease sterile operations until the
277 condition(s) have been corrected:

- 278
- 279 • Vermin (e.g., insects, rodents) observed in ISO 5 areas or in immediately adjacent
280 areas.
 - 281 • Visible microbial contamination (e.g., bacteria, mold) in the ISO 5 area or in
282 immediately adjacent areas.
 - 283 • Non-microbial contamination in the ISO 5 area (e.g., rust, glass shavings, hairs).
 - 284 • Performing aseptic manipulations outside of the ISO 5 area.
 - 285 • Exposing unprotected sterile product, including stock solutions, to lower than ISO 5
286 quality air (e.g., removing it from the ISO 5 area without a robust and intact container
287 closure system).
 - 288 • Cleanroom areas with unsealed, loose ceiling tiles.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 289 • Production of drugs while construction is underway in an adjacent area without
290 adequate controls to prevent contamination of the production environment and
291 product.
- 292 • Consistent and frequent pressure reversals from areas of less clean air to areas of
293 higher cleanliness.
- 294 • The “sterilizing filter” is not adequate to accomplish sterilization and is not
295 pharmaceutical grade.
- 296 • Temperature and time conditions used for heat sterilization are not lethal to heat-
297 resistant microorganisms.

298
299 If a compounding facility decides to initiate a recall, it should notify its local FDA District recall
300 coordinator as soon as the decision to recall is made.⁸ The compounding facility should also
301 notify the applicable State regulatory body in the State(s) to which the facility ships drugs,
302 consistent with State laws and guidance.

303
304 In addition to the immediate actions recommended above, if a compounding facility has
305 insanitary conditions, it should undertake a comprehensive assessment of its operations,
306 including, as applicable, facility design, procedures, personnel, processes, materials, and
307 systems, and should consider consulting a third party with relevant drug production expertise to
308 conduct this comprehensive evaluation and to assist in implementing appropriate corrective
309 actions.

310
311 Compounding facilities producing purportedly sterile drug products under insanitary conditions
312 should not rely on a passing sterility test as an indication of sterility assurance because microbial
313 contamination, when present, is not uniformly distributed within a batch and may not be
314 identified by a sterility test. Furthermore, compounding facilities must correct all insanitary
315 conditions at their facility,⁹ regardless of whether the drugs pass a sterility test.¹⁰

D. Regulatory Action

316
317
318
319 If a compounding facility produces drugs under insanitary conditions, the facility and responsible
320 individuals may be subject to Federal regulatory actions including, but not limited to, a warning
321 letter, seizure of product, and/or injunction. FDA may also recommend that the facility initiate a
322 recall of some or all of its drugs and cease operations until the insanitary conditions have been
323 adequately addressed. In addition, the applicable State regulatory agency may pursue regulatory
324 action against the facility under applicable State authorities.

⁸ See the FDA guidance, *Product Recalls, Including Removals and Corrections*.

⁹ See section 501(a)(2)(A) of the FD&C Act.

¹⁰ USP Chapter <71> concerning sterility testing states, “these Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by validation of the sterilization process or of the aseptic processing procedures.”

Attachment 10

Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Sara Rothman (CDER) at 301-796-3110.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Compliance/OU DLC**

**July 2016
Compounding and Related Documents**

Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

Additional copies are available from:

Office of Communications

Division of Drug Information, WO51, Room 2201

Center for Drug Evaluation and Research

Food and Drug Administration

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)
Office of Compliance/OU DLC**

July 2016

Compounding and Related Documents

Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

I.	INTRODUCTION AND SCOPE	1
II.	BACKGROUND	2
A.	Section 503B of the FD&C Act	2
B.	Compounding, Generally	3
C.	Compounded Drugs that are Essentially Copies of Approved Drug Products	3
D.	Compounded Drugs that are Essentially Copies of Unapproved Non-Prescription Drug Products.....	4
III.	POLICY	4
A.	Definition of <i>Essentially a Copy of an Approved Drug</i>	4
B.	Recordkeeping.....	12
	APPENDICES A & B	13

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry¹

**Compounded Drug Products That Are Essentially Copies of
Approved Drug Products Under Section 503B of the Federal Food,
Drug, and Cosmetic Act**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or the Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed in the title page.

I. INTRODUCTION AND SCOPE

For a drug product compounded by an outsourcing facility to qualify for the exemptions under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act), it must not be “essentially a copy of one or more approved drug products,”² and must meet the other conditions in section 503B.³ This guidance sets forth the FDA’s or policies concerning the *essentially a copy* provision of section 503B.⁴

In general, FDA’s guidance documents 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.

¹ This guidance was prepared by multiple offices in the Center for Drug Evaluation and Research, in consultation with the Office of Regulatory Affairs at the Food and Drug Administration.

² See section 503B(a)(5).

³ See section 503B(a)(11).

⁴ This guidance does not apply to drugs compounded for use in animals, to biological products subject to licensure in a biologics license application, or to repackaged drug products. For proposed policies pertaining to compounding drug products from bulk drug substances for use in animals, see FDA’s draft guidance *Compounding Animal Drugs from Bulk Drug Substances*. For proposed policies pertaining to mixing, diluting, and repackaging biological products, see FDA’s draft guidance *Mixing, Diluting, and Repackaging Biological Products Outside the Scope of an Approved Biologics License Application*. For proposed policies pertaining to repackaged drug products, see FDA’s draft guidance *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities*.

All FDA guidances are available on the FDA guidance web page. FDA updates guidances regularly. To make sure you have the most recent version of a guidance, always consult the guidance web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

II. BACKGROUND

A. Section 503B of the FD&C Act

In 2013, the Drug Quality and Security Act created a new section 503B of the FD&C Act, which describes a new category of compounders called *outsourcing facilities*.⁵ Section 503B of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility to qualify for exemptions from the following three sections of the FD&C Act:

- Section 502(f)(1) (concerning the labeling of drugs with adequate directions for use)
- Section 505 (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs))
- Section 582 (concerning drug supply chain security requirements).

In contrast to drug products compounded under section 503A of the FD&C Act, drug products compounded by outsourcing facilities under section 503B cannot qualify for exemption from current good manufacturing practice (CGMP) requirements in section 501(a)(2)(B) of the FD&C Act. Outsourcing facilities are also subject to FDA inspections according to a risk-based schedule, specific adverse event reporting requirements, and other conditions that help to mitigate the risks of the drug products they compound.

One of the conditions that must be met for a compounded drug product to qualify for the exemptions under section 503B of the FD&C Act is that “the drug is not essentially a copy of one or more approved drugs.”⁶ Section 503B(d)(2) defines *essentially a copy of an approved drug* as —

- A drug that is identical or nearly identical to an approved drug, or a marketed drug not subject to section 503(b) and not subject to approval in an application submitted under section 505, unless, in the case of an approved drug, the drug appears on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing (section 503B(d)(2)(A)); or
- A drug, a component of which is a bulk drug substance that is a component of an approved drug or a marketed drug that is not subject to section 503(b) and is not subject to approval in an application submitted under section 505, unless there is a change that produces for an individual patient a clinical difference, as determined

⁵ See Pub.L. No.113-54, §102(a), 127 Stat. 587, 587-588 (2013). Under section 503B(b), a compounder can elect to register with FDA as an outsourcing facility. Section 503B(d)(4) defines an *outsourcing facility* as a facility at one geographic location or address that is engaged in the compounding of sterile drugs; has elected to register as an outsourcing facility; and complies with all of the requirements of section 503B. An outsourcing facility is not required to be a licensed pharmacy, although compounding must be by or under the direct supervision of a licensed pharmacist. In addition, an outsourcing facility may or may not obtain prescriptions for identified individual patients.

⁶ See section 503B(a)(5).

Contains Nonbinding Recommendations

Draft — Not for Implementation

66 by the prescribing practitioner, between the compounded drug and the comparable
67 approved drug (section 503B(d)(2)(B)).
68

69 A compounded drug product only qualifies for the exemptions in section 503B if it is
70 compounded by an outsourcing facility that compounds all of its drugs, both sterile and non-
71 sterile, in accordance with all of the conditions of section 503B.⁷ A complete list of the
72 conditions that must be met for a drug product to qualify for the exemptions in section 503B
73 appears in the guidance *For Entities Considering Whether to Register As Outsourcing Facilities*
74 *Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.
75

B. Compounding, Generally

76
77
78 Compounded drug products serve an important role for patients whose clinical needs cannot be
79 met by an FDA-approved drug product such as for a patient who has an allergy and needs a
80 medication to be made without a certain dye contained in an FDA-approved drug product, or an
81 elderly patient or a child who cannot swallow a pill and needs a medicine in a liquid form that is
82 not available in an approved product. Drug products for identified individual patients can be
83 compounded by licensed pharmacists in State-licensed pharmacies and Federal facilities and by
84 licensed physicians operating under section 503A of the FD&C Act.⁸ Drug products can also be
85 compounded by outsourcing facilities for identified individual patients pursuant to prescriptions
86 or for distribution to health care practitioners without receiving prescriptions. Sections 503A and
87 503B restrict compounding drug products that are essentially copies of commercially available
88 (section 503A) or approved drug products (section 503B).
89

C. Compounded Drugs that are Essentially Copies of Approved Drug Products

90
91
92 Although compounded drugs can serve an important need, they also pose a higher risk to patients
93 than FDA-approved drugs. Drug products compounded by outsourcing facilities in accordance
94 with the conditions of section 503B are exempt from FDA drug approval requirements and the
95 requirement to be labeled with adequate directions for use. Because they are not FDA-approved,
96 they have not undergone FDA premarket review for safety, effectiveness, and quality. Although
97 outsourcing facilities must comply with CGMP requirements and are inspected by FDA
98 according to a risk-based schedule, their drugs also lack a premarket inspection and finding of
99 manufacturing quality that is part of the drug approval process. Because they are subject to a
100 lower regulatory standard, drugs compounded by outsourcing facilities should only be distributed
101 to health care facilities or dispensed to patients to fulfill the needs of patients whose medical
102 needs cannot be met by an FDA-approved drug.
103

⁷ See sections 503B(a)(11) and 503B(d)(4)(A)(iii).

⁸ Section 503A of the FD&C Act describes the conditions that must be met for a human drug product compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to qualify for exemptions from sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act. The conditions applicable to compounders seeking to operate under section 503A are discussed in separate guidance documents applicable to these entities.

Contains Nonbinding Recommendations

Draft — Not for Implementation

104 The restrictions on compounding drugs that are essentially copies of approved products ensure
105 that outsourcing facilities do not compound drug products under the exemptions in section 503B
106 for use in patients who could use an approved product. Compounding copies of these products
107 would unnecessarily expose patients to drug products that have not been shown to be safe and
108 effective.

109
110 In addition to these immediate public health risks, section 503B’s prohibition on producing a
111 drug product that is essentially a copy of an approved drug product protects the integrity and
112 effectiveness of the new drug and abbreviated new drug approval processes. Sponsors would be
113 less likely to invest in and seek approval of innovative, life-saving medications if an outsourcing
114 facility could, after a drug is approved, compound “substitutes” that may be less expensive
115 because they have not gone through the drug approval process.

116
117 Sponsors would also be less likely to seek approval of an ANDA for a generic drug if
118 outsourcing facilities were permitted to compound drugs that are essentially copies of approved
119 drugs without going through the ANDA process. An ANDA must include data to demonstrate
120 that the drug has the same active ingredient and is bioequivalent to an approved drug. FDA also
121 conducts a premarketing inspection of proposed manufacturing facilities before approving the
122 application. Section 503B’s restrictions on producing a drug product that is essentially a copy of
123 an approved drug product protect the integrity of both the new drug and the abbreviated new
124 drug approval processes.

125

D. Compounded Drugs that are Essentially Copies of Unapproved Non-Prescription Drug Products

126

127

128

129 The definition of *essentially a copy of an approved drug* in section 503B(d)(2) also refers to drug
130 products that are not subject to section 503(b) (i.e., non-prescription drug products) and that are
131 not subject to approval in an application submitted under section 505. Congress did not provide
132 exemptions under section 503B for such drugs, which ensures that outsourcing facilities do not
133 compound unapproved over-the-counter drug products under the exemptions in section 503B.
134 Such products may be produced only under the same requirements that apply to other drug
135 manufacturers. Section 503B also protects FDA’s drug monograph process. FDA has an
136 ongoing process to evaluate the safety and effectiveness of over-the-counter (OTC) medications,
137 and if the Agency determines that an OTC drug meeting certain conditions is generally
138 recognized as safe and effective, it will publish a final monograph specifying those conditions.
139 Compounding copies of such drug products would undermine the process that drug
140 manufacturers must comply with, which includes a set of specific regulatory requirements that
141 limit the formulation of the drug product, and both the content and format of its labeling.

142

III. POLICY

143

144

145 Under section 503B(a)(5) of the FD&C Act, a compounded drug must not be essentially a copy
146 of one or more approved drugs.

147

A. Definition of *Essentially a Copy of an Approved Drug*

148

149

Contains Nonbinding Recommendations

Draft — Not for Implementation

150 The definition of *essentially a copy of an approved drug* has two components, specified in
151 sections 503B (d)(2)(A) and 503B(d)(2)(B) of the Act. Section 503B (d)(2)(A) applies to a
152 compounded drug that is “identical or nearly identical” to an approved drug or an unapproved
153 non-prescription drug. All other compounded drugs are evaluated under section 503B (d)(2)(B).
154 FDA applies these provisions as depicted in the diagrams in Appendices A and B.

155
156 The definition of *essentially a copy of an approved drug* in section 503B(d)(2) addresses both
157 drug products approved under section 505 and marketed drug products that are not subject to
158 section 503(b) and that are not subject to approval in an application submitted under section 505.

159
160 For purposes of this provision:

- 161
- 162 • *Approved drug* means a drug product that is approved under section 505 of the FD&C
163 Act and does not appear on the list described in subsection 503B(a)(4) of drugs that have
164 been withdrawn or removed from the market because such drugs or components of such
165 drugs have been found to be unsafe or not effective.
 - 166 • *Marketed drug not subject to section 503(b) and not subject to approval in an application*
167 *submitted under section 505* means any non-prescription drug product marketed without
168 an approved application.⁹ We refer to these products as *covered OTC drug products*
169 throughout the remainder of this guidance document.
 - 170 • A drug appears on the drug shortage list in effect under section 506E if the drug is in
171 “currently in shortage” status (and not in “resolved” status), as indicated in FDA’s drug
172 shortage database.¹⁰

173
174 In the discussion that follows, in subsection 1, we explain how we intend to apply the definition
175 of *essentially a copy of an approved drug* in section 503B(d)(2) when the compounded drug is
176 compared to an approved drug, and then in subsection 2, we explain how we intend to apply this
177 definition when the compounded drug is compared to a covered OTC drug product.

- 178
- 179 1. *Application of the “Essentially a Copy” Definition in Section 503B(d)(2) When the*
180 *Compounded Drug Is Compared to an Approved Drug (see Appendix A)*
 - 181 a. Compounded drugs that are identical or nearly identical to an approved drug (section
182 503B(d)(2)(A))

183
184
185 Under section 503B(d)(2)(A), a compounded drug is essentially a copy of an approved
186 drug if the compounded drug is identical or nearly identical to an approved drug unless
187 the approved drug appears on the drug shortage list in effect under section 506E at the
188 time of compounding, distribution, and dispensing.

189

⁹ This includes unapproved OTC drugs whether they are marketed under FDA’s OTC Drug Monograph Review program or outside the monograph system.

¹⁰ See <http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

190 i. Identical or nearly identical (Appendix A, box 1)

191
192 FDA intends to consider a compounded drug product to be identical or nearly identical to
193 an approved drug if the compounded drug product and the FDA-approved drug have the
194 same:

- 195 • active ingredient(s),
- 196 • route of administration,
- 197 • dosage form,
- 198 • dosage strength, and
- 199 • excipients.¹¹

200
201 A compounded drug product that has all of these characteristics in common with an
202 FDA-approved drug product is essentially a copy of an approved drug, unless the
203 approved drug appears on FDA's drug shortage list at the time of compounding,
204 distribution, and dispensing. If a compounded drug product is identical or nearly
205 identical to an approved drug that is *not* on FDA's drug shortage list at the time of
206 compounding, distribution, and dispensing, the compounded product is essentially a copy
207 and an outsourcing facility may not produce it under section 503B.

208
209 In establishing this policy, FDA considered the following. Under section 503B(d)(2)(A),
210 the identical or nearly identical compounded product cannot be exempted from the
211 copying restriction by a prescriber determination that there is a change to the
212 compounded product that produces a clinical difference for an individual patient.
213 Compounded products meeting the criteria outlined above are not expected to contain
214 changes from an approved drug that would produce such a difference.

215
216 A compounded drug that is identical or nearly identical to an approved drug is not
217 considered essentially a copy if the approved drug is in shortage at the time of
218 compounding, distribution, and dispensing.¹² In such a case, the outsourcing facility can
219 compound the drug provided that it complies with the other conditions of 503B. It is
220 important to patients and prescribers that compounded drugs prepared to address a
221 shortage closely resemble the drug in shortage, and for that reason, the statute seeks to
222 allow compounders to compound drugs that are as close as possible to the drug in
223 shortage.¹³ A compounded drug product with the characteristics described in our policy
224 would be the same as the approved drug in several important respects. The active
225 ingredient is the substance in a drug product that is intended to furnish pharmacological

¹¹ In some cases, information about the excipients contained in an approved drug is not publicly available and not known to the outsourcing facility. In such cases, FDA does not intend to consider whether the compounded drug has the same excipients that the approved drug is labeled to contain in determining whether a compounded drug is identical or nearly identical to an approved drug.

¹² *Distribution* means that a compounded human drug product has left the facility in which the drug was compounded. Distribution includes delivery or shipment to a physician's office, hospital, or other health care setting for administration and dispensing to an agent of a patient or to a patient for the patient's own use.

¹³ See footnote 11.

Contains Nonbinding Recommendations

Draft — Not for Implementation

226 activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention
227 of disease or to affect the structure or function of the body. Dosage form is the way of
228 identifying the drug in its physical form, and route of administration describes the way a
229 drug is administered to the body. Inactive ingredients (also known as “excipients”) may
230 include preservatives, dyes, and flavorings. The dosage strength of a drug product
231 indicates the amount of the active ingredient that is present in each dosage.
232

233 If the outsourcing facility compounds a product that differs on one or more of these
234 characteristics, we generally would not consider the product to be identical or nearly
235 identical. As described below, if the compounded drug product is not considered
236 identical or nearly identical under section 503B(d)(2)(A), it would then be evaluated
237 under section 503B(d)(2)(B).
238

239 Outsourcing facilities seeking to compound drugs under this provision should also take
240 note that other provisions of the FD&C Act contain requirements for drug product
241 formulation and packaging that are important for patient safety. In particular, drug
242 products compounded in accordance with section 503B remain subject to adulteration
243 and misbranding provisions of the FD&C Act including, but not limited to, section
244 501(b) (concerning drug products that are recognized in an official compendium and
245 whose strength differs from, or whose quality or purity falls below, the standards set forth
246 in such compendium) and section 502(g) (concerning drug products that are recognized
247 in an official compendium and that are not packaged and labeled as prescribed therein).
248

249 ii. Compounded drugs that are identical or nearly identical to an approved
250 drug on FDA’s drug shortage list after the shortage is resolved (Appendix
251 A, box 2)
252

253 As explained above, under section 503B (d)(2)(A), a compounded drug is not essentially
254 a copy of an approved drug if the approved drug appears on FDA’s drug shortage list at
255 the time of compounding, distribution, and dispensing. However, FDA recognizes that
256 there may be circumstances in which a drug product is in shortage when the outsourcing
257 facility compounds the drug, but the shortage is resolved before the outsourcing facility
258 distributes it. FDA does not intend to take action against an outsourcing facility for
259 filling orders that it received for a compounded drug that is identical or nearly identical to
260 an approved drug that was on FDA’s drug shortage list at the time that the outsourcing
261 facility received the order, provided the drug also appeared on the FDA drug shortage list
262 within 60 days of the outsourcing facility distributing or dispensing the drug.¹⁴

¹⁴ An outsourcing facility may not be able to predict when a drug shortage will be resolved, and the facility may have orders for a compounded drug in-house that were in progress when the drug was removed from FDA’s drug shortage list (e.g., the outsourcing facility may have compounded a drug while it was in shortage, but the shortage ended while the outsourcing facility awaited the results of sterility testing before release). This policy provides some regulatory flexibility when an outsourcing facility fills orders that it received for a compounded drug while the drug was in shortage. FDA may take regulatory action, however, if an outsourcing facility continues to fill new orders for the compounded drug after the approved drug is removed from FDA’s drug shortage list, or if it continues to fill orders more than 60 days after the drug has been removed from FDA’s drug shortage list.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 263
264 b. Compounded drugs that contain a bulk drug substance that is a component of an
265 approved drug (see Appendix A, boxes 3 and 4)
266

267 Under section 503B(d)(2)(B), a compounded drug product is essentially a copy of an
268 approved drug if a component of the compounded drug product is a bulk drug substance¹⁵
269 that is also a component of an approved drug, unless there is a change that produces for
270 an individual patient a clinical difference, as determined by the prescribing practitioner,
271 between the compounded drug and the comparable approved drug.
272

- 273 i. Using the same bulk drug substance (Appendix A, box 3)
274

275 If a component of the compounded drug is a bulk drug substance that is also a component
276 of an approved drug, the compounded drug product is essentially a copy of an approved
277 drug and cannot be compounded under section 503B, unless there is a prescriber
278 determination of clinical difference, as described below.¹⁶ This provision applies to a
279 compounded drug whether it was compounded from bulk drug substances or from drugs
280 in finished form.
281

- 282 ii. Prescriber determination of clinical difference (Appendix A, box 4)
283

284 If an outsourcing facility compounds a drug, the component of which is a bulk drug
285 substance that is a component of an approved drug, there must be a change that produces
286 a clinical difference for an individual patient as determined by the prescribing
287 practitioner. If an outsourcing facility intends to rely on such a determination to establish
288 that a compounded drug is not essentially a copy of an approved drug, the outsourcing
289 facility should ensure that the determination is on the prescription or order (which may be
290 a patient-specific prescription or a non-patient specific order) for the compounded drug.
291

292 FDA is aware that a health care practitioner who orders a compounded drug from an
293 outsourcing facility for office stock will not know the identity of the individual patients
294 who will receive the compounded drug at the time of the order. In that case, the
295 outsourcing facility should obtain a statement from the practitioner that specifies the
296 change between the compounded drug and the comparable approved drug and indicates
297 that the compounded drug will be administered or dispensed only to a patient for whom
298 the change produces a clinical difference, as determined by the prescribing practitioner
299 for that patient. Such assurances should be provided by a person able to make the
300 representation for the health care practitioner.

¹⁵ Title 21, section 207.3(4) of the Code of Federal Regulations defines the term *bulk drug substance* to mean “any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.”

¹⁶ FDA expects that if a compounded drug has the same bulk drug substance as an approved drug, the two drugs have the same active ingredient.

Contains Nonbinding Recommendations

Draft — Not for Implementation

301
302 For example, a hospital may need an FDA-approved drug combined with a particular
303 diluent in infusion bags to administer to patients during surgery. The pharmacy manager
304 for the hospital could order the compounded drug from an outsourcing facility and
305 document on the order that the compounded drug will only be administered to patients for
306 whom the prescriber determines that this formulation will produce a clinical difference
307 from the comparable approved drug. Similarly, a physician who regularly treats patients
308 with an allergy to an inactive ingredient in a particular approved injectable drug product
309 could order a compounded version of the drug for office use from an outsourcing facility
310 provided that he or she includes a statement on the order that removing the particular
311 inactive ingredient produces a clinical difference for his or her individual patients and
312 that he or she will provide the drug only to patients with that particular clinical need.

313
314 Many outsourcing facilities compound non-sterile drugs in addition to sterile drugs.¹⁷ All
315 drugs compounded by an outsourcing facility must be compounded in accordance with
316 section 503B, including the prohibition on compounding drug products that are
317 essentially copies of approved drug products in order for any of them to qualify for the
318 exemptions provided in section 503B.¹⁸ For example, a hospice may need a compounded
319 liquid formulation of a drug that is only approved in capsules to treat elderly patients who
320 cannot swallow capsules. The pharmacy manager for the hospice could order the
321 compounded drug from an outsourcing facility and document on the order that the liquid
322 formulation produces a clinical difference for hospice patients who are unable to swallow
323 capsules and that the compounded drug will be dispensed only to a patient whose
324 prescribing practitioner determines that the liquid formulation will produce this clinical
325 difference for the patient.

326
327 FDA does not believe that a particular format is needed, provided that an order for office
328 stock (i.e., not patient-specific) clearly identifies the relevant change and the clinical
329 difference produced for patient(s), as determined by the prescriber. For example, the
330 following would be sufficient:

- 331
- 332 • “Liquid form, compounded drug will be prescribed to patients who can’t swallow
333 tablet” (if the comparable drug is a tablet)
 - 334 • “Dilution for infusion solution to be administered to patients who need this
335 formulation during surgery” (if the comparable drug is not available at that
336 concentration, pre-mixed with the particular diluent in an infusion bag)
 - 337 • “1 mg, pediatric patients need lower dose” (if the comparable drug is only
338 available in 25 mg dose)
- 339

¹⁷ An entity that *only* compounds non-sterile drugs does not meet the statutory definition of an outsourcing facility in section 503B(d)(4) of the FD&C Act. The definition states, in part, that an outsourcing facility “is engaged in the compounding of sterile drugs” (section 503B(d)(4)(i)).

¹⁸ Under section 503B(a)(11), a compounded drug can qualify for the exemptions from section 503B only if all of the facility’s compounded drugs are compounded in accordance with section 503B.

Contains Nonbinding Recommendations

Draft — Not for Implementation

340 An order that only identifies the product formulation, without more information, would
341 not be sufficient to establish that the determination described by section 503B(d)(2)(B)
342 has been made.

343
344 Many outsourcing facilities also compound drug products based on prescriptions for
345 identified individual patients. The following are examples of statements on a patient-
346 specific prescription that could be used to document the prescriber’s determination that a
347 compounded drug has a change that produces a clinical difference for a particular patient:
348

- 349 • “No Dye X, patient allergy” (if the comparable drug contains the dye)
- 350 • “Liquid form, patient can’t swallow tablet” (if the comparable drug is a tablet)
- 351 • “150 mg drug X in 120 ml cherry-flavored Syrup USP, patient needs alcohol-free
352 preparation (if the comparable drug is only available in formulations that contain
353 alcohol)

354
355 However, if a prescription identifies only a patient name and product formulation, this
356 would not be sufficient to establish that the determination described by section
357 503B(d)(2)(B) has been made.

358
359 Note also that the clinical difference identified on either a patient-specific prescription or
360 order, or non-patient specific order, must be produced by the “change” between the
361 outsourcing facility’s product and the approved drug (i.e., a change in product
362 formulation). Other factors such as a lower price are not sufficient to establish that the
363 compounded product is not essentially a copy of the approved drug.

364
365 If a prescription or order does not make clear that the determination required by section
366 503B(d)(2)(B) has been made, the outsourcing facility may contact the prescriber or
367 health care facility, and if the prescriber or health care facility confirms it, make a
368 notation on the prescription or order that the prescriber has determined that the
369 compounded product contains a change that produces a clinical difference for patient(s).
370 The notations should be as specific as those described above, and the date of the
371 conversation with the health care facility or prescriber should be included on the
372 prescription or order.

373
374 FDA generally does not intend to question the determinations of clinical difference that
375 are documented in a prescription or order as described above. However, we do intend to
376 consider whether a prescription or order relied upon by an outsourcing facility to
377 establish that a drug is not essentially a copy documents that the determination was made.

- 378
- 379 iii. Essentially a copy of one or more approved drug products

380
381 Under section 503B(a)(5), a compounded drug product must not be essentially a copy of
382 **one or more** (emphasis added) approved drug products. When applying section
383 503B(d)(2)(B), FDA intends to consider a compounded drug product that has bulk drug
384 substances that are components of one or more approved drugs to be essentially a copy of

Contains Nonbinding Recommendations

Draft — Not for Implementation

385 an approved drug product, unless the prescribing practitioner determines that there is a
386 change that produces a clinical difference for an individual patient between the
387 compounded drug product and the comparable approved drug. For example, if there are
388 two approved drug products that are tablets, one containing 5 mg of active ingredient A
389 and the other containing 10 mg of active ingredient B and the outsourcing facility
390 compounded a tablet that offered both active ingredients in the same dosage strengths, the
391 compounded drug would be essentially a copy absent a prescriber determination of
392 clinical difference.

393

394 2. *Application of the “Essentially a Copy” Definition in Section 503B(d)(2) When the*
395 *Compounded Drug Is Compared to a Covered OTC Drug Product (Appendix B)*

396

397 a. Compounded drugs that are identical or nearly identical to a covered OTC drug
398 product (section 503B(d)(2)(A)) (Appendix B, box 1)

399

400 Under section 503B(d)(2)(A), a compounded drug is not considered essentially a copy of
401 an approved drug if it is identical or nearly identical to **an approved drug** that appears on
402 FDA’s drug shortage list at the time of compounding, distribution, and dispensing. The
403 statute does not provide a similar exemption from the definition in section 503B(d)(2) if
404 the compounded drug is identical or nearly identical to a **covered OTC drug** on FDA’s
405 drug shortage list. Therefore, FDA intends to apply the same policy described above in
406 section III.A.1.a to OTC monograph drugs, with one exception.

407

408 If a compounded drug is identical or nearly identical to a covered OTC drug under
409 section 503B(d)(2)(A), the compounded drug is essentially a copy of an approved drug,
410 and the appearance of the covered OTC drug on FDA’s shortage list does not change that
411 result; the drug cannot be compounded under section 503B.¹⁹ If the compounded drug is
412 not identical or nearly identical to a comparable drug, it must be evaluated under section
413 503B(d)(2)(B), as described below.

414

415 b. Compounded drugs that contain a bulk drug substance that is a component of an
416 covered OTC drug product (section 503B(d)(2)(B)) (Appendix B, box 2)

417

418 Under section 503B(d)(2)(B), a compounded drug product is essentially a copy and
419 cannot be compounded under section 503B if a component of the compounded drug
420 product is a bulk drug substance²⁰ that is also a component of a covered OTC drug,
421 unless there is a change that produces for an individual patient a clinical difference, as
422 determined by the prescribing practitioner, between the compounded drug and the
423 comparable **approved** drug. A clinical difference between the compounded drug and an
424 unapproved drug (such as a covered OTC drug) does not exempt the compounded drug
425 from the definition in section 503B(d)(2)(B).

¹⁹ The compounded drug would not be essentially a copy if it was also identical or nearly identical to an approved drug on FDA’s drug shortage list, but this would be a very rare case.

²⁰ See footnote 15.

Contains Nonbinding Recommendations

Draft — Not for Implementation

426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459

c. Essentially a copy of one or more approved drug products²¹

Under section 503B(a)(5), a compounded drug product must not be essentially a copy of **one or more** approved drug products. When applying section 503B(d)(2)(B), FDA intends to consider a compounded drug product that has bulk drug substances that are components of one or more approved drugs to be essentially a copy of an approved drug product unless the prescribing practitioner determines that there is a change that produces a clinical difference for an individual patient between the compounded drug product and the comparable approved drug. For example, if there are two approved drug products that are tablets, one containing active ingredient A and the other containing active ingredient B, and the outsourcing facility compounded a tablet that offered both active ingredients, the compounded drug containing active ingredients A and B would be essentially a copy absent a prescriber determination of clinical difference.

If a bulk drug substance is a component of a covered OTC drug *and* an approved drug, the bulk drug substance can be evaluated as a component of an approved drug, as described in section III.A.1 of this guidance.

B. Recordkeeping

Outsourcing facilities should maintain records to demonstrate compliance with the essentially a copy provision in section 503B(a)(5). For example, where an outsourcing facility has compounded a drug that is evaluated under 503B(d)(2)(B) and a component of the compounded drug is a bulk drug substance that is a component of an approved drug, the outsourcing facility should maintain prescription or order records of a prescriber's determination of clinical difference as described above in section III.A.1.b.ii.

In addition, if the outsourcing facility compounded a drug that is identical or nearly identical to an approved drug product that appeared on FDA's drug shortage list, the outsourcing facility should maintain documentation (e.g., a notation on the order for the compounded drug) regarding the status of the drug on FDA's drug shortage list at the time of compounding, distribution, and dispensing.

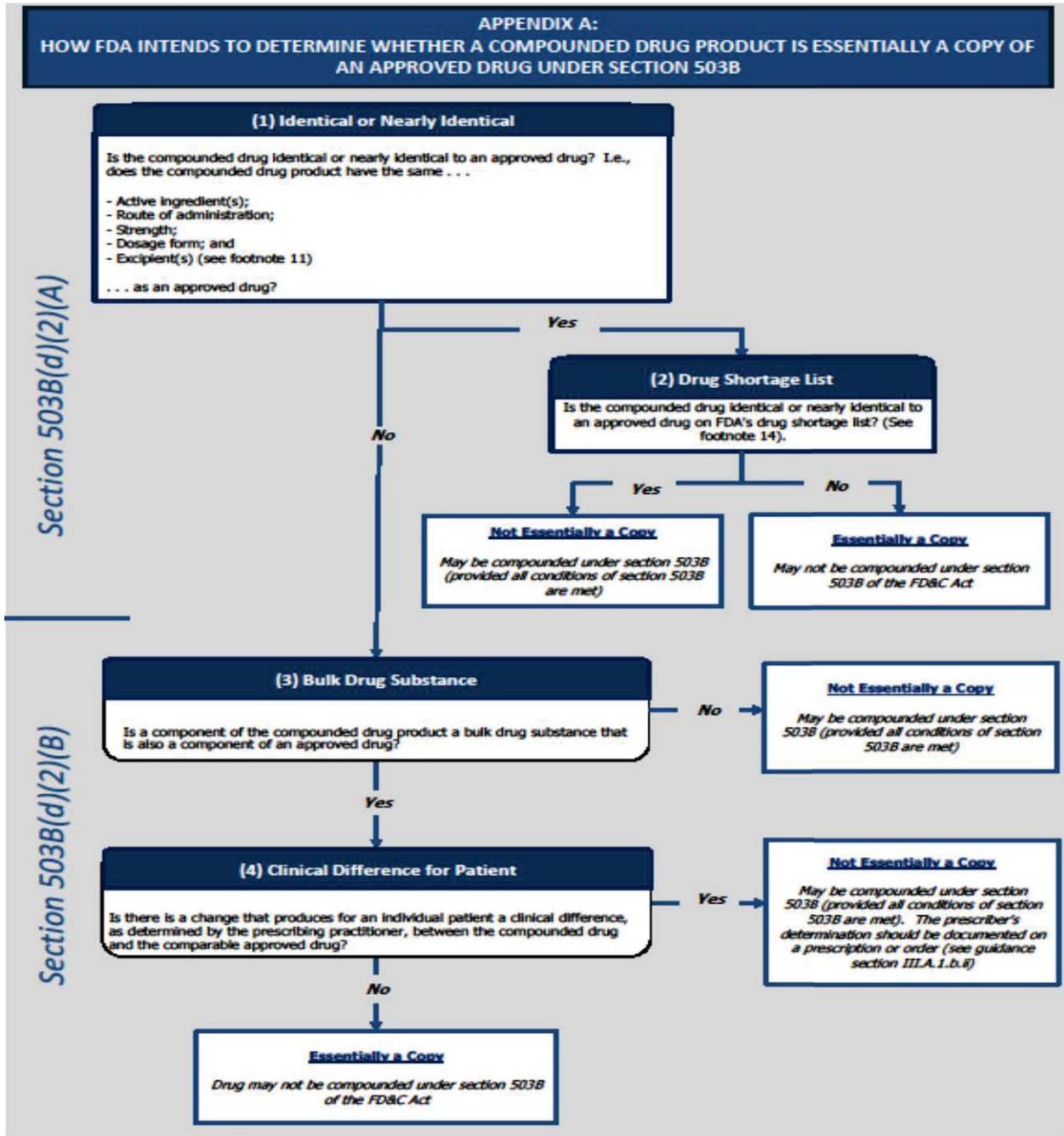
²¹ This scenario is not depicted in the diagrams in the appendices.

Contains Nonbinding Recommendations

Draft — Not for Implementation

APPENDICES A & B

460

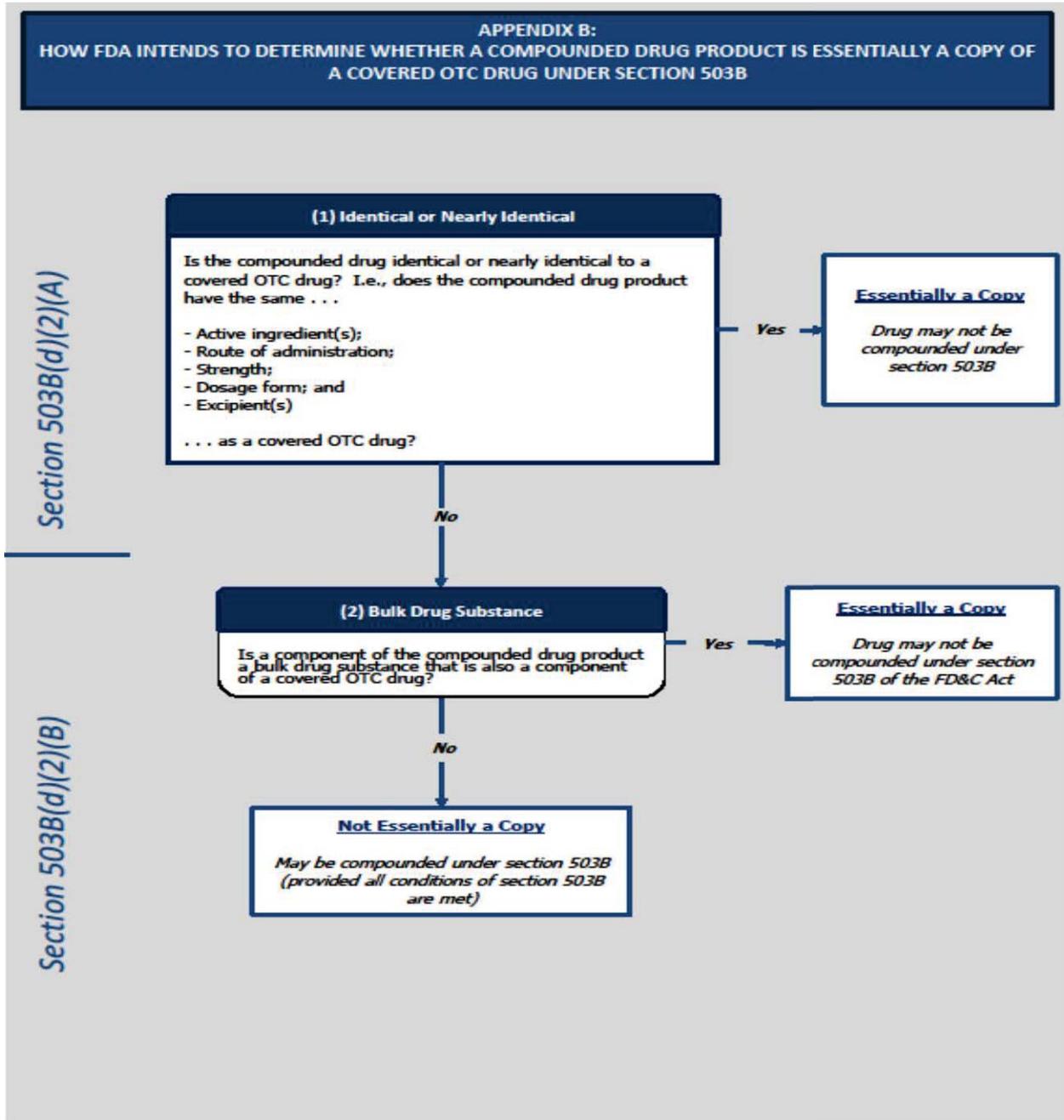


461

462

Contains Nonbinding Recommendations

Draft — Not for Implementation



Attachment 11

**Interim Policy on Compounding
Using Bulk Drug Substances
Under Section 503A of the
Federal Food, Drug, and
Cosmetic Act
Guidance for Industry**

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Compliance/OU DLC**

**June 2016
Compounding and Related Documents**

Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: 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)
Office of Compliance/OU DLC

June 2016
Compounding and Related Documents

TABLE OF CONTENTS

- I. INTRODUCTION AND SCOPE 1**
- II. BACKGROUND 2**
 - A. Compounding From Bulk Drug Substances Under Section 503A of the Act..... 2**
 - B. Efforts to Develop the List of Bulk Drug Substances under Section 503A..... 4**
- III. POLICY 9**
 - A. Compounding from Bulk Drug Substances under Section 503A 9**
 - B. Bulk Drug Substances Not Nominated or Nominated Without Adequate Support 10**
 - C. Comments about Nominated Bulk Drug Substances..... 10**
- APPENDIX: SUMMARY OF POLICY 11**

Guidance for Industry¹

Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION AND SCOPE

This guidance sets forth the Food and Drug Administration's (FDA or Agency) interim regulatory policy concerning compounding using bulk drug substances under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act). Section 503A of the FD&C Act includes certain restrictions on the bulk drug substances² that can be used in compounding and directs FDA to develop a list of bulk drug substances that can be used in compounding under that section. FDA is developing this list of bulk drug substances (the 503A bulks list), and this guidance describes FDA's interim regulatory policy for licensed pharmacists in State-licensed pharmacies and Federal facilities and for licensed physicians that compound human drug products using bulk drug substances while the list is being developed.^{3,4}

¹ This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research (CDER), in consultation with the Office of Regulatory Affairs at the Food and Drug Administration.

² Section 503A references the definition of bulk drug substances in FDA regulations at 21 CFR 207.3(a)(4), which defines *bulk drug substance* as "any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances."

³ This guidance does not apply to drugs compounded from bulk drug substances for use in animals. For proposed policies pertaining to compounding drug products from bulk drug substances for use in animals, see FDA's draft guidance, *Compounding Animal Drugs from Bulk Drug Substances*.

All FDA guidances are available on the FDA guidance web page. FDA updates guidances regularly. To make sure you have the most recent version of a guidance, always consult the guidance web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁴ FDA is developing a separate list of bulk drug substances that can be used in compounding under section 503B of the FD&C Act. Because section 503B contains different criteria for that list and provides for a different process for its development, the section 503B bulks list is covered under a separate guidance (see guidance for industry, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*).

Contains Nonbinding Recommendations

In general, FDA's guidance documents 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. Compounding From Bulk Drug Substances Under Section 503A of the Act

Section 503A of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to be exempt from the following three sections of the FD&C Act: section 505 (concerning the approval of drugs under new drug applications or abbreviated new drug applications); section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and section 501(a)(2)(B) (concerning current good manufacturing practice requirements).

One of the conditions that must be met for a compounded drug product to qualify for these exemptions is that a licensed pharmacist, or licensed physician compounds the drug product using bulk drug substances that:

1. Comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding;
2. If such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or
3. If such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, appears on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A.⁵

A bulk drug substance is defined, in part, as a substance that "becomes an active ingredient or a finished dosage form of the drug, but does not include intermediates used in the synthesis of such substances" (see section 503A(b)(1)(A) and 21 CFR 207.3(4)). FDA has interpreted "an applicable USP or NF monograph" to mean an official USP or NF **drug substance** monograph. Accordingly, FDA does not consider USP monographs for dietary supplements to be "applicable" USP or NF monographs within the meaning of section 503A(b)(1)(A)(i)(I).

⁵ See Section 503A(b)(1)(A)(i) of the FD&C Act.

Contains Nonbinding Recommendations

Under section 503A(c)(1), before developing this list through regulation, FDA must convene and consult an advisory committee on compounding unless FDA determines that the issuance of such regulation before consultation with the advisory committee is necessary to protect the public health. FDA must also consult with USP when promulgating the regulations.⁶ The criteria for determining which bulk drug substances should appear on the section 503A bulks list “shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify.”⁷

Bulk drug substances used in compounding under section 503A must also meet certain other requirements, including: (1) the bulk drug substance must be manufactured by an establishment registered under section 510 of the FD&C Act and (2) the bulk drug substance must be accompanied by a valid certificate of analysis (COA).⁸

In July 2014, FDA issued a guidance, *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*, that states:

Until a bulk drug substances list is published in the *Federal Register* as a final rule, human drug products should be compounded using only bulk drug substances that are components of drugs approved under section 505 of the FD&C Act, or are the subject of USP or NF monographs.⁹

FDA has received comments that this policy could be causing unnecessary and inappropriate disruptions in patient care because there are patients receiving drugs compounded with bulk drug substances that are not components of FDA-approved drugs, or the subject of an applicable USP or NF monograph, but that may ultimately be included on the 503A bulks list, and those patients’ care should not be disrupted while the list is under development. After considering this issue, FDA has decided to use this guidance to describe its interim policy concerning compounding with bulk drug substances while the 503A bulks list is being developed. FDA has revised the July 2014 guidance to state:

FDA’s interim policy concerning bulk drug substances that are not components of drugs approved under section 505 of the FD&C Act or that are not the subject of applicable USP or NF monographs can be found in the guidance, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug and Cosmetic Act*.

FDA seeks to avoid unnecessary disruption to patient treatment while the Agency considers the bulk drug substances that were nominated with sufficient support to permit FDA to evaluate them and promulgates the regulations required under section 503A. Therefore, as described

⁶ See section 503A(c)(2) of the FD&C Act.

⁷ See section 503A(c)(2) of the FD&C Act.

⁸ See section 503A(b)(1)(A) of the FD&C Act.

⁹ See page 5 of the guidance, *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*.

Contains Nonbinding Recommendations

further below, FDA is issuing this interim guidance stating that it does not intend to take regulatory action for compounding drug products under section 503A using a bulk drug substance when an applicable USP or NF monograph for the substance does not exist and the substance is not a component of an FDA-approved product if, among other conditions, FDA has determined that the nomination for the bulk drug substance included adequate information for FDA to evaluate the substance and at this time, the substance does not appear to present significant safety risks.

B. Efforts to Develop the List of Bulk Drug Substances under Section 503A

1. Section 503A Bulks List — Early History

Section 503A was enacted in 1997 as part of the Food and Drug Administration Modernization Act. In the *Federal Register* of April 7, 1998 (63 FR 17011), FDA invited all interested persons to nominate bulk drug substances for inclusion on the list of bulk drug substances that can be used in compounding under section 503A and received nominations for 41 different drug substances. In November 1998, FDA published a guidance for industry, *Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act*. In this guidance, FDA announced that it would not normally take regulatory action relating to a drug product that had been compounded with a bulk drug substance that had been nominated for inclusion on the bulk drug substances list on or before November 21, 1999, while the substance was being evaluated, as long as the compounding complied with the other effective requirements in section 503A and did not appear to present a significant safety risk.¹⁰

In January 1999, after evaluating the nominated drug substances and consulting with the Pharmacy Compounding Advisory Committee (PCAC) as required by section 503A, FDA published a proposed rule listing 20 drug substances on the section 503A bulks list (64 FR 996, January 7, 1999). The preamble to the proposed rule indicated that 10 of the 41 nominated drug substances were the subject of a USP or NF monograph, or components of FDA approved drugs and did not need to be considered for inclusion on the list.¹¹ The proposed rule also described 10 nominated drug substances that were still under consideration for the bulk drug substances list and stated that one of the substances was withdrawn by its nominator at the first meeting of the PCAC. The PCAC reconvened in May 1999 to discuss bulk drug substances included in the proposed rule, in addition to other bulk drug substances (64 FR 19791; April 22, 1999).

However, after a 2002 U.S. Supreme Court decision holding that certain provisions of section 503A were unconstitutional,¹² FDA suspended its efforts to develop the bulk drugs list under section 503A.

¹⁰ The 1998 guidance was withdrawn in the *Federal Register* notice announcing the availability of the draft guidance *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*. See 78 FR 72901 (Dec. 4, 2013). The final guidance was published in July 2014.

¹¹ See 64 FR 996, at 997 (January 7, 1999).

¹² For additional legal history of section 503A, see the guidance *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*.

Contains Nonbinding Recommendations

Because of the amount of time that had passed between the publication of the proposed rule and the enactment of the 2013 Drug Quality and Security Act, which removed the provisions of the FD&C Act that the U.S. Supreme Court held to be unconstitutional in 2002, FDA felt it was necessary to begin again to develop the section 503A bulk drug substance list. In the December 4, 2013, *Federal Register* (78 FR 72841), FDA published a notice withdrawing the 1999 proposed rule and inviting all interested persons to nominate bulk drug substances for inclusion on a list of bulk drug substances that can be used for compounding under section 503A of the FD&C Act.

2. Current Nominations for the 503A Bulks List

In response to the December 2013, *Federal Register* notice, over 2,000 substances were nominated for the 503A bulks list. However, many of the substances nominated for the 503A list were for substances that can be compounded without being on the list because they are the subject of an applicable USP or NF monograph or are a component of an FDA-approved drug. In addition, many of the nominations were not for bulk drug substances used in compounding as active ingredients, or did not include sufficient information for FDA to evaluate the nominated substances for inclusion on the list. To improve the efficiency of the process for developing the 503A bulks list, FDA reopened the nomination process in July 2014 (79 FR 37742) and provided more detailed information on what it needs to evaluate nominations for the 503A bulks list. FDA stated that bulk drug substances that were previously nominated would not be considered further unless they were re-nominated with adequate support to permit a meaningful evaluation. Substances that were already eligible for use in compounding or that were not adequately supported would not be evaluated for placement on the 503A bulks list.

In response to this request for nominations, approximately 740 unique substances were nominated. Of the nominated substances:

- Approximately 315 substances are already eligible for use in compounding under section 503A.

These are components of an FDA-approved drug product or the subject of an applicable USP or NF monograph, which can be used in compounding pursuant to sections 503A(b)(1)(A)(i)(I) and (II) and, therefore, can be compounded without being included on the 503A bulks list. To determine if a bulk drug substance is the subject of an applicable USP or NF monograph, see the *USP-NF* available at www.USPNF.com. To determine if a bulk drug substance is a component of an FDA approved drug, see the FDA's *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, available at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

- At least one¹³ of the nominated substances is not a bulk drug substance.

¹³ The over-the-counter finished drug product Maalox was nominated. Maalox is not a bulk drug substance.

Contains Nonbinding Recommendations

This is a finished drug product that was nominated by its brand name. Finished drug products are not eligible for the 503A bulks list because they do not meet the definition of a bulk drug substance in 21 CFR 207.3(4).

- At least one of the substances is considered a biological product subject to approval in a biologics license application (BLA) under section 351 of the Public Health Service (PHS) Act when used for the indication proposed in the nomination.

This substance is not eligible for the 503A bulks list because biological products subject to approval in a BLA under section 351 of the PHS Act are not eligible for the exemptions in section 503A of the FD&C Act.¹⁴ No biological products subject to approval in a BLA will be considered for the 503A bulks list.

- At least four of the nominated substances appear on the list published by FDA of substances that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (withdrawn or removed list).¹⁵

Such substances cannot be used in compounding under section 503A of the FD&C Act and, therefore, are not eligible for inclusion on the 503A bulks list.

- One of the nominated substances has no currently accepted medical use and is included on Schedule I of the Controlled Substances Act (CSA) (21 U.S.C. § 812(c)).¹⁶

The CSA does not allow possession or distribution of Schedule I substances (21 USC §§ 841(a)(1) and 829), except for research purposes (21 U.S.C. § 823(f)), and these substances will not be considered for the 503A bulk drug substances list at this time. Those desiring to do research on a Schedule I substance can apply to do so under an investigational new drug application (IND).

- Of the substances that are not components of an approved drug or the subject of an applicable USP or NF monograph and that are not biological products subject to licensure in a BLA or included on Schedule I of the CSA, and do not appear on the withdrawn or removed list, approximately 350 substances were nominated without sufficient supporting evidence for FDA to evaluate them.

¹⁴ The nominated substance is sodium hexachloroplatinate (IV) hexahydrate. See the draft guidance, *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application* for FDA's proposed policies regarding State-licensed pharmacies, Federal facilities, and outsourcing facilities that mix, dilute, or repackage biological products outside the scope of an approved BLA.

¹⁵ See Section 503A(b)(1)(C) of the FD&C Act. See also 21 CFR 216.24. The four substances are: chloroform reagent, cobalt chloride hexahydrate, cobalt gluconate, and phenacetin.

¹⁶ An extract of cannabidiol (CBD) and tetrahydrocannabinol (THC) derived from marijuana (marihuana) was nominated. Marijuana (marihuana) is a Schedule I substance.

Contains Nonbinding Recommendations

- The remaining substances may be eligible for inclusion on the 503A list and were nominated with sufficient supporting information for FDA to evaluate them. However, FDA has identified significant safety risks relating to the use of some of these bulk drug substances in compounded drug products.

FDA's website¹⁷ identifies the following categories of substances nominated for the 503A bulks list:

503A Category 1 – Bulk Drug Substances Under Evaluation: These bulk drug substances may be eligible for inclusion on the 503A bulks list, were nominated with sufficient supporting information for FDA to evaluate them, and do not appear on any other list.

503A Category 2 – Bulk Drug Substances That Raise Significant Safety Risks: These bulk drug substances were nominated with sufficient supporting information to permit FDA to evaluate them and they may be eligible for inclusion on the 503A bulks list. However, FDA has identified significant safety risks relating to the use of these bulk drug substances in compounding, and therefore does not intend to adopt the policy described for the bulk drug substances in Category 1. If FDA adds a substance to Category 2, it will publish a public communication (e.g., a safety alert) describing the safety risks and will post the communication on FDA's human drug compounding website,¹⁸ advising that the substance has been added to Category 2 and is no longer eligible for the policies that apply to substances in Category 1.

503A Category 3 – Bulk Drug Substances Nominated Without Adequate Support: These bulk drug substances may be eligible for inclusion on the 503A bulks list, but were nominated with insufficient supporting information for FDA to evaluate them. These substances can be re-nominated with sufficient supporting information through a docket that FDA has established, as discussed below in section III.B.

3. Process for Developing the 503A List

FDA is currently evaluating the bulk drug substances that were nominated for the 503A bulks list in response to the July 2014 *Federal Register* notice with sufficient information to permit evaluation. FDA is considering a number of factors in prioritizing the order in which it reviews the nominated bulk drug substances, including but not limited to the following:

- Safety concerns about use of the bulk drug substance in compounding
- Whether the bulk drug substance was nominated by multiple parties or identified as necessary by medical professional organizations

¹⁷ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf>.

¹⁸ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/default.htm>. FDA also encourages compounding facilities to subscribe to FDA's list serve to receive updates at: http://service.govdelivery.com/service/subscribe.html?code=USFDA_429.

Contains Nonbinding Recommendations

- The efficiency with which the evaluation can be completed, based on ease of acquiring the necessary information to conduct the review, available resources, and other logistical issues

FDA may also group some nominated drug substances to facilitate efficient review and discussion. These include drugs that raise similar issues (e.g., vitamins or botanicals) or have been nominated for the treatment of the same condition (e.g., warts).

In conducting its evaluations, FDA reviews the information provided in support of the nomination and other available information to assess each bulk drug substance according to the following four criteria discussed at the PCAC meeting on February 23, 2015:

- The physical and chemical characterization of the substance
- Any safety issues raised by the use of the substance in compounded drug products
- Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature
- The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists

In evaluating candidates for the 503A bulks list under these criteria, FDA is using a balancing test. No single one of these criteria is dispositive; rather, FDA is considering each criterion in the context of the others and balancing them, on a substance-by-substance basis, to evaluate whether a particular substance is appropriate for inclusion on the list.

Once the evaluation of a substance is complete, FDA will present the results of its review to the PCAC to obtain its advice on whether to include the substance on the list.¹⁹

Section 503A requires that FDA create the 503A bulks list by regulation in consultation with the USP. To this end, FDA has been periodically meeting with USP and discussing the list. FDA will publish a notice of proposed rulemaking (NPRM) that identifies substances FDA proposes for placement on the 503A bulks list and the substances FDA has evaluated but is not proposing to include on the 503A bulks list. After publication of the NPRM, the public will have an opportunity to comment on the proposed rule, and FDA will again consult with USP. After consulting with USP and considering the comments submitted to the docket, FDA will publish a final rule that establishes the 503A bulks list and identifies the substances that were considered and will not be placed on the list. FDA does not intend to evaluate all of the sufficiently supported nominations before publishing the first NPRM. Instead, after FDA has made a decision on whether to propose a group of substances (e.g., 10 substances) it intends to publish an NPRM with respect to that group of substances and continue to prepare the list on a rolling basis.

¹⁹ See Section 503A(c)(1) of the FD&C Act.

Contains Nonbinding Recommendations

A final rule will list the substances that FDA has determined can be used in compounding under section 503A and those substances that have been evaluated and not placed on the section 503A bulks list, if any.

After a final rule is published, drug products compounded using the substances on the 503A bulks list will be eligible for the section 503A exemptions provided the drug product is compounded in compliance with the other conditions of section 503A.

III. POLICY²⁰

A. Compounding from Bulk Drug Substances under Section 503A

Under section 503A of the FD&C Act, a bulk drug substance that is not the subject of an applicable USP or NF monograph or is not a component of an FDA-approved drug cannot be used in compounding unless it appears on a list promulgated as a regulation pursuant to section 503A(b)(1)(A)(i)(III) of the FD&C Act. This list will be codified at 21 CFR part 216 subpart E.

However, until a substance has been evaluated and is identified in a final rule as being included or not included on the 503A bulks list, FDA does not intend to take action against a State-licensed pharmacy, Federal facility, or licensed physician compounding a drug product using a bulk drug substance that is not a component of an FDA-approved drug product and that is not the subject of an applicable USP or NF monograph, provided that the following conditions are met:

1. The bulk drug substance appears in 503A Category 1 on FDA's website at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf>. A Category 1 substance may be eligible for inclusion on the 503A bulks list, was nominated with sufficient supporting information for FDA to evaluate it and has not been identified by FDA as a substance that presents a significant safety risk in compounding prior to the publication of a final rule.
2. The original manufacturer and all subsequent manufacturers of the bulk drug substance are establishments that are registered under section 510 (including foreign establishments that are registered under section 510(i)) of the FD&C Act);
3. The bulk drug substance is accompanied by a valid COA; and
4. The drug product compounded using the bulk drug substance is compounded in compliance with all other conditions of section 503A of the FD&C Act.

Original manufacturer means the entity that originally produced the bulk drug substance and not a subsequent packer, repacker, labeler, or distributor.

²⁰ See the Appendix for a chart summarizing FDA's interim policy.

Contains Nonbinding Recommendations

This policy does not apply to a licensed pharmacist in a State-licensed pharmacy or Federal facility, or a licensed physician, that compounds a drug using a bulk drug substance that does not meet each of the above conditions, and the bulk drug substance is not a component of an FDA-approved drug, or the subject of an applicable USP or NF monograph.,

B. Bulk Drug Substances Not Nominated or Nominated Without Adequate Support

As stated above, one of the categories of bulk drug substances FDA has identified on its website is bulk drug substances that may be eligible for inclusion on the 503A bulks list, but that FDA is unable to evaluate for inclusion on the list at this time because the substances were nominated with insufficient supporting evidence for FDA to evaluate them (503A Category 3). In the *Federal Register* of October 27, 2015, FDA established a docket (October docket) where these substances can be re-nominated with sufficient supporting information or to receive nominations for substances that were not previously nominated. FDA does not intend to evaluate these submissions until it completes its review of the substances that were nominated for the 503A bulks list with adequate supporting information pursuant to the July 2, 2014, request for nominations (79 FR 37747).²¹

Once FDA completes its review of substances nominated pursuant to the July request for nominations, a determination will be made as to whether the nominations made to the October docket are supported with sufficient information to allow FDA to evaluate them. After FDA makes that determination, nominated substances will be placed in one of the three categories described in section II.B.2 above, and the categorization will be published on the FDA website. Once this information is published, FDA intends to apply the policy described in Section III.A. of this guidance to the substances nominated to the October docket. Please note that until substances nominated for the October docket have been categorized, the policy does *not* apply.

C. Comments about Nominated Bulk Drug Substances

If you feel that a substance that you nominated does not appear on the appropriate list or category as described in this guidance you can submit your comment to docket number FDA-2015-N-3534. If you have new information on a previously nominated substance that was placed in Category 3, the substance can be re-nominated with the additional information.

²¹ Patients with medical conditions that need to be treated with drug products that are made from bulk drug substances that cannot be used in compounding may be able to obtain the drug products through FDA's Expanded Access programs. For information about these programs, visit FDA's website at <http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm>.

Contains Nonbinding Recommendations

APPENDIX: SUMMARY OF POLICY

The following table summarizes the interim policy set forth in this guidance:

Category	FDA Policy
<p>The bulk drug substance appears in 503A Category 1 on FDA’s website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf.</p> <p>Such substances may be eligible for inclusion on the 503A bulks list, were nominated with sufficient supporting information for FDA to evaluate them, and do not appear to present a significant safety risk.</p>	<p>FDA does not intend to take action for compounding a drug product from a bulk drug substance in Category 1 that does not meet the conditions of section 503A(b)(1)(A)(i), provided that the bulk drug substance was manufactured by an establishment registered with FDA under section 510 of the FD&C Act and is accompanied by a valid COA from the entity that originally produced the bulk drug substance and provided that the drug compounded from the bulk drug substance is compounded in compliance with the other conditions of section 503A.</p>
<p>The bulk drug substance is a component of an FDA-approved drug and/or the subject of an applicable USP or NF monograph.</p>	<p>The bulk drug substance can be used in compounding under section 503A of the FD&C Act, provided it complies with the standards of the monograph (if one exists) and is compounded in compliance with the other conditions of section 503A.</p>
<p>The bulk drug substance appears on the withdrawn or removed list.</p>	<p>The bulk drug substance cannot be used in compounding under section 503A of the FD&C Act. A drug compounded using the bulk drug substance is subject to regulatory action.</p>
<p>The bulk drug substance appears in 503A Category 2 on FDA’s website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf. The substance has been identified by FDA as presenting a significant safety risk.</p>	<p>The bulk drug substance cannot be used in compounding under section 503A of the FD&C Act unless and until FDA publishes a final rule authorizing its use under section 503A.</p>
<p>The bulk drug substance is a biological product subject to approval in a BLA.</p>	<p>The substance is not eligible for the 503A bulks list. FDA has issued a separate draft guidance document describing the Agency’s proposed policies concerning mixing, diluting, and repackaging biological products subject to approval in a BLA.²²</p>
<p>The bulk drug substance appears in 503A Category 3 on FDA’s website at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf. The substance may be eligible for inclusion on the 503A bulks list, but was nominated with insufficient supporting information for FDA to evaluate it.</p>	<p>The bulk drug substance cannot be used in compounding under section 503A of the FD&C Act., See section III.B of this guidance for information about re-nominating substances that were previously nominated with insufficient supporting information.</p>

²² See FDA’s draft guidance, *Mixing, Diluting, and Repackaging Biological Products Subject to Approval in a Biologics License Application*.

Attachment 12

Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Guidance

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**June 2016
Compounding and Related Documents
Revision 2**

Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Guidance

Additional copies are available from:

*Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
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>

or

*Office of Policy
Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-4830*

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**June 2016
Compounding and Related Documents
Revision 2**

Contains Nonbinding Recommendations

TABLE OF CONTENTS

I. INTRODUCTION	1
II. BACKGROUND	2
III. POLICY	2
A. Conditions of Section 503A	3
B. Provisions of Section 503A That Require Regulations or Other FDA Actions	5
IV. GUIDANCE ON REGULATORY ACTION.....	6
A. Requirements Applicable to Drug Products That Meet the Conditions of Section 503A	6
B. Enforcement Action When a Drug Does Not Meet the Conditions of Section 503A	7
C. Enforcement Approach	8

Guidance¹
**Pharmacy Compounding of Human Drug Products Under Section
503A of the Federal Food, Drug, and Cosmetic Act**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create any rights for or on any person and is not binding on FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed in the title page.

I. INTRODUCTION

This guidance announces FDA's intention with regard to enforcement of section 503A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 353a) to regulate entities that compound drugs, now that section 503A has been amended by Congress to remove the advertising and solicitation provisions that were held unconstitutional by the U.S. Supreme Court in 2002 (see section II below). Several parts of section 503A require rulemaking and consultation with a Pharmacy Compounding Advisory Committee to implement. This guidance explains how the provisions will be applied pending those consultations and rulemaking. This guidance also describes some of the possible enforcement actions FDA can bring against individuals or firms that compound drugs in violation of the FD&C Act.

This guidance does not apply to registered *outsourcing facilities* under section 503B of the FD&C Act.² Guidance for outsourcing facilities will be issued separately.

In general, FDA's guidance documents 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.

¹ This guidance was prepared by the Office of Compliance, Center for Drug Evaluation and Research at the Food and Drug Administration.

² Title I of the Drug Quality and Security Act created a new section 503B of the FD&C Act, entitled "Outsourcing Facilities." See Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

Contains Nonbinding Recommendations

II. BACKGROUND

Section 503A was added to the FD&C Act by the Food and Drug Administration Modernization Act of 1997 (Public Law 105-115) (the Modernization Act). Section 503A describes the conditions that must be satisfied for drug products compounded by a licensed pharmacist or licensed physician to be exempt from the following three sections of the FD&C Act: (1) section 501(a)(2)(B) (concerning current good manufacturing practice); (2) section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and (3) section 505 (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)).³

Previously, the conditions of section 503A of the FD&C Act also included restrictions on the advertising or promotion of the compounding of any particular drug, class of drug, or type of drug and the solicitation of prescriptions for compounded drugs. These provisions were challenged in court and held unconstitutional by the U.S. Supreme Court in 2002.⁴ Following that decision, in May 2002 FDA issued a compliance policy guide entitled *Pharmacy Compounding* (May 2002 CPG), which described how FDA intended “to address pharmacy compounding of human drugs in the immediate future” as a result of the Supreme Court decision.⁵ In 2013, section 503A was amended by the Drug Quality and Security Act (DQSA)⁶ to remove the advertising, promotion, and solicitation provisions. As a result, the May 2002 CPG is no longer relevant, and it is necessary to explain FDA’s current thinking with regard to section 503A.

The *Federal Register* notice announcing the availability of the draft version of this guidance withdrew the May 2002 CPG as well as the November 1998 guidance for industry entitled *Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act*.⁷

III. POLICY

³ Section 503A of the FD&C Act and this guidance do not apply to positron emission tomography (PET) drugs as defined in section 201(ii) of the FD&C Act or radiopharmaceuticals (see section 503A(e) of the FD&C Act). Section 503A(e) specifically states that section 503A does not apply to radiopharmaceuticals or to PET drugs as defined in section 201(ii). PET drugs are subject to the current good manufacturing practice requirements of 21 CFR part 212. Section 503A also does not apply to drugs intended for use in animals. The statutory and regulatory provisions governing the compounding of human drug products differ from those governing the compounding of animal drug products. All relevant statutory and regulatory requirements relating to the compounding of animal drug products remain in effect, subject to the requirements of section 512 of the FD&C Act (21 U.S.C. 360b) and 21 CFR part 530.

⁴ See *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002).

⁵ See 67 FR 39,409 (June 7, 2002).

⁶ See Pub. L. No. 113-54 (2013).

⁷ 78 FR 72,901 (Dec. 4, 2013).

Contains Nonbinding Recommendations

A drug product intended for use in humans that is compounded in compliance with section 503A and its associated regulations is exempt from the requirements in sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act. However, all other applicable provisions of the FD&C Act remain in effect for compounded drugs, even if the conditions of section 503A are met.

FDA expects state boards of pharmacy to continue their oversight and regulation of the practice of pharmacy, including pharmacy compounding. FDA also intends to continue to cooperate with state authorities to address pharmacy activities that may be violative of the FD&C Act, including section 503A. FDA's enforcement approach with respect to such violations is described in section IV.C., below.

A. Conditions of Section 503A

Under section 503A of the FD&C Act, a compounded drug product is exempt from sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act if it meets the conditions of section 503A of the FD&C Act. Specifically, the compounded drug product qualifies for the exemptions if:

1. The drug product is compounded for an identified individual patient based on the receipt of a valid prescription order, or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient (section 503A(a) of the FD&C Act).
2. The compounding of the drug product is performed:
 - By a licensed pharmacist in a state licensed pharmacy or a Federal facility, or by a licensed physician on the prescription order for an individual patient made by a licensed physician or other licensed practitioner authorized by state law to prescribe drugs; or
 - By a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient and:
 - is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the human drug product; and
 - those orders have been generated solely within an established relationship between the licensed pharmacist or licensed physician and either such patient for whom the prescription order will be provided or the physician or other licensed practitioner who will write such prescription order (sections 503A(a)(1) and (2) of the FD&C Act).
3. The drug product is compounded in compliance with the United States Pharmacopoeia (USP) chapters on pharmacy compounding⁸ using bulk drug substances, as defined in 21 CFR 207.3(a)(4), that comply with the standards of an applicable USP or National Formulary (NF) monograph, if one exists.

⁸ After the Modernization Act was enacted in 1997, the USP moved its chapter on pharmacy compounding to chapter <795> and added chapter <797>, which specifically addresses sterile compounding and is referenced in chapter <795>.

Contains Nonbinding Recommendations

If such a monograph does not exist, the drug substance(s) must be a component of an FDA-approved human drug product. If a monograph does not exist and the drug substance is not a component of an FDA-approved human drug product, it must appear on a list of bulk drug substances for use in compounding developed by FDA through regulation (section 503A(b)(1)(A)(i) of the FD&C Act). See section III.B.2 below for the interim policy for this provision.

4. The drug product is compounded using bulk drug substances that are manufactured by an establishment that is registered under section 510 of the FD&C Act (including a foreign establishment that is registered under section 510(i) of the FD&C Act) (section 503A(b)(1)(A)(ii) of the FD&C Act).
5. The drug product is compounded using bulk drug substances that are accompanied by valid certificates of analysis for each bulk drug substance (section 503A(b)(1)(A)(iii) of the FD&C Act).
6. The drug product is compounded using ingredients (other than bulk drug substances) that comply with the standards of an applicable USP or NF monograph, if one exists, and the USP chapters on pharmacy compounding⁹ (section 503A(b)(1)(B) of the FD&C Act).
7. The drug product does not appear on the list, published at 21 CFR 216.24, that includes drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (section 503A(b)(1)(C) of the FD&C Act). See section III.B.1 below.
8. The licensed pharmacist or licensed physician does not compound regularly or in inordinate amounts any drug products that are essentially copies of commercially available drug products (section 503A(b)(1)(D) of the FD&C Act).
9. The drug product is not a drug product identified by FDA by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product (section 503A(b)(3)(A) of the FD&C Act). See section III.B.3 below.
10. The drug product is compounded in a state that has entered into a memorandum of understanding (MOU) with FDA that addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a state agency of complaints relating to compounded drug products distributed outside such state; or, in states that have not entered into such an MOU with FDA, the licensed pharmacist, licensed pharmacy, or licensed physician does not distribute, or cause to be distributed, compounded drug products out of the state in which they are compounded, more than 5% of the total prescription orders dispensed or distributed by such pharmacy

⁹ *Id.*

Contains Nonbinding Recommendations

or physician (sections 503A(b)(3)(B)(i) & (ii) of the FD&C Act). See section III.B.4 below for the interim policy for this provision.

B. Provisions of Section 503A That Require Regulations or Other FDA Actions

Specific provisions of section 503A of the FD&C Act require rulemaking or other action by FDA. FDA's policy related to these specific provisions is described below.

1. Withdrawn or Removed List

FDA promulgated a final rule, codified at 21 CFR 216.24, which lists drug products that cannot be compounded because they have been withdrawn or removed from the market because the drug products or components of the drug products have been found to be unsafe or not effective. ***FDA intends to update this list periodically, and expects compounders to comply with the list as it currently exists and with any final updates.***

2. Bulk Drug Substances List

Section 503A(b)(1)(A)(i)(III) of the FD&C Act provides that a drug product can be compounded using bulk drug substances that do not have an applicable USP or NF monograph (section 503A(b)(1)(A)(i)(I) of the FD&C Act) and are not components of FDA-approved drugs (section 503A(b)(1)(A)(i)(II) of the FD&C Act) if the bulk drug substances appear on a list developed by FDA and issued through regulation.

In the Federal Register of April 7, 1998 (63 FR 17,011), FDA invited all interested persons to nominate bulk drug substances for inclusion on the list. In the Federal Register of January 7, 1999 (64 FR 996), FDA published a proposed rule listing bulk drug substances that can be used in pharmacy compounding. In the Federal Register of December 4, 2013 (78 FR 72,841), FDA published a notice withdrawing the 1999 proposed rule and inviting all interested persons to nominate bulk drug substances for inclusion on a list of bulk drug substances that can be used for compounding under section 503A of the FD&C Act. FDA's interim policy concerning bulk drug substances that are not components of drugs approved under section 505 of the FD&C Act or that are not the subject of applicable USP or NF monographs can be found in the guidance, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug and Cosmetic Act*.

3. "Demonstrable Difficulties" for Compounding

Under section 503A(b)(3)(A) of the FD&C Act, a compounded drug product would not qualify for the exemptions provided in subsection (a) if it is identified by FDA through regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of the drug product. In the *Federal Register* of December 4, 2013 (78 FR 72,840), FDA published a notice inviting all interested persons to nominate drug products or categories of drug products for inclusion on a list of drug products that present demonstrable difficulties for compounding (difficult-to-compound list). This provision is not enforceable until FDA promulgates an implementing regulation.

Contains Nonbinding Recommendations

4. Memorandum of Understanding Between FDA and the States

Section 503A(b)(3) of the FD&C Act states that FDA, in consultation with the National Association of Boards of Pharmacy (NABP) will develop a standard MOU for use between FDA and the states that will address the interstate distribution of inordinate amounts of compounded drug products and provide for appropriate investigation by a state agency of complaints relating to compounded drug products distributed outside that state. On January 21, 1999, FDA published a notice in the *Federal Register* announcing the availability of a draft standard MOU, developed in consultation with the NABP. This draft MOU was not finalized. FDA intends to publish a new draft MOU for comment that will replace the January 1999 draft.

Under section 503A(b)(3)(B)(ii), an individual or firm in a state that does not enter into an MOU with FDA that distributes, or causes to be distributed, compounded drug products out of the state in which they are compounded, can compound for interstate distribution outside the state only 5% of the total prescription orders dispensed or distributed by the individual or firm. FDA does not intend to enforce the 5% limit on interstate distribution until after FDA has finalized an MOU and made it available to the states for their consideration and signature. The *Federal Register* notice that will announce the availability of the draft MOU will specify a time period during which the MOU will be made available to the states to sign. After this time period expires, FDA intends to begin enforcing the 5% limit in states that have not signed the MOU.

IV. GUIDANCE ON REGULATORY ACTION

A. Requirements Applicable to Drug Products that Meet the Conditions of Section 503A

As stated above, a compounded drug product intended for use in humans that meets the conditions of section 503A of the FD&C Act and its associated regulations is exempt from the requirements under sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act.

However, individuals and firms may be subject to a warning letter, seizure of product, injunction, and/or criminal prosecution for violations of other requirements of the FD&C Act. Such violations may include, but are not limited to, the following:

1. The drug product must not consist in whole or in part of any filthy, putrid, or decomposed substance, or be prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth or whereby it may have been rendered injurious to health. (Sections 501(a)(1) and (a)(2)(A) of the FD&C Act)
2. If the drug product purports to be a drug that is recognized in an official compendium, its strength must not differ from, and its quality or purity must not fall below, the standards set forth in the compendium, unless the difference is plainly stated on its label. (Section 501(b) of the FD&C Act)

Contains Nonbinding Recommendations

3. For a drug product not subject to section 501(b) of the FD&C Act, the drug's strength must not differ from, and its quality or purity must not fall below, that which it purports to have. (Section 501(c) of the FD&C Act)
4. If the drug product purports to be a drug that is recognized in an official compendium, it must be packaged and labeled as prescribed in the compendium. (Section 502(g) of the FD&C Act)
5. The drug product's labeling, advertising, and promotion must not be false or misleading. (Sections 502(a), 502(bb),¹⁰ and 201(n) of the FD&C Act)

B. Enforcement Action When a Drug Does Not Meet the Conditions of Section 503A

If FDA determines that an individual or firm compounds a drug product that does not meet the conditions of section 503A, then in addition to the violations listed above in section IV.A., the individual or firm that compounds the drug product may also be subject to a warning letter, seizure of product, injunction, and/or criminal prosecution for violations of sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act.¹¹ Such violations may include, but are not limited to, the following:

1. Producing Adulterated Drugs

In accordance with section 501(a)(2)(B) of the FD&C Act and 21 CFR parts 210 and 211, the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and holding of a drug must conform with current good manufacturing practice (CGMP) requirements. If an individual or firm compounds any drug products that do not meet the conditions of section 503A of the FD&C Act, those drug products would be subject to CGMP requirements.

2. Producing Unapproved New Drugs

In accordance with section 505(a) of the FD&C Act, an individual or firm must not introduce or deliver for introduction into interstate commerce any new drug unless an approved NDA or ANDA is in effect for that drug product. If an individual or firm compounds any drug products that do not meet the conditions of section 503A of the FD&C Act, those drug products would be subject to the new drug approval requirements.

3. Misbranded Drugs

¹⁰ Section 502(bb) was added to the FD&C Act by section 103(b) of the DQSA.

¹¹ See *Medical Ctr. Pharm. v. Mukasey*, 536 F.3d 383, 405 (5th Cir. 2008) (“compounded drugs are in fact ‘new drugs’ as defined by [21 U.S.C.] § 321(p) but are exempt from the requirements of [21 U.S.C.] §§ 351(a)(2)(B), 352(f)(1), and 355 if and only if they comply with the conditions set forth in [21 U.S.C.] § 353a.”).

Contains Nonbinding Recommendations

In accordance with section 502(f)(1) of the FD&C Act and 21 CFR part 201.5, drug products that are not labeled with adequate directions for use are misbranded. If an individual or firm compounds any drug products that do not meet the conditions of section 503A of the FD&C Act, those drug products would be subject to the requirements for adequate directions for use.

In addition to sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act, an individual or firm that compounds any drug products that do not meet the conditions of section 503A of the FD&C Act would be subject to the requirements listed in section IV.A, above, as well as other requirements of the FD&C Act and FDA regulations.

C. Enforcement Approach

Generally, FDA expects to employ a risk-based enforcement approach with respect to violative compounded drugs, giving the highest enforcement priority to compounded drugs and violations of the FD&C Act and FDA regulations that pose the greatest public health risks. However, FDA emphasizes that it need not identify a particular safety problem before pursuing enforcement action.

Attachment 13

Fraud concerns grow as spending on handmade ‘compounded’ drugs soars

By Julie Appleby July 17

Kaiser Health News

Government spending has skyrocketed on “compounded” drugs that retail pharmacists custom make, drawing federal investigators’ attention for potential fraud and overbilling.

Spending on these medications in Medicare’s Part D program rose 56 percent last year, with topical creams and gels, among the costliest products, now priced at hundreds or thousands of dollars per tube. And over just four years, the federal workers’ compensation program saw its spending on compounded medications spike from \$2.35 million to \$214 million.

The increases, along with a sharp jump in the number of patients getting compounded drugs, “may indicate an emerging fraud trend,” said Miriam Anderson, who helped oversee a June [report](#) on Medicare spending by the inspector general at the Health and Human Services Department.

Some prescriptions may not have been medically necessary and others not even dispensed, according to the report.

The practice of compounding, which is done by mixing drugs in pharmacies or special compounding centers, is as old as the pharmacy profession itself. The specifically tailored medications are aimed at patients who cannot take commercially prepared treatments. Patients who cannot swallow pills can get liquid formulations, for example, or those allergic to certain dyes can get products made without them.

But use among Medicare beneficiaries and federal employees in workers’ comp insurance plans has recently soared, according to Anderson’s report and a separate Postal Service inspector general’s [study](#) released in March. Similar run-ups in use and spending also have been noted by private-sector benefit managers.

In the Part D drug program, the number of beneficiaries getting compounded drugs has grown 281 percent since 2006 to nearly 280,000 in 2015. Spending on such drugs reached \$509 million — up 625 percent since 2006, the HHS inspector general report noted, although that amount remained a tiny fraction of the Part D’s total drug spending.

Topical creams and gels, which are often used for pain, are among the fastest-growing category of compounded drugs. Part D spending on those rose 3,466 percent over the decade; the average cost per prescription hit \$331, up from \$40 in 2006.

New rules from the Labor Department went into effect July 1, aimed at slowing spending increases for the federal workers' comp program. Among other changes, the agency will limit initial prescriptions to 90 days.

While legitimately prescribed compounded drugs "can dramatically improve a patient's quality of life," it is important to have "proper controls around billing," John Voliva, executive vice president of the International Academy of Compounding Pharmacists, said Monday in a statement. The HHS inspector general's report demonstrated that such controls "are not in place," he said.

The scrutiny itself has been increasing since a 2012 meningitis outbreak linked to a Massachusetts compounding pharmacy that sold tainted injectable medications. Sixty-four people died.

In the wake of that case, some states tightened their oversight of the industry, particularly of pharmacies making products that must be sterile. Those drugs are not considered approved by the Food and Drug Administration, although the agency does get involved when it is concerned that a site might not be making medications properly or has started to mass-produce treatments rather than preparing them for individual patients.

At times, compounded drugs can be more cost-effective. When Turing Pharmaceuticals last year raised the price of a drug used for patients with compromised immune systems from \$13.50 a pill to \$750, Express Scripts, one of the nation's largest pharmacy benefit managers, partnered with a compounding pharmacy to produce its own version for \$1 a pill.

"Some compounding we should be happy for," said Glen Stettin, senior vice president for clinical, research and new solutions at Express Scripts.

Still, sharp increases in spending prompted Express Scripts to crack down on what pharmacy-made products it will cover — which cut about 1,000 ingredients from the list. The company has since seen its clients' spending on pharmacy-made drugs fall sharply. It also has been targeted by two antitrust lawsuits filed by compounding pharmacies in federal court.

Nationally since 2012, pharmacies have been required to report all ingredients they use to make a compounded drug. The idea was to provide insurers with more information about what they were being billed for and ensure there were no hidden elements.

The effect on drug prices is up for debate. Stettin and others said a few unscrupulous pharmacies began adding more ingredients so they could charge more.

"They are [creating] combinations of things that have never been tested together," he said. "We saw a diaper cream that was billed at \$1,000, where a patient could get one over the counter for \$2.50."

In California, federal investigators say a marketer for one pharmacy paid doctors to write prescriptions for compounded pain creams formulated to include a “five-pack” of the most expensive ingredients. Then the pharmacy could bill the state worker’s compensation program \$3,000 per tube for creams that cost about \$20 to make, according to a federal indictment filed in June.

Also last month, federal prosecutors in Florida unsealed an indictment against a doctor who allegedly was given kickbacks — including a \$72,000 BMW — for sending prescriptions to a particular pharmacy, which then billed Medicare, the military program Tricare and other government health programs for compounded creams. Prices ranged from about \$900 to \$21,000 for a one-month supply, according to court documents.

Medicare has not detailed the actions it might take. The HHS inspector general’s report does not make any recommendations, although investigators expect to issue a follow-up report that will.

Kaiser Health News is a national health policy news service that is part of the nonpartisan Henry J. Kaiser Family Foundation.