



**ENFORCEMENT AND COMPOUNDING COMMITTEE REPORT  
JANUARY 4, 2017**

Amy Gutierrez, PharmD, Chair, Board President

Greg Lippe, Public Member, Vice Chair

Stan Weisser, Licensee Member

Allen Schaad, Licensee Member

Ricardo Sanchez, Public Member

Valerie Muñoz, Public Member

**II. Public Comments on Items Not on the Agenda/Agenda Items for Future Meetings**

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

**III. Enforcement Matters**

**a. CURES 2.0 Prescription Drug Monitoring Program**

**Attachment 1**

**1. Presentation by the California Department of Justice, including Features for Pharmacists**

During this meeting, the committee will hear a presentation on CURES 2.0, California's prescription drug monitoring system for controlled substances.

CURES 2.0 contains features that were not available to pharmacists in the prior system. Mike Small from the Department of Justice will provide an overview of the new system and highlight the new features that can be accessed by pharmacists.

In the coming months, the DOJ intends to convert CURES solely to the 2.0 system, and stop supporting the CURES 1.0 system. Mr. Small will also describe what this means to CURES users.

**2. Discussion and Consideration of CURES System Components**

After Mr. Small's presentation, the committee will have an opportunity to discuss CURES system components, and what features could provide greater utility in the future, and how to ensure wide use of the system by pharmacists.

Staff also is ready to do one last mailing to pharmacists who have not submitted applications to access CURES.

**b. Discussion and Consideration of the University of California, San Diego's Pilot Program to Permit Patients to Access Medications From an Automated Drug Delivery System Not Immediately Adjacent to the Pharmacy**

Background

At the 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 drug delivery system (ADDS) 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 for first time fills.

Since that time the committee received quarterly updates on the study, including usage of the system.

As authorized by the board, UCSD will collect data through the first quarter of 2017 and report their findings at the May 2017 Board Meeting. UCSD will be allowed to continue operating the kiosk until a decision about the expanded use of the ADDS is made.

Prior Committee Discussion

At the August 2016 Enforcement and Compounding Committee Meeting Dr. Hirsch provided an update of the study via telephone and responded to questions from the committee.

During its most recent discussion in August 2016, the committee sought information on patient consultation. The committee was advised that patients receive a text to alert them that their medication is available for pick-up. New prescriptions are placed on hold until a telephone consultation has been completed. Consultations are available 24 hours per day, seven days a week. Upon request, consultations are available for refill prescriptions and OTC medications. If a pharmacist wishes to discuss a prescription with a patient, the pharmacist can place a hold on the medication.

The committee was also advised that this study is not designed to evaluate patient consultation, but a prior study has been done on this topic.

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

During this meeting the committee will hear an update from Dr. Hirsch. **Attachment 2** includes her Power Point presentation as well as the patient consultation study referenced during the last meeting.

**c. Disposal of Sharps in Pharmacy-Operated Drug Take-Back Programs: Discussion and Consideration of Statutory and Regulatory Framework and Possible Changes**

Background

Since late 2014, the board has been working on drug take-back regulations for pharmacies. The rulemaking file to implement the board's regulation requirements was submitted to the Department of Consumer Affairs in December 2016. We hope to have the regulation in effect sometime late in the first quarter of 2017.

During this Meeting

The committee will resume discussions about how to address the return of sharps by the public to pharmacy collection of household pharmaceutical waste. Of particular concern is the increasing widespread distribution and availability of EpiPens to respond to various emergencies in locations such as schools and restaurants.

The board's pending drug take-back regulation provides requirements that signage for collection receptacles contain the following prohibition: "Medical sharps and needles (e.g., insulin syringes) shall not be deposited." This is consistent with pharmacy law. In order to proceed with the rulemaking, the board decided to consider the issue of sharps, which includes such items as needles, syringes, lancets and EpiPens, as a separate piece.

When disposing of sharps, laws have directed that sharps be handled separately and apart from collection of unwanted pharmaceuticals. Towards the end of the board's efforts to develop the take-back regulations, there were requests that the collection receptacles also accept the return of sharps.

At this meeting the committee will discuss how sharps may be disposed of in pharmacy collection processes, and if so, identify possible routes and impediments to such collection.

**Attachment 3** contains some of the relevant laws.

**d. Automated Drug Delivery Systems (ADDS)**

The board's staff continues to be contacted with questions from entities seeking to use automated drug delivery systems (ADDS) in California. Some of these ADDS offer new features not addressed in pharmacy law. During this portion of the meeting, the committee will be able to hear from interested parties about ADDS with new features, discuss current laws and identify possible options for future implementations.

For reference by the committee, multiple laws that govern ADDS are provided in **Attachment 4**.

## **1. Presentation(s) Regarding Options and Features Currently Available in ADDS**

In past months, staff have received inquiries from companies interested in installing their ADDS in facilities in California. During this portion of the meeting, the committee will be able to hear from entities interested in describing the features of their ADDS.

## **2. Discussion and Consideration of Refilling of ADDS in Skilled Nursing Facilities**

In skilled nursing facilities, ADDS units are sometimes installed to permit furnishing of emergency medications or to start initial doses to patients receiving care in the facilities.

The board's staff believes that California law directs that since the undispensed drugs in the ADDS are the stock of the pharmacy, the pharmacy is responsible for restocking the device (pharmacist, or pharmacist intern or pharmacy technician under pharmacist supervision). However, some skilled nursing facilities have begun using nursing staff or perhaps other employees to refill the ADDS.

The California Department of Public Health's consultants and board inspectors note that the refilling of an ADDS is similar to the restocking of the emergency kits in SNFs, which after medication is removed from a kit, the kit is returned to the pharmacy for inventory, restocking and recordkeeping functions.

During this portion of the meeting, the committee will see a presentation about the use of these machines in a skilled nursing facility and begin discussion about restocking duties.

## **3. Discussion and Consideration of Next Steps by the Committee or Board**

Following the above presentations, the committee will discuss future activities and actions involving ADDS.

## **e. Discussion and Consideration of Possible Regulations Regarding Patient Enrollment in Automated Refill Programs for Prescription Medications**

**Attachment 5**

### Background

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.

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 through 2013, the board received over 100 complaints directly related to auto refill programs. 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.

In 2013, the Federal Centers for Medicare & Medicaid Services (CMS) proposed new regulations which resulted in additional rules for auto-refill programs for Medicare patients receiving prescriptions from mail order pharmacies. 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.

#### Prior Committee Discussion

The committee discussed developing requirements for pharmacies to retain signed documentation that patients have "opted in" to a pharmacy's auto-refill program.

Items that the committee has under consideration are:

- 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, additional requirements for pharmacies to notify patients upon pick up, both verbally and in writing (on the receipt), if the prescription was refilled automatically.
- Whether the above requirement for notification should be documented in writing by the pharmacy.
- With respect to both community pharmacies and mail order pharmacies consider requirements for written policies and procedures related to auto-refill. 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.

Committee members supported a motion for board staff to develop an analysis and presentation for the next committee meeting to evaluate options for authorization and maintenance of auto-refill documentation in community and mail order pharmacies. A copy of the draft policy on Automated Refill Programs is included in **Attachment 5**.

**f. Discussion and Consideration of the National Council of State Boards of Nursing (NCSBN) Nursys® e-Notify system**

**Attachment 6**

The board heard public comment about the e-Notify system during a prior meeting and expressed interest in learning about this system. During this meeting, the committee will have an opportunity to learn about this system.

The National Council of State Boards of Nursing (NCSBN)® e-Notify system is a nurse licensure notification system that provides employers of registered nurses, licensed practical nurses, and licensed vocational nurses with real-time email notifications about nurses they employ. This e-Notify system alerts subscribers when changes are made to a nurse's record, including changes to: license status, license expiration, pending license renewal, and public disciplinary action, resolution and alerts. Their website states:

The Nursys nurse licensure and disciplinary database is the repository of the license and disciplinary data of the NCSBN member boards of nursing. Through a written agreement, participating individual boards of nursing designate Nursys as a primary source equivalent database. NCSBN posts the information in Nursys when, and as, submitted by the individual boards of nursing.

There is no charge to subscribe to this system.

**g. Discussion and Consideration of Possible Revision to Title 16 California Code of Regulations Section 1707, Off-Site Storage Waivers, to Address Licensees With Previous Records Violations**

**Attachment 7**

Existing board regulations require that pharmacies retain records of all acquisitions and dispositions of drugs for at least three years. Some pharmacies lack sufficient space within the licensed premises to store these records. Board regulations also authorize the off-site storage of pharmacy acquisition and disposition records for records older than one year for dangerous drugs and two years for controlled drugs if a board-issued waiver is secured for off-site storage. These requirements are specified in section 1707. **Attachment 7** contains copies of these requirements, including the underlying statutory laws referenced in section 1707.

When the regulation permitting off-site storage of records was promulgated (section 1707), only licensees that had no records violations were eligible for an off-site storage waiver. In 2015/16, the board issued 178 off-site records storage waivers and denied approximately 10.

In recent months, the board has identified several pharmacies that wanted off-site storage waivers but were ineligible for waivers because they had been cited for storing records off-site without a waiver. Their attempt to get a waiver was generated by the citation, and a desire to come into compliance, however, the regulation's provisions provide no option for the board to grant such a request for five years.

Staff is requesting that the board reconsider the full prohibition and authorize discretion in the award of off-site waivers. Specifically, staff proposes the following modification to section 1707:

(a) Pursuant to subdivision (e) of Section 4105 of the Business and Professions Code and subdivision (c) of Section 4333 of the Business and Professions Code, a waiver ~~shall~~ may be granted to any entity licensed by the board for off-site storage of the records described in subdivisions (a), (b) and (c) of Section 4105 of the Business and Professions Code ~~unless the applicant has, within the preceding five years, failed to produce records pursuant to Section 4081 of the Business and Professions Code or has falsified records covered by Section 4081 of the Business and Professions Code.~~

**Attachment 7** contains the full text of section 1707 and the additional sections referenced within that regulation's text.

#### **h. Discussion and Consideration of a Possible Amendment to New Business and Professions Code 4316 Regarding Cease and Desist Orders**

##### Proposed Amendment to B&PC 4316

Last year, one provision contained in the board's sunset bill, SB 1193 (Hill, Chapter 484, Statutes of 2016), provided the board with the ability to issue a cease and desist order to an unlicensed entity operating within the board's regulatory jurisdiction without a license where one is required. However, following enactment of SB 1193, staff identified items in this provision needing clarification.

Below are the proposed modifications to section 4316 of the Business and Professions Code. Staff is seeking the committee's recommendation to pursue enactment of these modifications during the 2017 Legislative Session.

(a) The board through its executive officer, is authorized to issue a cease and desist order for operating any facility under this chapter

that requires licensure or for practicing any activity under this chapter that requires licensure without obtaining such licensure.

(b) Whenever the board issues a cease and desist order pursuant to subdivision (a), the board shall immediately issue the facility a notice setting forth the acts or omissions with which it is charged, specifying the pertinent code section or sections and any regulations.

(c) The order shall provide that the facility, within 15 days of receipt of the notice, may request a hearing before the president of the board to contest the cease and desist order. Consideration of the facility's contest of the cease and desist order shall comply with the requirements of Section 11425.10 of the Government Code. The hearing shall be held no later than five days from the date the request of the owner is received by the board. The president shall render a written decision within five days of the hearing. In the absence of the president of the board, the vice president of the board may conduct the hearing permitted by this subdivision. Review of the decision of the president of the board may be sought by the owner or person in possession or control of the ~~pharmacy~~ facility pursuant to Section 1094.5 of the Code of Civil Procedure.

**i. Discussion and Consideration of U.S. Department of Health and Human Services Food and Drug Administration's Article, *Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification Guidance for Industry***

**Attachment 8**

On November 27, 2013, the Drug Supply Chain Security Act (Title II of Public Law 113-54) was signed into law. This law requires the Food and Drug Administration (FDA) to issue guidance to aid trading partners in identifying a suspect product and terminating notifications. A suspect product is defined as product for which there is reason to believe it is potentially counterfeit, diverted, or stolen; is potentially intentionally adulterated, such that the product would result in serious adverse health consequences or death to humans; is potentially the subject of a fraudulent transaction; or appears otherwise unfit for distribution such that the product would result in serious adverse health consequences or death to humans.

In December 2016, the FDA published a guidance document titled *Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification Guidance for Industry* to clarify when manufacturers and other trading partners should notify the FDA if there is a high risk that a product is illegitimate. The FDA is seeking comments and suggestions regarding this document. The comment period ends



February 7, 2017. As part of this discussion, the committee may wish to consider if the board should submit comments.

The guidance identifies specific scenarios that could significantly increase the risk of a suspect product entering the pharmaceutical distribution supply chain; provides recommendations on how trading partners can identify a product and determine whether a product is a suspect product as soon as practicable; and sets forth the process by which trading partners should notify FDA of illegitimate product or products with a high risk of illegitimacy, and how they must terminate the notifications, in consultation with FDA.

Board of Pharmacy Supervising Inspector Michael Ignacio will provide a presentation on components provided in this guidance document concerning suspect product found in the pharmaceutical supply chain and addressed by the Drug Supply Chain Security Act.

#### **j. Discussion and Consideration of Beyond Use Labels in Institutional Settings**

#### **Attachment 9**

At the December 14, 2016, board meeting, the board received a request for a modification of the expiration date used on prescription labels from “exp” to “do not start after.” The specific request is:

Providence Health & Services in Southern California shares the same inpatient medication label template in our EMR system.

The DOPs (covering 6 inpatient, acute-care facilities) met and discussed replacing the current “**Exp:**” field on the med label with “**Do Not Start after:**”.

Part of that decision had to do with using terminology that nursing staff can easily speak to (vs. using the term BUD). The group felt that using language that nurses can articulate will help with compliance.

The behind-the-scenes EMR work is extensive and we wanted to solicit feedback from the Board of Pharmacy before making any changes to our medication labels. I have attached the image of the mock-up. Would you mind giving us some feedback as to the acceptability of using this language on our med labels? If you have any other suggestions, we would appreciate your guidance.

A copy of a sample label for a compounded product submitted by Providence Hospitals as part of their request is provided in **Attachment 9**.

With respect to existing law, Title 16 California Code of Regulations section 1735.1(b) effective 1/1/17 provides that:

(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).

The committee will be able to discuss this request during the meeting.

#### **IV. Compounding Matters**

##### **a. Discussion and Consideration of Statistics for Board-issued Citations and Fines for Compounding Violations**

Board member Schaad will provide information on this topic during the meeting.

##### **b. Update and Discussion of Compounding Construction Waivers for New Requirements in Title 16 California Code of Regulations, Sections 1735 et seq., and 1751 et seq.**

During this portion of the meeting, Supervising Inspector Christine Acosta will provide an update on the number of requests for construction wavier received, granted and denied since the October 2016 Board Meeting.

The committee will also discuss the waiver process and discuss the type of waivers sought.

##### **c. Discussion and Consideration of the United States Government Accountability Office Report to Congressional Committees, *Drug Compounding, FDA Has Taken Steps to Implement Compounding Law, but Some States and Stakeholders Reported Challenges***

#### **Attachment 10**

In mid-November 2016, the GAO released a report on the regulation of compounding by states following the 2012 New England Compounding Center public health emergency. The board was interviewed and provided information for this report.

Below is the executive summary of the 70 page report. The full report is available in **Attachment 10** (<http://www.gao.gov/products/GAO-17-64> )

During this meeting, the committee will have an opportunity to review the findings of the report.

#### **What GAO Found**

GAO’s survey of state pharmacy regulatory bodies found that drugs are compounded in a variety of health care settings, and some data

are collected on the number of entities that compound drugs (drug compounders), but not the volume of compounded drugs. In addition to pharmacies, drug compounding settings include physicians' offices and outsourcing facilities—a new type of facility established by law in 2013, which can compound sterile drugs without patient-specific prescriptions and register with and are inspected by the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS). While FDA and some states collect data on drug compounders, only one state reported collecting data on the number of prescriptions or the volume of compounded drugs. In addition, states GAO surveyed and stakeholders GAO interviewed did not collect data specific to the extent of compounding performed by nonpharmacists, such as physicians.

Nearly all of the states GAO surveyed reported having drug compounding laws, regulations, or policies, though few apply to nonpharmacists, and states conduct inspections and can take actions to enforce them. Less than 20 percent of states reported having laws, regulations, or policies specific to compounding by nonpharmacists (e.g., physicians), and these state laws varied. To help ensure compliance, most states reported inspecting drug compounders, such as pharmacies and outsourcing facilities, and most states can take several types of actions against pharmacies, including monetary fines, and suspension and revocation of a license or registration. Most states reported being satisfied with their communication with FDA and other states, although some reported challenges. About three quarters of the states reported participating in FDA-sponsored activities, such as intergovernmental meetings, and obtaining information from FDA's website. Some states reported challenges with this communication, such as getting FDA to respond to requests for information. In terms of communication between states, most survey respondents reported that they are satisfied with this communication, which occurs through conferences and other activities.

FDA has taken steps to implement its regulatory responsibilities to oversee drug compounding, but states and stakeholder organizations have cited challenges and concerns. FDA has issued numerous draft and final guidance documents related to drug compounding, and conducted more than 300 inspections of drug compounders, which resulted in actions such as FDA issuing warning letters and voluntary recalls of potentially contaminated compounded drugs. Some stakeholder organizations said the amount of time it takes FDA to finalize the guidance and other documents—including those required by the 2013 law—is challenging. FDA officials noted that reviewing the large number of comments received has contributed to the time the agency has taken to finalize them. States and stakeholder organizations also

cited concerns related to access to compounded drugs and differences between states and FDA on the appropriate inspection protocols to use when inspecting drug compounders. In August 2016, FDA changed its procedures to address concerns about the appropriate protocols to use for these inspections.

**d. Review and Discussion of California Law Governing Compounding and Conflicts with USP Section 800**

Staff has been made aware of possible conflicts between our new compounding regulation and USP 800 and other regulatory requirements. We wish to have a public discussion on USP 800 and the California regulations where there are possible conflicts.

Moreover, additional discussion is needed regarding California Business and Professions Code section 4127.7 as it relates to USP 800 and our new regulations requirements for hazardous drugs.

Supervising Inspector Christine Acosta will provide information on this topic to the committee and provide suggested recommendations to address these possible conflicts.

**e. Presentation on Requirements for Sterile Compounding Master Formulas**

During this portion of the meeting, Supervising Inspector Christie Acosta will provide examples of what the board's inspectors will review with respect to master formulas.

**f. Discussion and Consideration of the Proposed Food and Drug Administration Rule, "List of Bulk Drug Substances That Can Be Used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act"**

**Attachments 11**

On December 16, 2016, the Food and Drug Administration proposed rule, [List of Bulk Drug Substances that can be used to Compound Drug Products](#), addressing six bulk drug substances the agency has evaluated and is proposing for inclusion on a list of bulk drug substances that can be used in compounding under section 503A of the Food, Drug, and Cosmetic Act. The proposed rule also proposes that four other bulk drug substances that FDA evaluated not be included on the 503A bulks list. If the proposed rule is finalized, the six bulk drug substances proposed for inclusion will be the first ones included on the 503A bulks list.

As part of its discussion, the committee may wish to discuss if the board should submit comments.

The public comment period on the proposed rule closes in on March 16, 2017. This item is on the agenda in the event the committee recommends that the board submit comments in response to this proposed rule.

Additional information can be found at <https://www.federalregister.gov/documents/2016/12/16/2016-30109/list-of-bulk-drug-substances-that-can-be-used-to-compound-drug-products-in-accordance-with-section> on in attachments section of these materials.

**V. Enforcement Statistics**

- a. Citations and Fines
- b. Medication Errors
- c. Other Enforcement Statistics

**VI. Meeting Dates for 2017**

- April 18, 2017
- July 12, 2017
- October 17, 2017

**ADJOURN**

**4:00 p.m. (or upon conclusion of business)**

# **Attachment 1**

*California Department of Justice*

# CURES 2.0

*Prescription Drug Monitoring Program*

*May, 2016*

# CURES 2.0

## *CURES/PDMP Program*

CURES stores and reports Schedule II, III and IV prescription dispensation data reported by dispensers to DOJ.

Pharmacies and Direct Dispensers are required to report dispensations at least weekly.

CURES receives about one million prescription reports per week.

CURES data reflects dispensing information exactly as it is reported to DOJ.



# CURES 2.0

## *CURES/PDMP Program*

DOJ does not add, modify, or delete prescription data reported to CURES.

DOJ does not validate the accuracy or truthfulness of the data.

The pharmacy or direct dispenser creates and owns the prescription record submitted to DOJ. DOJ is a custodian (and not editor) of these aggregated prescription records.

# CURES 2.0

## *CURES/PDMP Program*

CURES provides registered prescribers and dispensers with a Patient Activity Report (PAR) up to one year patient prescription history to assist health practitioners prescribe safely and to identify patients at risk of addiction.

All California licensed pharmacists and all California licensed prescribers who are authorized to prescribe scheduled drugs are required to register with CURES by July 1, 2016 or upon licensure, whichever occurs later.

SB482 (stats 2016, Chapter 708, Lara) adds H&S section 11165.4, requiring prescribers to consult the CURES database prior to first-time prescribing of a Schedule II, III or IV controlled substance and at least every four months thereafter if the substance remains part of the treatment of the patient.

# CURES 2.0

## *CURES 2.0 Business Analysis*

The iatrogenically addicted patient vs. the doctor shopper

~

The clinical community requires more data presentation than CURES 1.0's simple provisioning of a basic 12-month PAR.

~

Today's technology can provide better monitoring of at-risk prescribing thresholds and is capable of reactive reporting when therapy levels become at-risk.

~

Technology affords the capability to denote treatment exclusivity compacts, and provide prescribers the ability to communicate securely across health care plans.

# CURES 2.0

## *CURES 2.0 User Features*

### *Automated Registration*

California clinical users are provided a fully automated registration process.

### *Delegation Authority*

Prescribers and dispensers can easily assign delegates who can initiate CURES 2.0 patient inquiries on their behalf.

### *Patient Safety Alerts/Messaging*

Prescribers are alerted daily with information regarding their patients who reach various prescribing thresholds.

# CURES 2.0

## *CURES 2.0 User Features*

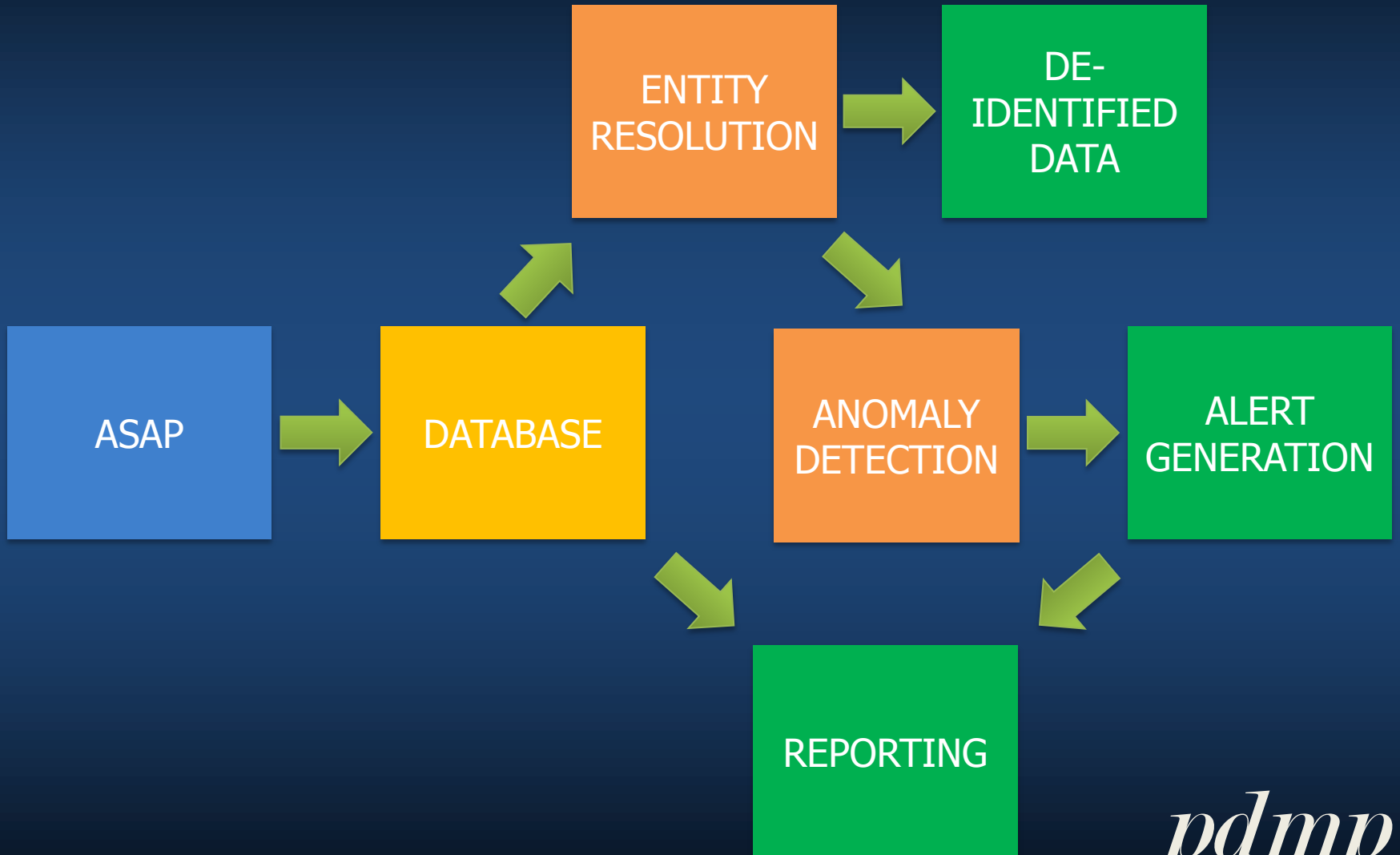
### *Compact Flagging*

Prescribers can easily notate their patients with treatment exclusivity compacts, forewarning other providers that additional prescribing to these patients can be potentially counter-productive to their existing treatment regimen.

### *Peer-to-Peer Communication*

Prescribers and dispensers can instigate alert messages to fellow doctors and pharmacists about mutual patients of concern.

# CURES 2.0



# CURES 2.0

## *De-Duplication*

**PDMP patient data lacks positive identifiers.**

John Doe, Johnnie Doe, John J. Doe, Jack Doe

06/19/1953, 06/19/1935, 06/19/1963

2101 Columbus Avenue, Sacramento, CA 95814

2101 Columbus Street, Sacramento, CA 95814

1201 Columbus Boulevard, San Diego, CA 95828

# CURES 2.0

## *De-Duplication*

Every day approximately 145K new Rx records are added to the CURES 2.0 data base. With this new data, the analytics engine must re-resolve patient, prescriber and dispenser entities across the 1TB database every night.

Person entities are resolved by:

Name and DOB and Zip(5)

OR

Name and Street Address and City

The de-duplicated data also contributes to the quarterly and annual systematic production of 58 county and one statewide de-identified data sets for use by public health officers and researchers.



# CURES 2.0

## *De-Duplication*

Name *and* DOB *and* Zip(5) **OR** Name *and* Street Address *and* City

John Doe  
04/19/1963  
2101 Columbus Ave  
Sacramento, CA 95814

John J. Doe  
04/19/1963  
2100 Columbia Way  
Sacramento, CA 95814

John Doe  
04/19/1963  
1201 Columbus Boulevard  
San Diego, CA 92111

Johnnie Doe  
04/19/1936  
2101 Columbus Avenue  
Sacramento, CA 95814

Jack Doe  
04/19/1963  
2101 Columbus Ave.  
Sacramento, CA 95814

**One John Doe  
Entity**

# CURES 2.0

## *Medicinal Computations*

Once the data is de-duplicated nightly, the analytics engine identifies the resolved person entity's current prescriptions based on date filled and number of days supply.

The resolved person entity's current prescription medicinal therapy levels are calculated and compared against pre-established thresholds. Therapy levels exceeding those thresholds trigger Patient Safety Alerts to current prescribers.

# CURES 2.0

## *Patient Safety Alerts*

1. Rx Recipients Who are Currently Prescribed More than 100 Morphine Milligram Equivalency Per Day
2. Rx Recipients Who Have Obtained Prescriptions from 6 or More Prescribers or 6 or More Pharmacies During Last 6 Months
3. Rx Recipients Who Are Currently Prescribed More than 40 Milligrams Methadone Daily
4. Rx Recipients Who Are Currently Prescribed Opioids More Than 90 Consecutive Days
5. Rx Recipients Who Are Currently Prescribed Both Benzodiazepines and Opioids

# CURES 2.0

## *De-Identified Data*

CURES 2.0 systematically de-identifies county and statewide data sets for County Health Officers and researchers.

Quarterly and annual de-identified data sets are produced.

This data enables counties to calculate current rates of prescriptions, examine variations within the state, and track the impact of safe prescribing initiatives.

# CURES 2.0

[www.oag.ca.gov/cures](http://www.oag.ca.gov/cures)

[CURES@doj.ca.gov](mailto:CURES@doj.ca.gov)

(916) 227-3843

CURES Program  
P.O. Box 160447  
Sacramento, CA 95816

# **Attachment 2**

# Patient request for pharmacist counseling and satisfaction: Automated prescription delivery system versus regular pick-up counter

Jan D. Hirsch, Austin Oen, Suzie Robertson, Nancy Nguyen, and Charles Daniels

## Abstract

**Objectives:** To assess the rate of patient-requested pharmacist counseling for refill prescriptions and satisfaction with pick-up process for patients using an automated prescription delivery system (APDS) versus those using a regular pick-up counter and to explore patient willingness to use an APDS as a tool for pharmacist monitoring of medication therapy outcomes.

**Methods:** In this uncontrolled, cross-sectional, survey study, we assessed use of APDS or the regular counter by 116 patients picking up refill prescriptions at two community pharmacies. The main outcome measures were number of patients requesting pharmacist counseling for refill prescriptions, patient satisfaction with pick-up process, and patient willingness to use an APDS to report medication therapy outcomes.

**Results:** None of the regular counter users and only two APDS users (3.7%) requested counseling for their refill prescription ( $P = 0.126$ ). Almost all patients agreed that they were able to talk to a pharmacist about their prescription if they wanted to do so (95.1% regular counter and 92.3% APDS;  $P = 0.268$ ). The majority (75%) of patients using APDS indicated that they would be willing to use the system to answer questions or perform simple tests to provide information that the pharmacist could use to improve medication effectiveness or reduce adverse effects.

**Conclusion:** Very few patients (ADPS or regular counter) asked to speak to a pharmacist about their refill medications, although it appeared that no perceived barriers to pharmacist access existed. Most APDS patients were willing to use this new technology to provide information about therapy outcomes to the pharmacist. Further exploration and testing of the APDS as a data collection tool to enhance pharmacist access to therapy outcomes is warranted.

**Keywords:** Automation, patient satisfaction, technology, counseling (patient).

*J Am Pharm Assoc.* 2009;49:73–77.  
doi: 10.1331/JPhA.2009.08037

An automated prescription delivery system (APDS) is a new technology, similar to an automated teller machine (ATM), that can be electronically integrated with a pharmacy's management system, allowing patients to use a password to pay for and pick up their refill prescriptions after the normal pharmacist dispensing and verification process has been completed.<sup>1</sup> The California Board of Pharmacy approved the use of APDS on January 26, 2007, but use on a case-by-case basis via a waiver system has been allowed since October 2004.<sup>2</sup> Key requirements were that APDS be used for previously dispensed prescriptions only, that the patient provide written consent expressing desire to use APDS, and that the APDS be located adjacent to the secure pharmacy area. In addition, the regulation specified that APDS should not be used if the pharmacist determines that a patient should be counseled on the dispensed medication and that the pharmacy must provide an immediate consultation with a pharmacist (in person or via telephone) if the patient so requests.

Traditionally, pharmacist contact has been facilitated through the prescription pick-up process when a clerk alerts

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the pharmacist of the need to counsel during the transaction (mandated by law only for new prescriptions in California). Obtaining refill prescriptions at an APDS “kiosk” separate from the regular counter removes patients from this process. At the advent of mail service pharmacy in the late 1980s, similar concerns were raised about changes in direct pharmacist and patient interaction. However, many of these initial concerns have been addressed by mail, fax, or phone service consultations and provision of written patient information.<sup>3</sup>

Implementing APDS technology has potential benefits and risks. Potential benefits for the patient are convenience, less waiting, and ability to pick up refill prescriptions after regular pharmacy hours. Possible benefits to the pharmacy include enhanced patient flow, less congestion, more pharmacist time for patients at the regular pick-up counter, and possibly reduced clerk labor needs. Possible risks of an APDS include lack of patient–pharmacist contact and, thus, less opportunity for pharmacist consultations and appropriate medication management interventions.<sup>4</sup> Opponents of APDS have also argued that the system may not be secure or accurate.<sup>1</sup>

Because the potential benefits of APDS technology are enticing, widespread adoption of this technology could be rapid and affect pharmacy practice considerably. Evaluating the effect of using APDS on patient–pharmacist interactions is warranted at this early stage of APDS evolution.

**Objectives**

We sought to assess the rate of patient-requested pharmacist counseling for patients using APDS versus those using a regular pick-up counter to obtain refill prescriptions, to assess the satisfaction of patients using APDS versus those using a regular pick-up counter to obtain refill prescriptions, and to explore patient willingness to use APDS in the future as a tool for pharmacist monitoring of medication therapy outcomes.

**Methods**

This study was conducted at two community pharmacies, which were under the same corporate ownership, in northern San Diego, CA. These pharmacies were the first in California to use APDS technology. The APDS (ScriptCenter—Asteres; Figure 1) had been in use for at least 12 months at each location prior to the study. The pharmacies were 15 miles apart within an upper-middle-class, primarily English-speaking area. Pharmacy operating characteristics were fairly similar at each site (Table 1). Using APDS did not change the manner in which the refill prescription was ordered by the patient or filled by the pharmacist. The only difference in the process was that completed prescriptions were placed inside the APDS instead of being placed in the traditional holding area for pick-up at the counter. A description of the technical and security features of the APDS used in this study can be found at [www.asteres.com](http://www.asteres.com). Inclusion criteria were that the patient was receiving a refill prescription either at the regular counter or APDS, was able to read and understand written information, and was 18 years of age or older. Patients picking up their prescription at the APDS had already decided to do so before participating in this study

**Table 1.** Descriptive characteristics of pharmacy sites and survey respondents by site<sup>a</sup>

Characteristic	Site 1	Site 2	P
Operating hours per week			
Pharmacy	82	82	
APDS	119	168	
Average no. prescriptions per day	250	232	
Average refill (%)	60	60	
n	39	77	0.021
No. regular counter (%)	15 (38.5)	47 (61.0)	
No. APDS (%)	24 (61.5)	30 (39.0)	
Gender, no. (%)			0.712
Men	14 (36.0)	25 (32.5)	
Women	25 (64.0)	52 (67.5)	
Age, no. (%) <sup>b</sup>			0.004
18–40 years	8 (22.2)	37 (48.1)	
41–64 years	20 (55.6)	36 (46.8)	
≥65 years	8 (22.2)	4 (5.2)	
Person picking up prescription, no. (%)			0.165
Patient	30 (76.9)	67 (87.0)	
Other for patient	9 (23.1)	10 (13.0)	

Abbreviation used: APDS, automated prescription delivery system.

<sup>a</sup>Patients with complete data collected during study time periods.

<sup>b</sup>Missing three patients for site 1.



**Figure 1.** The ScriptCenter, an automated prescription delivery system



**Table 2.** Characteristics respondents: regular counter versus APDS users (sites combined)

	Regular counter		APDS	<i>P</i>
	No. (%)	No. (%)	No. (%)	
n	62	54		
Gender <sup>a</sup>				0.786
Men	20 (32.8)	19 (35.2)		
Women	41 (67.2)	35 (64.8)		
Age <sup>b</sup>				0.186
18–40 years	20 (32.8)	25 (48.1)		
41–64 years	35 (57.4)	21 (40.4)		
≥65 years	6 (9.8)	6 (11.5)		
Person picking up prescription				0.053
Patient	48 (77.4)	49 (90.7)		
Other for patient	14 (22.6)	5 (9.3)		

Abbreviation used: APDS, automated prescription delivery system.

<sup>a</sup>Missing for one regular counter patient.

<sup>b</sup>Missing for two APDS and 1 regular counter patient.

and had been trained and received their username via regular pharmacy operations.

This study was approved by the University of California, San Diego, Human Research Protection Program. Data were collected during a 1-week period (February 5–10, 2007), Monday through Friday, 3:00 pm to 7:00 pm, and Saturday, 11:00 am to 2:00 pm. These times were chosen based on historical data indicating that they were the busiest days and times of the week. A student pharmacist, trained in the study data collection requirements, was stationed in the pharmacy area during these times to answer questions. The student was instructed not to reveal the specific objectives or comparative nature of the study. Data collection forms were completed for each patient picking up a refill prescription from the regular counter or APDS during the study period (Appendix 1 in the electronic version of this article, available online at [www.japha.org](http://www.japha.org)). Questions regarding whether the patient or someone else picked up the prescription, if they requested to speak to a pharmacist, and, if so, the category of information needed (medication, payment related, or other) were self-reported by patients using the APDS and observed and recorded by the pharmacy clerk or attending student pharmacist for patients using the regular counter. All other questions were self-reported. Three questions assessed patient satisfaction with wait time, convenience of the pick-up process, and access to a pharmacist. A 5-point Likert-type scale (strongly agree to strongly disagree), was used to quantify responses as described previously.<sup>5,6</sup> An additional question for APDS users assessed patient willingness to use the system in the future to answer questions or perform simple tests to provide information that the pharmacist could use to improve medication effectiveness or reduce adverse effects. Patients responded on a 5-point Likert-type scale ranging from very willing to strongly unwilling.

Statistical analyses were performed using SPSS version 15.0 (SPSS, Chicago). Descriptive statistics were calculated for each study variable. Frequency distributions were used to

**Table 3.** Counseling request and satisfaction: regular counter versus APDS users

	Regular counter		APDS	<i>P</i>
	No. (%)	No. (%)	No. (%)	
Asked to speak to a pharmacist?				0.126
Yes	0 (0.0)	2 (3.7)		
No	62 (100.0)	52 (96.3)		
Was able to talk to pharmacist if wanted <sup>a</sup>				0.268
Strongly agree	31 (50.8)	22 (42.3)		
Agree	27 (44.3)	26 (50.0)		
Not sure	1 (1.6)	2 (3.8)		
Disagree	0 (0.0)	2 (3.8)		
Strongly disagree	2 (3.3)	0 (0.0)		
Waited a long time to pick up prescription <sup>b</sup>				0.188
Strongly agree	1 (1.6)	2 (3.7)		
Agree	5 (8.2)	1 (1.9)		
Not sure	3 (4.9)	0 (0.0)		
Disagree	21 (34.4)	17 (31.5)		
Strongly disagree	31 (50.8)	34 (63.0)		
Overall process to pick up prescription was convenient <sup>b</sup>				0.583
Strongly agree	31 (50.8)	29 (53.7)		
Agree	22 (36.1)	22 (40.7)		
Not sure	2 (3.3)	0 (0.0)		
Disagree	3 (4.9)	2 (3.7)		
Strongly disagree	3 (4.9)	1 (1.9)		
Willing to use APDS to provide information to improve medication management <sup>c</sup>				NA
Very willing	NA	16 (30.8)		
Somewhat willing	NA	23 (44.2)		
Not sure	NA	8 (15.4)		
Unwilling	NA	5 (9.6)		
Strongly unwilling	NA	0 (0.0)		

Abbreviation used: APDS, automated prescription delivery system; NA, not applicable.

<sup>a</sup>Missing for two APDS and one regular counter patient.

<sup>b</sup>Missing for one regular counter patient.

<sup>c</sup>Missing for two APDS patients.

examine patient demographics, to examine counseling rates, and to describe the responses to satisfaction questions. Comparisons among groups were conducted using chi-square analyses. Statistical significance was based on an alpha of 0.05.

## Results

A total of 116 respondents returned completed surveys; 39 from site 1 and 77 from site 2 (Table 1). The majority of survey respondents were women and were picking up a prescription for themselves at each site. A larger percentage of respondents at site 1 were 65 years of age or older ( $P = 0.004$ ) and used the APDS as opposed to the regular counter ( $P = 0.021$ ) to pick up their refill prescriptions. Based on historical data for the average number of refill prescriptions dispensed per day at each site and an estimate of 1.5 prescriptions per patient, the 39 respondents at site 1 and 77 respondents at site 2 represented approximately 20% and 39% of the daily number of patients

picking up refill prescriptions during the study data collection time brackets, respectively.

When data from the two sites were combined for subsequent analyses due to small sample sizes at each site, the response rate was approximately 29%.

#### APDS versus regular counter users

No difference was observed in the gender or age distribution of respondents picking up their prescription at an APDS versus regular counter ( $P = 0.786$  and  $P = 0.186$ , respectively) (Table 2). The patient was almost always the person picking up their refill prescription at the APDS (90.7%) compared with the regular counter, where 22.6% of prescriptions were picked up by someone other than the patient ( $P = 0.053$ ).

#### Counseling requests and satisfaction

Very few patients asked to speak to a pharmacist when receiving their refill prescription (no regular counter users and only two [3.7%] APDS users;  $P = 0.126$ ) (Table 3). One APDS patient had a question about payment and the other had a nonmedication question. Almost all patients agreed that they were able to talk to a pharmacist about their prescription if they wanted to do so (95.1% regular counter and 92.3% APDS;  $P = 0.268$ ). The majority of regular counter and APDS users disagreed that they had waited a long time to pick up their prescription (85.2% regular counter and 94.5% APDS;  $P = 0.188$ ) and agreed that the pick-up process was convenient (86.9% regular counter and 94.4% APDS;  $P = 0.583$ ). The majority (75%) of patients using APDS also indicated that they would be willing to use the system to answer questions or perform simple tests to provide information that the pharmacist could use to improve medication effectiveness or reduce adverse effects.

### Discussion

This is the first study, to our knowledge, that has systematically assessed the rate of patient request for pharmacist counseling for patients receiving their refill prescriptions at an APDS versus regular pharmacy counter. No significant difference was observed in the age or gender of patients using APDS or regular counter to pick up refill prescriptions. However, APDS users were more likely to be the patient picking up their own prescription compared with regular counter users. This was not unexpected because APDS requires a personal username and password for use.

Although pharmacist counseling for prescriptions has been generally accepted as an important part of the medication dispensing process and is required by law for new prescriptions in California, the results of this study suggest that counseling is rarely requested by patients for their refill prescriptions. Although only two patients asked to speak to a pharmacist about their refill medication, almost all patients (APDS and regular counter) felt that they were able to speak to a pharmacist if they had wanted to do so. The majority of patients also agreed that their wait time was not long and that the overall prescription pick-up process was convenient at both APDS and the regular counter. This implies that no perceived barriers to pharmacist

access for patients at the regular counter or APDS existed, but instead that patients simply did not feel the need to ask the pharmacist questions about their refill medication. Potential reasons for patients not asking questions about their refill medication include a lower need for information for a continuing medication compared with a new medication, availability of information via other sources (e.g., printed information with prescriptions or via Internet sources), or lack of patient time. A similar study of an ambulatory clinic-based community pharmacy in San Diego found a similar low rate (3%) of counseling for refill prescriptions despite the fact that patients receiving any prescription medications (refill or new) in this pharmacy were routinely asked if they would like to speak to a pharmacist.<sup>7</sup>

Any new prescription delivery technology will elicit controversy, but the possible future benefits should also be considered. It was encouraging that the majority of APDS users indicated that they were willing to use the system to answer questions or perform simple tests to provide information that the pharmacist could use to improve medication effectiveness or reduce adverse effects. Using APDS to collect patient-reported outcomes could fill an information void for the pharmacist. Most community pharmacists today do not have the same degree of access to documented clinical outcomes for patients as a physician or nurse would have in a clinic setting. Expanding the APDS scope to allow patients to answer simple questions about their symptom response or possible adverse effect occurrence or to electronically download laboratory values (e.g., blood glucose history since last visit) could provide pharmacists with outcomes data on an ongoing basis. Future research should investigate opportunities to optimize the use of APDS technology to expand the effectiveness of the pharmacist's role in medication therapy management.

### Limitations

The major limitations of this study are that it was conducted on a small convenience sample of patients in only two pharmacies that were among the first to use APDS technology. Patients self-selected to use APDS or the regular counter for their refill pick up; however, this trend would occur in actual practice. Randomization, therefore, would have strengthened the study design but would not have been practical. Our observation period was limited to busy time periods in a single week, and our questionnaire had a very limited number of questions to minimize survey completion time; thus, the scope of our study is limited. Notably, the focus of our study was refill prescriptions because these were the only type of prescriptions delivered via APDS. Therefore, we only measured pharmacist counseling related to refill prescriptions. We did not examine any other patient-pharmacist interactions that occur throughout the course of pharmacy practice (e.g., new prescriptions, over-the-counter medication, disease questions, testing). Our results from two pharmacies cannot be considered representative of the APDS experience in community pharmacies overall but can be used to inform future studies.

Future studies need to include a larger number and wider

variety of pharmacies using APDS technology as its usage expands. Replicating this study at other pharmacy practice sites would provide, at a minimum, a benchmark for interpreting refill consultation rates—at APDS and the regular counter—that does not exist currently. In addition, although counseling for new prescriptions may be a legal requirement, measuring the rate of actual patient acceptance, and thus occurrence, of pharmacist counseling for new prescriptions is also warranted to provide a comparative value for refill counseling rates (APDS or regular counter). Further exploration and testing of APDS as a data collection tool that would give the pharmacist access to therapy outcomes is perhaps the most important next step. APDS technology has the potential to be more than a one-sided delivery mechanism; instead, it could be a new two-way communication system between the patient and the pharmacist for information that was not able to be systematically exchanged in the past. APDS could be used to facilitate the patient–pharmacist interaction to enhance the pharmacist’s ability to identify and resolve drug therapy problems and the patient’s knowledge of when to speak to a pharmacist (e.g., any new adverse effects).

### Conclusion

Very few patients using APDS or the regular counter asked to speak to a pharmacist about their refill medications, although almost all patients believed that they could speak to a pharmacist if they had wanted to do so. Because the majority of patients agreed that their wait time was not long and that the overall prescription pick-up process was convenient, no perceived barriers to pharmacist access appear to exist; patients simply did not perceive the need to ask the pharmacist questions about their refill. Further exploration and testing of APDS as a data collection tool to enhance pharmacist access to ther-

apeutic outcomes is warranted. The effect of APDS technology on pharmacist–patient interactions and data collection in the context of prescription-specific counseling versus the broader, more multifaceted, role of pharmacists providing medication therapy management services would also be useful to explore.

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**Appendix 1. Data collection form (APDS version)**

**1. Your Age:**  18-40  41-64  65 and older

**2. Your Gender:**  Male  Female

**3. Did you pick up your own prescriptions?**  Yes  No

**4. Did you request to speak to a Pharmacist?**  Yes  No

**5. If requested, why did you request to speak to pharmacist?**

- Medication related questions
- Payment or insurance questions
- Other

**6. I waited a long time to pick up prescription(s) from the ScriptCenter.**

Strongly Agree	Agree	Not Sure	Disagree	Strongly Disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**7. Overall the process to pick up prescription(s) was convenient**

Strongly Agree	Agree	Not Sure	Disagree	Strongly Disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**8. I feel I was able to talk with a pharmacist if I wanted to do so.**

Strongly Agree	Agree	Not Sure	Disagree	Strongly Disagree
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**9. In the future, the ScriptCenter may collect information the pharmacist can use to help improve your medication's effectiveness or reduce any side effects you may experience.**

**Please indicate your willingness to answer questions or perform a simple test to gather this information.**

Very Willing	Somewhat Willing	Not Sure	Unwilling	Strongly Unwilling
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

# Study of Expanded Use of an Automated Delivery Device

**UPDATE**  
**January 4, 2017**

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Jan D. Hirsch, BPharm, PhD

*UCSD Skaggs School of Pharmacy & Pharmaceutical Sciences*



# Update

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- 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



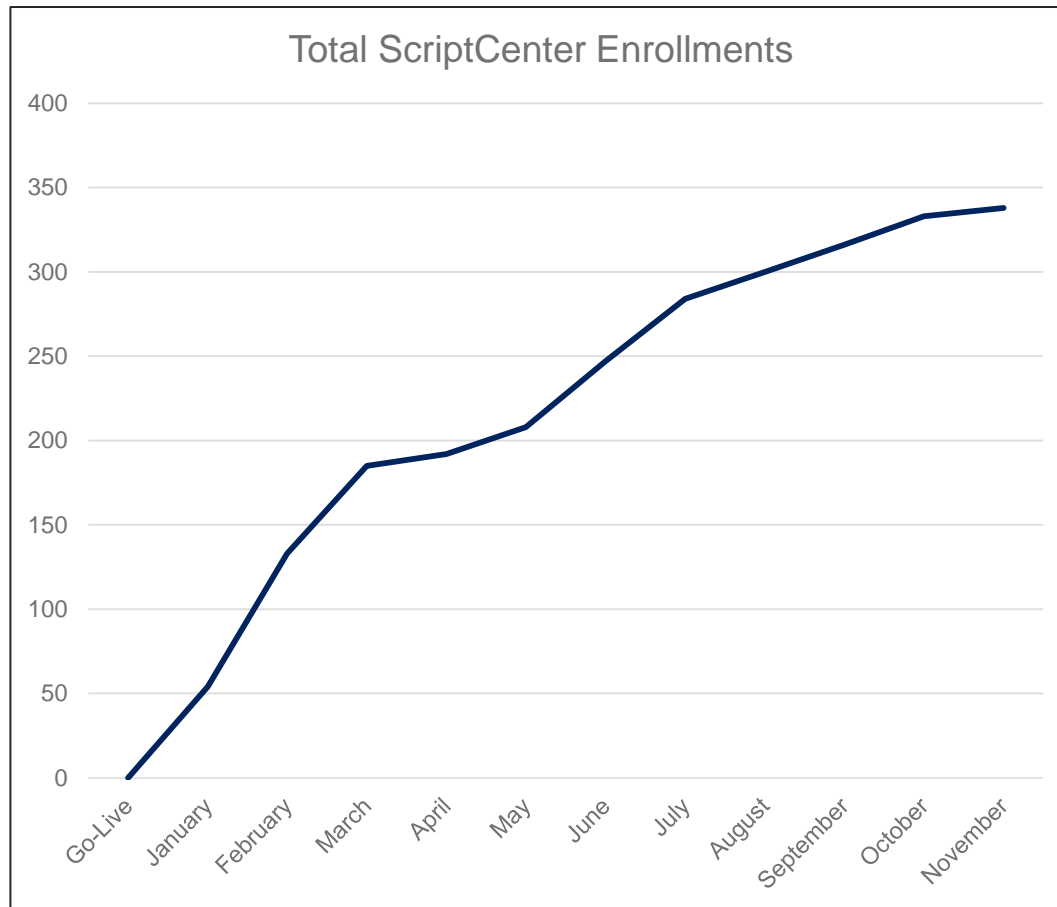
*First Floor Lobby Sharp Memorial Hospital*



# ScriptCenter Kiosk Activity 1/20/16 through 11/30/16

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

## ENROLLMENT



**338 users**  
(7% Campus Employees)

Total Campus Employees  
4,820

Day Shift = 2,592  
PM+ Variable = 2,228

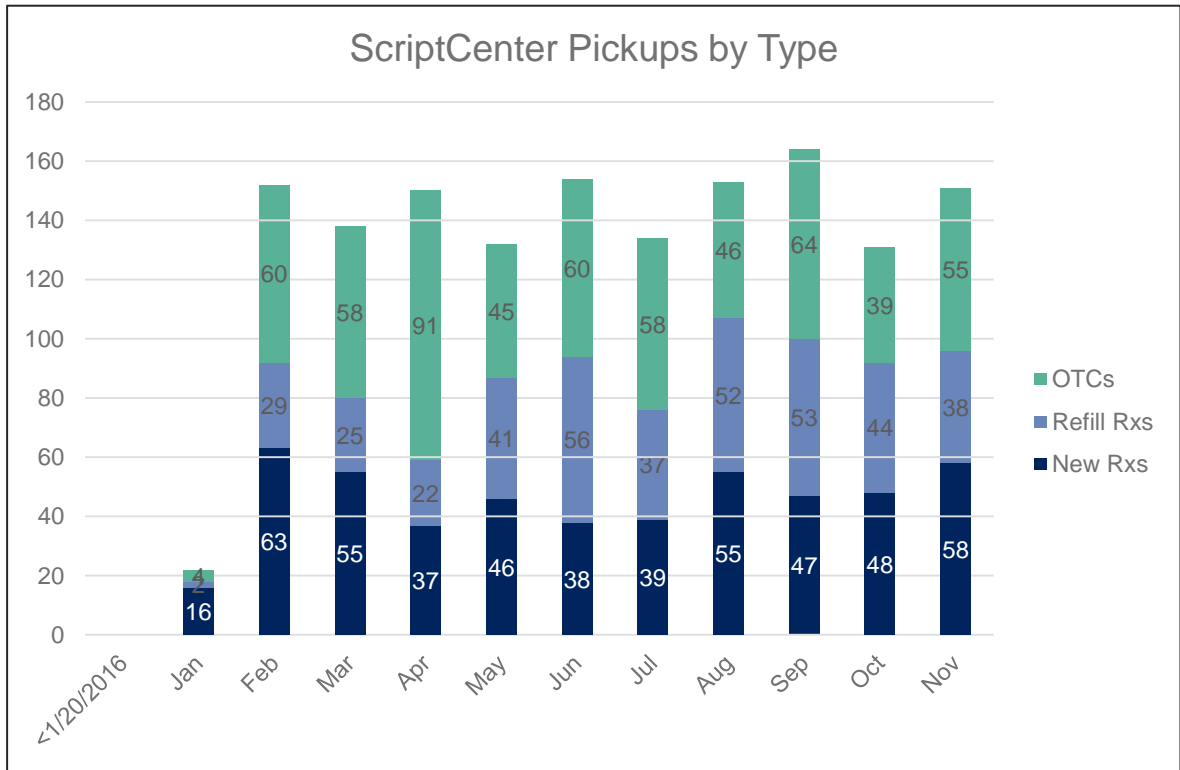
If estimate 2 per household  
= 9,640



# ScriptCenter Kiosk Activity 1/20/16 through 11/30/16

## Pickups by Type

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



- Average 88 Rxs per month
- Surpassed number needed for study on 12/7/16 (820)
- Data collection complete end of December

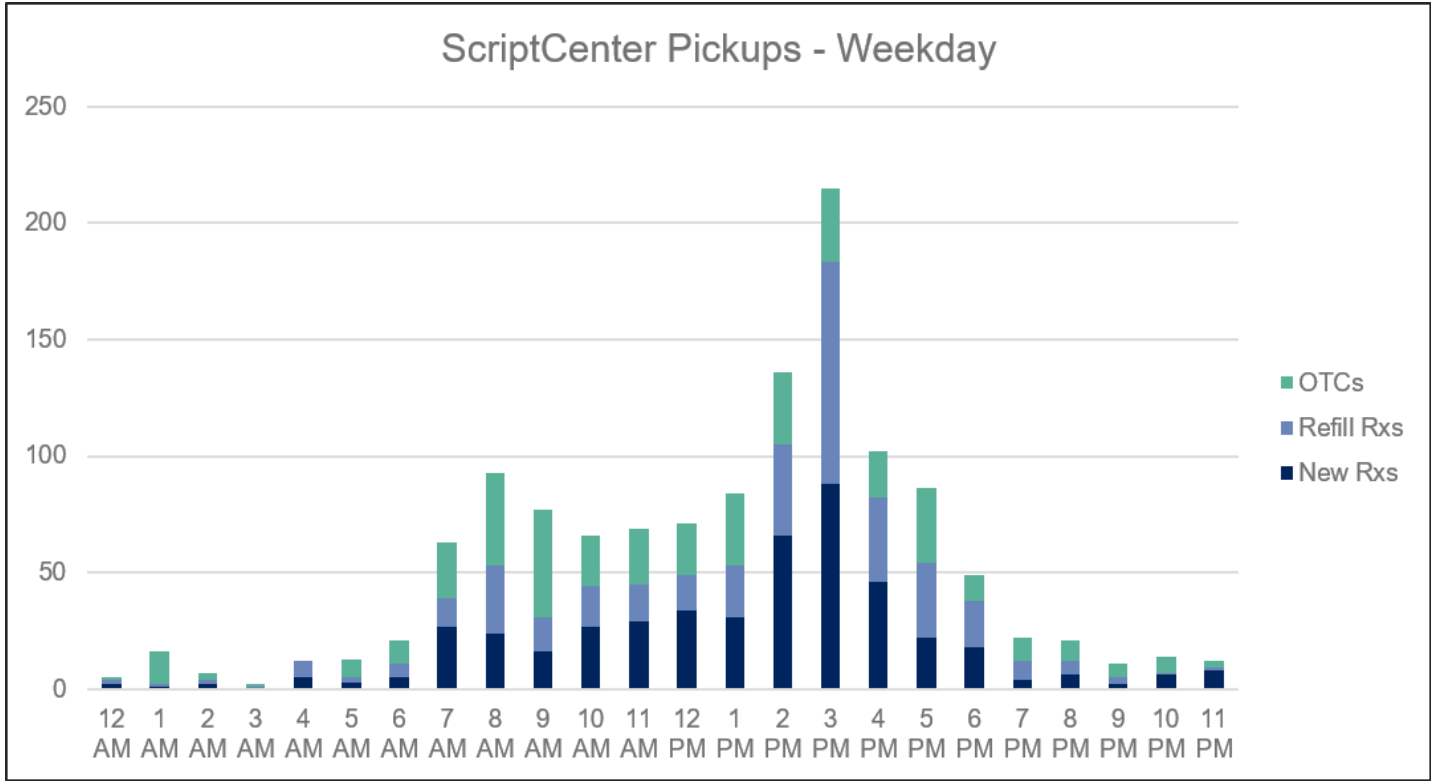
338 Users

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 11/30/16

Pickups by Time Weekday

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



Day Shift  
2,592

PM +  
Variable  
2,228

338 Users

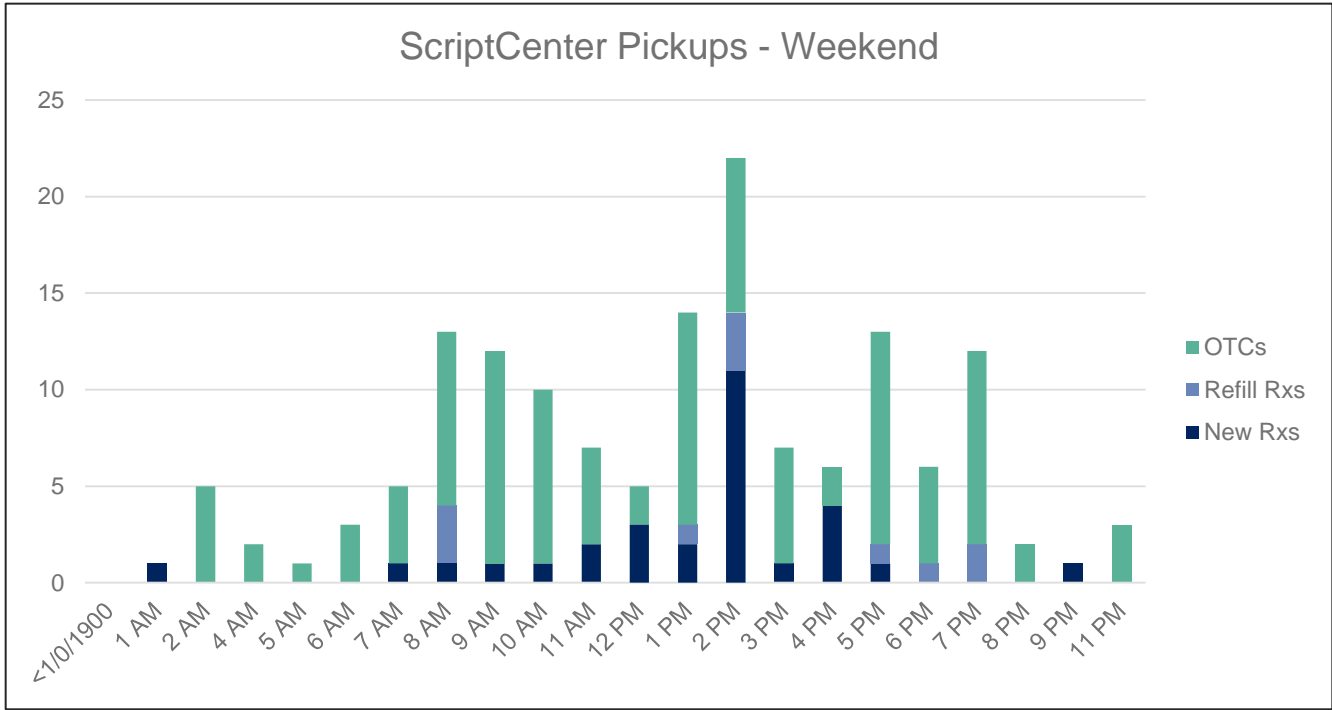
Pharmacy  
Closed

Pharmacy  
Closed

# ScriptCenter Kiosk Activity 1/20/16 through 11/30/16

Pickups by Time Weekend

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



Day Shift  
2,592

PM + Variable  
2,228

338 Users

Pharmacy Closed

# ScriptCenter Kiosk During vs. After Hours Pickup

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

## **1,481 Total Pickups**

1,064 (72%) During pharmacy hours  
417 (28%) After pharmacy hours

## **502 New Rx Pickups**

390 (78%) During pharmacy hours  
112 (22%) After pharmacy hours

## **399 Refill Rx Pickups**

325 (81%) During pharmacy hours  
74 (19%) After pharmacy hours

## **580 OTC Pickups**

349 (60%) During pharmacy hours  
231 (40%) After pharmacy hours

Day Shift 2,592

PM + Variable  
2,228

338 Users

Data is 1/20/16 through 11/30/16.  
After hours includes weekday & weekend times pharmacy is closed.

# ScriptCenter Kiosk Consultations Study Period (3/1/16 – 11/30/16)

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

	Total prescriptions with a new Rx #, pharmacist released for pick up at ScriptCenter	New Rxs Requiring Counseling (including transferred) Counseling Provided	New Rxs Not Requiring Counseling (due to Sharp re write with no changes) Counseling Not Required
March	49	28	21
April	37	17	20
May	41	28	13
June	42	22	20
July	45	32	13
August	63	33	30
September	55	23	32
October	49	16	33
November	59	38	21

- New prescription # (number) is Asteres tracking method, some may not be “new” to pharmacy or patient.
- Pharmacist releases Rx after required counseling provided.
- Total Rx’s released may not match number of pick-ups per month on slide 5 due to pick-up occurring in month following release.

# 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 Pickup
- Kiosk Patient Satisfaction

Regular Counter

- RTS rate\*
- Consultation Log (Sample: New Rx's weeks of 5/23&6/6 & 12/5)
- Time to Pickup\*

RTS = Return to Stock

\* For employees and dependents

# Study Timetable

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- Q4 2015 Pre-kiosk 6-month data collection phase
- Q1 2016 Implement Kiosk device (1/20/16)  
Refine data collection tools & process  
Deployment of program/enroll patients
- Q2-Q4 2016 Post-kiosk implementation  
Data collection March – December
- Q1 2017 Data analysis
- Q2 2017 Report Results to Board
  - April 18<sup>th</sup>, 2017 Enforcement Committee
  - May 3-4<sup>th</sup>, 2017 BoardContinue Kiosk operation until regulation

1713 revised





# Questions?

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**UC San Diego**  
SKAGGS SCHOOL OF PHARMACY  
AND PHARMACEUTICAL SCIENCES

# **Attachment 3**

**Title 16. Board of Pharmacy**  
**Third Modified Text (CLEAN)**

**Proposal to add** new Article 9.1 of Division 17 of Title 16 of the California Code of Regulations and a new Article title as follows:

**Article 9.1. Prescription Drug Take-Back Services**

**Proposal to add** § 1776 of Article 9.1 of Division 17 of Title 16 of the California Code of Regulations as follows:

**Section 1776 Prescription Drug Take-Back Services: Authorization**

Pharmacies, hospitals/clinics with onsite pharmacies, distributors and reverse distributors licensed by the board may offer, under the requirements in this article, specified prescription drug take-back services through collection receptacles and/or mail back envelopes or packages to provide options for the public to discard unwanted, unused or outdated prescription drugs. Each entity must comply with regulations of the federal Drug Enforcement Administration (DEA) and this article.

Only California-licensed pharmacies, hospitals/clinics with onsite pharmacies, and drug distributors (licensed wholesalers and third-party logistics providers) who are registered with the DEA as collectors and licensed in good standing with the board may host a pharmaceutical take-back receptacle as authorized under this article.

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

Reference: Sections 4005, 4026.5, and 4301, Business and Professions Code and Section 1317.40, Title 21 Code of Federal Regulations.

**Proposal to add** § 1776.1 of Article 9.1 of Division 17 of Title 16 of the California Code of Regulations as follows:

**Section 1776.1 Pharmacies**

- (a) Pharmacies may provide take-back services to the public. Retail pharmacies and hospital/clinics with onsite pharmacies may maintain collection receptacles in their facilities. Pharmacies may offer drug take-back services as specified in section 1776.4 in skilled nursing facilities licensed under Health and Safety Code section 1250(c).
- (b) There are multiple federal, state and local requirements governing the collection and destruction of dangerous drugs. Pharmacies are expected to know and adhere to these requirements when operating a prescription drug take-back program.
- (c) For purposes of this article, prescription drugs means dangerous drugs as defined by Business and Professions Code section 4022, which includes controlled substances. Controlled substances may be commingled in collection receptacles or mail back envelopes or packages with other dangerous drugs.
- (d) Once drugs are deposited into a collection receptacle or mail back envelopes or packages by a consumer, they are not to be removed, counted, sorted or otherwise individually handled.

- (e) The collection receptacle shall contain signage that includes:
  - (1) The name and phone number of the responsible pharmacy;
  - (2) Medical sharps and needles (e.g., insulin syringes) shall not be deposited; and
  - (3) Consumers may deposit prescription drugs including Schedule II-V controlled substances.
- (f) Prescription drugs that are eligible for collection as part of drug take-back services maintained by pharmacies are only those prescription drugs that have been dispensed by any pharmacy or practitioner to a consumer. Dangerous drugs that have not been dispensed to consumers for use (such as outdated drug stock in a pharmacy, drug samples provided to a medical practitioner or medical waste) may not be collected as part of a pharmacy's drug take-back service.
- (g) As part of its drug take-back services, a Pharmacy shall not:
  - (1) Review, accept, count, sort, or otherwise individually handle any prescription drugs from consumers.
  - (2) Accept or possess prescription drugs returned to the pharmacy from skilled nursing facilities, residential care homes, health care practitioners or any other entity.
  - (3) Dispose of quarantined, recalled or outdated prescription drugs from pharmacy stock.
- (h) A pharmacy must be registered with the federal DEA as a collector for purposes of maintaining a prescription drug take-back collection receptacle. Such pharmacies cannot employ anyone convicted of a felony related to controlled substances, or anyone who has had a DEA permit denied, surrendered or revoked.
- (i) Any pharmacy that maintains a drug take-back collection receptacle as authorized in this article shall notify the board in writing within 30 days of establishing the collection program. Additionally:
  - (1) Any pharmacy that ceases to maintain a drug take-back collection receptacle shall notify the board in writing within 30 days.
  - (2) Any pharmacy maintaining a collection receptacle shall disclose to the board that it provides such services annually at the time of renewal of the pharmacy license, and shall identify all locations where its collection receptacles are located.
  - (3) Any tampering with a collection receptacle or theft of deposited drugs shall be reported to the board in writing within 14 days.
  - (4) Any tampering, damage or theft of a removed liner shall be reported to the board in writing within 14 days.
- (j) If the pharmacy ceases to maintain a registered collection receptacle, the pharmacy must notify the DEA within 30 days.
- (k) A pharmacy shall not provide take-back services to consumers if, in the professional judgment of the pharmacist-in-charge, the pharmacy cannot comply with the provisions of this article or the DEA rules.
- (l) A pharmacy shall not provide take-back services to consumers if the pharmacy or the pharmacist-in-charge is on probation with the board, and, if the pharmacy had previously provided take-back services, the pharmacist-in-charge shall notify the board and the DEA as required in subsections (h) and (i), above.

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

Reference: Section 4005 and 4022, Business and Professions Code and Sections 1301.71, 1317.30, 1317.40, Title 21 Code of Federal Regulations.

**Proposal to add § 1776.2** of Article 9.1 of Division 17 of Title 16 of the California Code of Regulations as follows:

**1776.2 Pharmacies Offering Mail Back Envelope or Package Services**

- (a) Pharmacies that provide prescription drug take-back services may do so by providing preaddressed mailing envelopes or packages to allow a consumer to return prescription drugs to an authorized DEA destruction location.
- (b) All envelopes and packages must be preaddressed to a location registered with the DEA as a collector. The pharmacy is responsible for ensuring that all preaddressed envelopes and packages it makes available to the public are preaddressed for delivery to facilities that comply with this section.
- (c) The preaddressed envelopes and packages must be water and spill proof, tamper evident, tear resistant and sealable. The exterior shall be nondescript and not include markings that indicate the envelope or package contains prescription drugs. Postage shall be prepaid on each envelope or package.
- (d) The preaddressed envelope and package shall contain a unique identification number for each envelope and package, and instructions for users that indicate the process to mail back drugs.
- (e) A pharmacy shall not accept any mail back packages or envelopes that contain drugs unless they are registered as a collector and have an onsite method of destruction that complies with the DEA requirements. Instead, consumers shall be directed to mail the envelopes or packages.

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

Reference: Section 4005, Business and Professions Code and Sections 1317.70 and 1317.70, Title 21 Code of Federal Regulations.

**Proposal to add § 1776.3** of Article 9.1 of Division 17 of Title 16 of the California Code of Regulations as follows:

**1776.3 Collection Receptacles in Pharmacies**

- (a) A pharmacy may maintain a collection receptacle for the public to deposit their unwanted prescription drugs for destruction. The pharmacy is responsible for the management and maintenance of the receptacle. The receptacle shall be substantially constructed, with a permanent outer container and a removable inner liner. The collection receptacle shall be locked at all times to prevent access to the inner liner.
- (b) A pharmacy maintaining a collection receptacle must securely fasten the receptacle to a permanent structure so it cannot be removed. The receptacle shall be installed in an inside location. Except as provided in subsection (c), the receptacle is visible to pharmacy or DEA registrant employees, but not located in or near emergency areas, nor behind the pharmacy's counter.
- (c) In hospitals/clinics with a pharmacy on the premises, the collection receptacle must be located in an area that is regularly monitored by pharmacy or DEA registrant employees and not in the proximity of any emergency or urgent care areas. When no pharmacy or DEA registrant employees are present, the collection receptacle shall be locked so that

- drugs may not be deposited into the collection receptacle.
- (d) The receptacle shall include a small opening that allows deposit of drugs into the inside of the receptacle directly into the inner liner, but does not allow for an individual to reach into the receptacle's contents. During hours when the pharmacy is closed, the collection receptacle shall not be accessible to the public for deposit of drugs. The pharmacy shall lock the deposit opening on the collection receptacle.
  - (e) A pharmacy shall direct consumers to directly deposit drugs into the collection receptacle. A Pharmacy shall not accept, count, sort or otherwise handle prescription drugs from consumers.
  - (f) A liner as used in this article shall be made of material that is certified by the manufacturer to meet the American Society for Testing Materials (ASTM) D1709 standard test for impact resistance of 165 grams (drop dart test), and the ASTM D1922 standards for tear resistance of 480 grams in both parallel and perpendicular planes.
    - (1) The liner shall be waterproof, tamper evident and tear resistant.
    - (2) The liner shall be opaque to prevent viewing or removal of any contents once the liner has been removed from a collection receptacle. The liner shall be clearly marked to display the maximum contents (for example, in gallons). The liner shall bear a permanent, unique identification number established by the pharmacy or pre-entered onto the liner by the liner's manufacturer or distributor.
  - (g) The liner shall be removable as specified in this section. The receptacle shall allow the public to deposit prescription drugs into the receptacle for containment into the inner liner, without permitting access to or removal of prescription drugs already deposited into the collection receptacle and liner. Once a prescription drug or any other item is placed in the collection receptacle, the prescription drug or item cannot be removed, counted, sorted or otherwise individually handled.
  - (h) If the liner is not already itself rigid or already inside of a rigid container when it is removed from the collection receptacle, the liner must be immediately, without interruption, placed in a rigid container for storage, handling and transport. A rigid container may be disposable, reusable, or recyclable. Rigid containers shall be leak resistant, have sealable tight-fitting covers, and be kept clean and in good repair. All rigid containers must meet standards of the United States Department of Transportation.
  - (i) The liner may be removed from a locked collection receptacle only by or under the supervision of two employees of the pharmacy. Upon removal, the liner shall be immediately, without interruption, sealed and the pharmacy employees shall record, in a log, their participation in the removal of each liner from a collection receptacle. Liners and their rigid containers shall not be opened, x-rayed, analyzed or penetrated at any time by the pharmacy or pharmacy personnel.
  - (j) Liners and their rigid containers that have been filled and removed from a collection receptacle must be stored in a secured, locked location in the pharmacy no longer than 14 days.
  - (k) The pharmacy shall make and keep the records specified in 1776.6.
  - (l) The pharmacy shall ensure the sealed inner liners and their contents are shipped to a reverse distributor's registered location by common or contract carrier (such as UPS, FEDEX or USPS) or by licensed reverse distributor pick-up at the licensed pharmacy's premises.
  - (m) The collection receptacle shall contain signage that includes:

- (1) The name and phone number of the responsible pharmacy;
- (2) Medical sharps and needles (e.g., insulin syringes) shall not be deposited; and
- (3) Consumers may deposit prescription drugs including Schedule II-V controlled substances.

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

Reference: Section 4005, Business and Professions Code and Sections 1304.22, 1317.05, 1317.60, 1317.75, and 1317.80 Title 21 Code of Federal Regulations.

**Proposal to add § 1776.4 of Article 9.1 of Division 17 of Title 16 of the California Code of Regulations as follows:**

**1776.4 Drug Take-Back Services in Skilled Nursing Facilities**

A pharmacy may offer drug take-back services in skilled nursing facilities licensed under Health and Safety Code section 1250(c) as authorized by this article.

- (a) Skilled nursing facility employees or person lawfully entitled to dispose of the resident decedent's property may dispose of unwanted or unused prescription drugs by using mail back envelopes or packages. The pharmacy shall require skilled nursing facility employees to keep records noting the specific quantity of each prescription drug mailed back, the unique identification number of the mail back package and the preaddressed location to which the mail back envelope is sent.
- (b) Only pharmacies and hospitals/clinics with onsite pharmacies may establish collection receptacles in skilled nursing facilities for the collection and ultimate disposal of unwanted prescription drugs. A pharmacy and hospital/clinic with an onsite pharmacy maintaining a collection receptacle in a skilled nursing facility shall:
  - (1) Be registered and maintain registration with the DEA as a collector.
  - (2) Notify the board in writing within 30 days of establishing a collection receptacle.
  - (3) Notify the board in writing within 30 days when they cease to maintain the collection receptacle.
  - (4) Notify the board in writing within 14 days of any tampering of the collection receptacle or theft of deposited drugs.
  - (5) Notify the board in writing within 14 days of any tampering, damage or theft of a removed liner.
  - (6) List all collection receptacles it maintains annually at the time of renewal of the pharmacy license.
- (d) Within three business days after the permanent discontinuation of use of a medication by a prescriber, as a result of the resident's transfer to another facility or as a result of death, the skilled nursing facility may place the patient's unneeded prescription drugs into a collection receptacle. Records of such deposit shall be made in the patient's records, with the name and signature of the employee discarding the drugs.
- (e) A collection receptacle must be located in a secured area regularly monitored by skilled nursing facility employees.
- (f) The collection receptacle shall be securely fastened to a permanent structure so that it cannot be removed. The collection receptacle shall have a small opening that allows deposit of drugs into the inside of the collection receptacle and directly into the inner liner, but does not allow for an individual to reach into the receptacle's contents.
- (g) The receptacle shall be securely locked and substantially constructed, with a permanent

outer container and a removable inner liner.

- (1) The liner shall comply with provisions in this article. The receptacle shall allow deposit of prescription drugs into the receptacle for containment into the inner liner, without permitting access to or removal of prescription drugs already deposited into the collection receptacle and liner. Once a prescription drug or any other item is placed in the collection receptacle, the prescription drug or item cannot be removed, sorted, counted, or otherwise individually handled.
  - (2) If the liner is not already itself rigid or already inside of a rigid container when it is removed from the collection receptacle, the liner must be immediately placed in a rigid container for storage, handling and transport. A rigid container may be disposable, reusable, or recyclable. Rigid containers shall be leak resistant, have sealable tight-fitting covers, and be kept clean and in good repair. All rigid containers must meet standards of the United States Department of Transportation.
- (h) A liner as used in this article shall be made of material that is certified by the manufacturer to meet American Society for Testing Materials (ASTM) D1709 standard test for impact resistance of 165 grams (drop dart test), and the ASTM D1922 standards for tear resistance of 480 grams in both parallel and perpendicular planes.
- (1) The liner shall be waterproof, tamper evident and tear resistant.
  - (2) The liner shall be opaque to prevent viewing and discourage removal of any contents once the liner has been removed from a collection receptacle. The liner shall be clearly marked to display the maximum contents (for example, in gallons). The liner shall bear a permanent, unique identification number.
- (i) The collection receptacle shall contain signage that includes:
- (1) The name and phone number of the responsible pharmacy;
  - (2) Medical sharps and needles (e.g., insulin syringes) shall not be deposited; and
  - (3) Consumers may deposit prescription drugs including Schedule II-V controlled substances.
- (j) Once deposited, the prescription drugs shall not be counted, sorted or otherwise individually handled.
- (k) The installation, removal, transfer and storage of inner liners shall be performed only by:
- (1) One employee of the authorized collector pharmacy and one supervisory level employee of the long-term care facility (e.g., a charge nurse or supervisor) designated by the authorized collector, or
  - (2) By or under the supervision of two employees of the authorized collector pharmacy.
- (l) Sealed inner liners that are placed in a container may be stored at the skilled nursing facility for up to three business days in a securely locked, substantially constructed cabinet or a securely locked room with controlled access until transfer to a reverse distributor for destruction.
- (m) Liners still housed in a rigid container may be delivered to a reverse distributor for destruction by common or contract carrier or by reverse distributor pickup at the skilled nursing facility.
- (n) A pharmacy maintaining a collection receptacle in a skilled nursing facility shall make and keep the records as specified in 1776.6.

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

Reference: Sections 4005, Business and Professions Code and Sections 1304.22, 1317.05,



1317.40, 1317.60, 1317.75, 1317.80, and 1317.95, Title 21 Code of Federal Regulations

**Proposal to add § 1776.5 of Article 9.1 of Division 17 of Title 16 of the California Code of Regulations as follows:**

**1776.5 Reverse Distributors**

- (a) A licensed reverse distributor (either a reverse wholesaler or a reverse third-party logistics provider) registered with the DEA may accept the sealed inner liners of collection receptacles at the reverse distributor's registered location by common or contract carrier pick-up, or by reverse distributor pick-up at the collector's authorized collection location. Once received, the reverse distributor shall establish records required by this section.
- (b) A licensed reverse distributor may not open, survey, or otherwise analyze the contents of inner liners. All liners shall be destroyed by an appropriately licensed and registered DEA reverse distributor in a manner that makes the drugs irretrievable.
- (c) If a reverse distributor picks up the sealed inner liners from the collector's authorized location, at least two employees of the reverse distributor shall be present. If the sealed inner liners are delivered to the reverse distributor via common or contract carrier, at least one employee of the reverse distributor shall accept the receipt of the inner liners at the reverse distributor's registered location.
- (d) A reverse distributor shall not employ as an agent or employee anyone who has access to or influence over controlled substances, any person who has been convicted of any felony offense related to controlled substances or who at any time had a DEA registration revoked or suspended, or has surrendered a DEA registration for cause.
- (e) For each sealed liner or mail back envelopes or packages received pursuant to federal Title 21 CFR section 1317.55, the reverse distributor shall maintain records of the number of sealed inner liners or mail back envelopes or packages, including the:
  - (1) Date of acquisition;
  - (2) Number and the size (e.g., five 10-gallon liners, etc.);
  - (3) Unique Identification number of each liner or envelope/package;
  - (4) The method of delivery to the reverse distributor, the signature of the individuals delivering the liners to the reverse distributor, and the reverse distributor's employees who received the sealed liner;
  - (5) The date, place and method of destruction;
  - (6) Number of packages and inner liners received;
  - (7) Number of packages and inner liners destroyed;
  - (8) The name and signature of the two employees of the registrant that witnessed the destruction.
- (e) For liners only, the information specified in subsection (e)(1)-(8) above shall be created at the time of receipt and at the time of destruction.

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

Reference: Sections 4005, Business and Professions Code and Section 1301.71, 1304.21, 1304.22, 1317.15, and 1317.55 Title 21 Code of Federal Regulations.

**Proposal to add § 1776.6 of Article 9.1 of Division 17 of Title 16 of the California Code of Regulations as follows:**

**1776.6 Record Keeping Requirements for Board Licensees Providing Drug Take-Back Services**

Each entity authorized by this article to collect unwanted prescription drugs from patients shall maintain the records required by this article for three years.

- (a) For pharmacies maintaining collection receptacles, the pharmacy shall make and keep the following records for each liner:
- (1) Date each unused liner is acquired, its unique identification number and size (e.g., 5 gallon, 10 gallon). The pharmacy shall assign the unique identification number if the liner does not already contain one.
  - (2) Date each liner is installed in a collection receptacle, the address of the location where each liner is installed, the unique identification number and size (e.g., 5 gallon, 10 gallon), the registration number of the collector pharmacy, and the names and signatures of the two employees that witnessed each installation.
  - (3) Date each inner liner is removed and sealed, the address of the location from which each inner liner is removed, the unique identification number and size (e.g., 5 gallon, 10 gallon) of each inner liner removed, the registration number of the collector pharmacy, and the names and signatures of the two employees that witnessed the removal and sealing.
  - (4) Date each sealed inner liner is transferred to storage, the unique identification number and size (e.g., 5 gallon, 10 gallon) of each inner liner stored, and the names and signatures of the two employees that transferred each sealed inner liner to storage.
  - (5) Date each sealed inner liner is transferred for destruction, the address and registration number of the reverse distributor or distributor to whom each sealed inner liner was transferred, the unique Identification number and the size (e.g., 5 gallon, 10 gallon) of each liner transferred, and the names and signatures of the two employees who transferred each sealed inner liner to the reverse distributor or distributor, or the common carrier who delivered it, the company used, and any related paperwork (invoice, bill of lading).

Note: Authority cited: Section 4005, Business and Professions Code. Reference: Sections 4005, Business and Professions Code and Section 1304.22, Title 21 Code of Federal Regulations

# **Attachment 4**

## **Business and Professions Code**

### **4186. Automated Drug Delivery Systems**

(a) Automated drug delivery systems, as defined in subdivision (h), may be located in any clinic licensed by the board pursuant to Section 4180. If an automated drug delivery system is located in a clinic, the clinic shall develop and implement written policies and procedures to ensure safety, accuracy, accountability, security, patient confidentiality, and maintenance of the quality, potency, and purity of drugs. All policies and procedures shall be maintained at the location where the automated drug system is being used.

(b) Drugs shall be removed from the automated drug delivery system only upon authorization by a pharmacist after the pharmacist has reviewed the prescription and the patient's profile for potential contraindications and adverse drug reactions. Drugs removed from the automated drug delivery system shall be provided to the patient by a health professional licensed pursuant to this division.

(c) The stocking of an automated drug delivery system shall be performed by a pharmacist.

(d) Review of the drugs contained within, and the operation and maintenance of, the automated drug delivery system shall be the responsibility of the clinic. The review shall be conducted on a monthly basis by a pharmacist and shall include a physical inspection of the drugs in the automated drug delivery system, an inspection of the automated drug delivery system machine for cleanliness, and a review of all transaction records in order to verify the security and accountability of the system.

(e) The automated drug delivery system used at the clinic shall provide for patient consultation pursuant to Section 1707.2 of Title 16 of the California Code of Regulations with a pharmacist via a telecommunications link that has two-way audio and video.

(f) The pharmacist operating the automated drug delivery system shall be located in California.

(g) Drugs dispensed from the automated drug delivery system shall comply with the labeling requirements in Section 4076.

(h) For purposes of this section, an "automated drug delivery system" means a mechanical system controlled remotely by a pharmacist that performs operations or activities, other than compounding or administration, relative to the storage, dispensing, or distribution of prepackaged dangerous drugs or dangerous devices. An automated drug delivery system shall collect, control, and maintain all transaction information to accurately track the movement of drugs into and out of the system for security, accuracy, and accountability.

**State of California**

**HEALTH AND SAFETY CODE**

**Section 1261.6**

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1261.6. (a) (1) For purposes of this section and Section 1261.5, an “automated drug delivery system” means a mechanical system that performs operations or activities, other than compounding or administration, relative to the storage, dispensing, or distribution of drugs. An automated drug delivery system shall collect, control, and maintain all transaction information to accurately track the movement of drugs into and out of the system for security, accuracy, and accountability.

(2) For purposes of this section, “facility” means a health facility licensed pursuant to subdivision (c), (d), or (k), of Section 1250 that has an automated drug delivery system provided by a pharmacy.

(3) For purposes of this section, “pharmacy services” means the provision of both routine and emergency drugs and biologicals to meet the needs of the patient, as prescribed by a physician.

(b) Transaction information shall be made readily available in a written format for review and inspection by individuals authorized by law. These records shall be maintained in the facility for a minimum of three years.

(c) Individualized and specific access to automated drug delivery systems shall be limited to facility and contract personnel authorized by law to administer drugs.

(d) (1) The facility and the pharmacy shall develop and implement written policies and procedures to ensure safety, accuracy, accountability, security, patient confidentiality, and maintenance of the quality, potency, and purity of stored drugs. Policies and procedures shall define access to the automated drug delivery system and limits to access to equipment and drugs.

(2) All policies and procedures shall be maintained at the pharmacy operating the automated drug delivery system and the location where the automated drug delivery system is being used.

(e) When used as an emergency pharmaceutical supplies container, drugs removed from the automated drug delivery system shall be limited to the following:

(1) A new drug order given by a prescriber for a patient of the facility for administration prior to the next scheduled delivery from the pharmacy, or 72 hours, whichever is less. The drugs shall be retrieved only upon authorization by a pharmacist and after the pharmacist has reviewed the prescriber’s order and the patient’s profile for potential contraindications and adverse drug reactions.

(2) Drugs that a prescriber has ordered for a patient on an as-needed basis, if the utilization and retrieval of those drugs are subject to ongoing review by a pharmacist.

(3) Drugs designed by the patient care policy committee or pharmaceutical service committee of the facility as emergency drugs or acute onset drugs. These drugs may

be retrieved from an automated drug delivery system pursuant to the order of a prescriber for emergency or immediate administration to a patient of the facility. Within 48 hours after retrieval under this paragraph, the case shall be reviewed by a pharmacist.

(f) When used to provide pharmacy services pursuant to Section 4119.1 of the Business and Professions Code, the automated drug delivery system shall be subject to all of the following requirements:

(1) Drugs removed from the automated drug delivery system for administration to a patient shall be in properly labeled units of administration containers or packages.

(2) A pharmacist shall review and approve all orders prior to a drug being removed from the automated drug delivery system for administration to a patient. The pharmacist shall review the prescriber's order and the patient's profile for potential contraindications and adverse drug reactions.

(3) The pharmacy providing services to the facility pursuant to Section 4119.1 of the Business and Professions Code shall control access to the drugs stored in the automated drug delivery system.

(4) Access to the automated drug delivery system shall be controlled and tracked using an identification or password system or biosensor.

(5) The automated drug delivery system shall make a complete and accurate record of all transactions that will include all users accessing the system and all drugs added to, or removed from, the system.

(6) After the pharmacist reviews the prescriber's order, access by licensed personnel to the automated drug delivery system shall be limited only to drugs ordered by the prescriber and reviewed by the pharmacist and that are specific to the patient. When the prescriber's order requires a dosage variation of the same drug, licensed personnel shall have access to the drug ordered for that scheduled time of administration.

(7) (A) Systems that allow licensed personnel to have access to multiple drugs and are not patient specific in their design, shall be allowed under this subdivision if those systems have electronic and mechanical safeguards in place to ensure that the drugs delivered to the patient are specific to that patient. Each facility using such an automated drug system shall notify the department in writing prior to the utilization of the system. The notification submitted to the department pursuant to this paragraph shall include, but is not limited to, information regarding system design, personnel with system access, and policies and procedures covering staff training, storage, and security, and the facility's administration of these types of systems.

(B) As part of its routine oversight of these facilities, the department shall review a facility's medication training, storage, and security, and its administration procedures related to its use of an automated drug delivery system to ensure that adequate staff training and safeguards are in place to make sure that the drugs delivered are appropriate for the patient. If the department determines that a facility is not in compliance with this section, the department may revoke its authorization to use automated drug delivery systems granted under subparagraph (A).

(g) The stocking of an automated drug delivery system shall be performed by a pharmacist. If the automated drug delivery system utilizes removable pockets, cards,

drawers, similar technology, or unit of use or single dose containers as defined by the United States Pharmacopoeia, the stocking system may be done outside of the facility and be delivered to the facility if all of the following conditions are met:

(1) The task of placing drugs into the removable pockets, cards, drawers, or unit of use or single dose containers is performed by a pharmacist, or by an intern pharmacist or a pharmacy technician working under the direct supervision of a pharmacist.

(2) The removable pockets, cards, drawers, or unit of use or single dose containers are transported between the pharmacy and the facility in a secure tamper-evident container.

(3) The facility, in conjunction with the pharmacy, has developed policies and procedures to ensure that the removable pockets, cards, drawers, or unit of use or single dose containers are properly placed into the automated drug delivery system.

(h) Review of the drugs contained within, and the operation and maintenance of, the automated drug delivery system shall be done in accordance with law and shall be the responsibility of the pharmacy. The review shall be conducted on a monthly basis by a pharmacist and shall include a physical inspection of the drugs in the automated drug delivery system, an inspection of the automated drug delivery system machine for cleanliness, and a review of all transaction records in order to verify the security and accountability of the system.

(i) Drugs dispensed from an automated drug delivery system that meets the requirements of this section shall not be subject to the labeling requirements of Section 4076 of the Business and Professions Code or Section 111480 of this code if the drugs to be placed into the automated drug delivery system are in unit dose packaging or unit of use and if the information required by Section 4076 of the Business and Professions Code and Section 111480 of this code is readily available at the time of drug administration. For purposes of this section, unit dose packaging includes blister pack cards.

(Amended by Stats. 2016, Ch. 484, Sec. 54. (SB 1193) Effective January 1, 2017.)

# **Attachment**



**California State Board of Pharmacy**  
**DRAFT Policy on Automated Refill Programs:**

A retail or mail order pharmacy may only use a program that automatically refills non-controlled prescriptions that have existing refills available, in order to improve patient compliance and are consistent with the patient's current medication therapy when all of the following conditions are met:

(1) Written notice or disclaimer of the availability of an auto-refill program shall be given to the patient or patient's agent. The patient or patient's agent must affirmatively indicate they wish to enroll in such a program and the pharmacy shall maintain documentation of such indication. Notice shall have language that references instructions on how a patient can discontinue participation in the auto-refill program.

(a) A pharmacy patient or the patient's agent shall consent to participation in the auto-refill program with a "wet" signature or an e-signature. If the pharmacy has an online consent option, the patient may enroll in the auto-refill program through that method. The pharmacy shall keep this acknowledgement on file. If the retail pharmacy has an online consent option, the patient or patient's agent can register in that manner and the pharmacy shall keep said acknowledgement on file for one year from date of dispensing.

(b) A mail order pharmacy patient or the patient's agent shall consent to participation auto-refill program through the mail order pharmacy's website. The pharmacy shall keep this acknowledgement on file. If the mail order pharmacy does not have an online consent option, the pharmacy shall obtain a signature or email confirmation from the patient or patient's agent consenting to the auto-refill program. Acknowledgement of consent to participate in the auto-refill program shall be kept on file by the mail order pharmacy for one year from date of dispensing.

(2) The prescription is not a controlled substance.

(3) The Pharmacy shall have safeguards in place that ensure only medications that are eligible for the auto-refill program are enrolled in the program.

(4) The pharmacy must discontinue auto-refill program enrollment at the request of the patient or patient's agent in a timely manner.

(5) As is required for all prescriptions, a drug regimen review shall be completed on all prescriptions filled as a result of the auto-refill program. Special attention shall be noted for drug regimen review warnings of duplication of therapy and all such conflicts shall be resolved with the prescribing practitioner prior to refilling the prescription.

(6) The retail or mail order pharmacy must reaffirm annually each prescription to be enrolled in the auto-refill program.

(7) Upon a receipt of a new prescription from a provider, the patient or patient's agent shall identify if the prescription is to be included in the auto-refill program, even if the new prescription is a continuation of existing therapy.

(8) Each time a prescription is refilled a reminder notification will be provided to the patient or patient's agent, affirming that the prescription is enrolled in the auto-refill program.

(9) Pharmacies that use an auto refill program will have policies and procedures in place that address the auto-fill program. These policies and procedures will be available for inspection upon request of the board.

(10) The pharmacy shall provide a full refund to the patient or the patient's agent for an auto-refill prescription that is reported as unneeded or unnecessary if the patient or patient's agent can provide evidence or documentation that they did not register for the auto-refill program.

# **Attachment 6**

# Nursys® e-Notify System Keeps Employers Informed

The National Council of State Boards of Nursing (NCSBN) Nursys® e-Notify system is a nurse licensure notification system that provides employers with real-time e-mail notifications about nurses they employ. The system provides licensure and publicly available discipline data directly to the employer, without the employer having to seek it out.

Nursys is the only national database for verification of nurse licensure, discipline, and practice privileges for registered nurses and licensed practical/vocational nurses. It consists of data obtained directly from the licensure systems of participating national boards of nursing through frequent, secured updates. The e-Notify system alerts subscribers when changes are made to a nurse's record, including changes to:

- » License status.
- » License expirations.
- » Pending license renewal.
- » Public disciplinary action/resolutions and alerts.

There is no charge to subscribe to the service. Employers can learn more and sign up by visiting the Nursys website at <https://www.nursys.com>. An introductory video on the system is available on the website.

## New Website Format for the BRN

The BRN will soon implement a new look to its website! The new format is a statewide template and is being used by the BRN to make the website as helpful and user-friendly as possible by making frequently visited pages and needed information easier to locate, and overall navigation more efficient so that users can find the information they need quickly and easily. Please visit our website and take a minute or two to answer our website satisfaction survey and give us your feedback. The survey can be found at <https://www.dca.ca.gov/webapps/rn/survey.php>.



# **Attachment 7**

## Article 2. Pharmacies

### 1707. Waiver Requirements for Off-Site Storage of Records

(a) Pursuant to subdivision (e) of Section 4105 of the Business and Professions Code and subdivision (c) of Section 4333 of the Business and Professions Code, a waiver shall be granted to any entity licensed by the board for off-site storage of the records described in subdivisions (a), (b) and (c) of Section 4105 of the Business and Professions Code unless the applicant has, within the preceding five years, failed to produce records pursuant to Section 4081 of the Business and Professions Code or has falsified records covered by Section 4081 of the Business and Professions Code.

(b) An entity that is granted a waiver pursuant to subdivision (a) shall:

(1) maintain the storage area so that the records are secure, including from unauthorized access; and

(2) be able to produce the records within two business days upon the request of the board or an authorized officer of the law.

(c) In the event that a licensee fails to comply with the conditions set forth in subdivision (b), the board may cancel the waiver without a hearing. Upon notification by the board of cancellation of the waiver, the licensee shall maintain all records at the licensed premises.

(d) A licensee whose waiver has been cancelled pursuant to the provisions set forth in subsection (c) may reapply to the board when compliance with the conditions set forth in subsection (b) can be confirmed by the board.

(e) Notwithstanding any waiver granted pursuant to subdivision (a), all prescription records for non controlled substances shall be maintained on the licensed premises for a period of one year from the date of dispensing.

(f) Notwithstanding any waiver granted pursuant to subdivision (a), all prescription records for controlled substances shall be maintained on the licensed premises for a period of two years from the date of dispensing.

(g) Notwithstanding the requirements of this section, any entity licensed by the board may store the records described in subdivisions (a), (b) and (c) of Section 4105 of the Business and Professions Code in a storage area at the same address or adjoining the licensed premises without obtaining a waiver from the board if the following conditions are met:

(1) The records are readily accessible to the pharmacist-in-charge (or other pharmacist on duty, or designated representative) and upon request to the board or any authorized officer of the law.

(2) The storage area is maintained so that the records are secure and so that the confidentiality of any patient-related information is maintained.

Authority cited: Section 4005, Business and Professions Code. Reference: Sections 4081, 4105 and 4333, Business and Professions Code.

**BUSINESS AND PROFESSIONS CODE - BPC**

**DIVISION 2. HEALING ARTS [500 - 4999.129]**

*( Division 2 enacted by Stats. 1937, Ch. 399. )*

**CHAPTER 9. Pharmacy [4000 - 4426]**

*( Chapter 9 repealed and added by Stats. 1996, Ch. 890, Sec. 3. )*

**ARTICLE 5. Authority of Inspectors [4080 - 4086]**

*( Article 5 added by Stats. 1996, Ch. 890, Sec. 3. )*

**4081.**

(a) All records of manufacture and of sale, acquisition, receipt, shipment, or disposition of dangerous drugs or dangerous devices shall be at all times during business hours open to inspection by authorized officers of the law, and shall be preserved for at least three years from the date of making. A current inventory shall be kept by every manufacturer, wholesaler, third-party logistics provider, pharmacy, veterinary food-animal drug retailer, outsourcing facility, physician, dentist, podiatrist, veterinarian, laboratory, clinic, hospital, institution, or establishment holding a currently valid and unrevoked certificate, license, permit, registration, or exemption under Division 2 (commencing with Section 1200) of the Health and Safety Code or under Part 4 (commencing with Section 16000) of Division 9 of the Welfare and Institutions Code who maintains a stock of dangerous drugs or dangerous devices.

(b) The owner, officer, and partner of a pharmacy, wholesaler, third-party logistics provider, or veterinary food-animal drug retailer shall be jointly responsible, with the pharmacist-in-charge, responsible manager, or designated representative-in-charge, for maintaining the records and inventory described in this section.

(c) The pharmacist-in-charge, responsible manager, or designated representative-in-charge shall not be criminally responsible for acts of the owner, officer, partner, or employee that violate this section and of which the pharmacist-in-charge, responsible manager, or designated representative-in-charge had no knowledge, or in which he or she did not knowingly participate.

*(Amended by Stats. 2016, Ch. 484, Sec. 17. Effective January 1, 2017.)*

**BUSINESS AND PROFESSIONS CODE - BPC**

**DIVISION 2. HEALING ARTS [500 - 4999.129]**

*( Division 2 enacted by Stats. 1937, Ch. 399. )*

**CHAPTER 9. Pharmacy [4000 - 4426]**

*( Chapter 9 repealed and added by Stats. 1996, Ch. 890, Sec. 3. )*

**ARTICLE 6. General Requirements [4100 - 4107.5]**

*( Article 6 added by Stats. 1996, Ch. 890, Sec. 3. )*

**4105.**

(a) All records or other documentation of the acquisition and disposition of dangerous drugs and dangerous devices by any entity licensed by the board shall be retained on the licensed premises in a readily retrievable form.

(b) The licensee may remove the original records or documentation from the licensed premises on a temporary basis for license-related purposes. However, a duplicate set of those records or other documentation shall be retained on the licensed premises.

(c) The records required by this section shall be retained on the licensed premises for a period of three years from the date of making.

(d) (1) Any records that are maintained electronically shall be maintained so that the pharmacist-in-charge, or the pharmacist on duty if the pharmacist-in-charge is not on duty, shall, at all times during which the licensed premises are open for business, be able to produce a hardcopy and electronic copy of all records of acquisition or disposition or other drug or dispensing-related records maintained electronically.

(2) In the case of a veterinary food-animal drug retailer, wholesaler, or third-party logistics provider, any records that are maintained electronically shall be maintained so that the designated representative-in-charge or the responsible manager, or the designated representative on duty or the designated representative-3PL on duty if the designated representative-in-charge or responsible manager is not on duty, shall, at all times during which the licensed place of business is open for business, be able to produce a hardcopy and electronic copy of all records of acquisition or disposition or other drug or dispensing-related records maintained electronically.

(e) (1) Notwithstanding subdivisions (a), (b), and (c), the board may, upon written request, grant to a licensee a waiver of the requirements that the records described in subdivisions (a), (b), and (c) be kept on the licensed premises.

(2) A waiver granted pursuant to this subdivision shall not affect the board's authority under this section or any other provision of this chapter.

(f) When requested by an authorized officer of the law or by an authorized representative of the board, the owner, corporate officer, or manager of an entity licensed by the board shall provide the board with the requested records within



three business days of the time the request was made. The entity may request in writing an extension of this timeframe for a period not to exceed 14 calendar days from the date the records were requested. A request for an extension of time is subject to the approval of the board. An extension shall be deemed approved if the board fails to deny the extension request within two business days of the time the extension request was made directly to the board.

*(Amended by Stats. 2014, Ch. 507, Sec. 12. Effective January 1, 2015.)*

**BUSINESS AND PROFESSIONS CODE - BPC**

**DIVISION 2. HEALING ARTS [500 - 4999.129]**

*( Division 2 enacted by Stats. 1937, Ch. 399. )*

**CHAPTER 9. Pharmacy [4000 - 4426]**

*( Chapter 9 repealed and added by Stats. 1996, Ch. 890, Sec. 3. )*

**ARTICLE 20. Prohibitions and Offenses [4320 - 4343]**

*( Article 20 added by Stats. 1996, Ch. 890, Sec. 3. )*

**4333.**

(a) All prescriptions filled by a pharmacy and all other records required by Section 4081 shall be maintained on the premises and available for inspection by authorized officers of the law for a period of at least three years. In cases where the pharmacy discontinues business, these records shall be maintained in a board-licensed facility for at least three years.

(b) Any person who willfully fails to comply with subdivision (a) is guilty of a misdemeanor, and upon conviction thereof, shall be punished by a fine not exceeding two hundred dollars (\$200). Any person convicted of a second or subsequent offense shall be punished by a fine of not less than two hundred dollars (\$200) and not more than four hundred dollars (\$400).

(c) (1) Notwithstanding subdivisions (a) and (b), the board may, upon written request, grant a waiver of the requirement that the records described in subdivisions (a) and (b) be maintained on the licensed premises or, in the event the pharmacy discontinues business, that the records be maintained in a board licensed facility. A person who maintains records in compliance with that waiver is not subject to the penalties set forth in subdivision (b).

(2) A waiver granted pursuant to this subdivision shall not affect the board's authority under this section or any other provision of this chapter.

*(Amended by Stats. 1997, Ch. 549, Sec. 129. Effective January 1, 1998.)*

# **Attachment**

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# Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification Guidance for Industry

The portion of this guidance that describes when manufacturers should notify FDA if there is a high risk that a product is illegitimate, is being distributed for comment purposes only.

Comments and suggestions regarding this document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the 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*.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Office of Regulatory Affairs (ORA)**

**December 2016  
Procedural  
OMB Control No. 0910-0806  
Expiration Date 12/31/2018  
See additional PRA statement in section V of this guidance.**

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# Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification Guidance for Industry

*Additional copies are available from:*

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<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Office of Regulatory Affairs (ORA)**

**December 2016  
Procedural**

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# Guidance for Industry<sup>1</sup>

## Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification

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.<sup>2</sup> 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 office responsible for this guidance as listed on the title page.

### I. INTRODUCTION

This guidance is intended to aid trading partners<sup>3,4</sup> (manufacturers, repackagers, wholesale distributors, and dispensers) in identifying a suspect product as defined at section 581(21) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360eee(21)) and terminating notifications. It does not establish any rights for any person and, with the exception of section IV.B, it is not binding on FDA or the public. With respect to section IV.B, section 582 of the FD&C Act gives FDA authority to issue binding guidance on the process for terminating notifications of illegitimate product. Specifically, section 582(h)(2)(A) states that FDA “shall issue a guidance document to aid trading partners in the identification of a suspect product and notification termination. Such guidance document shall . . . set forth the process by which manufacturers, repackagers, wholesale distributors, and dispensers shall terminate notifications in consultation with the Secretary regarding illegitimate product . . . .”

As of January 1, 2015, a trading partner that determines a product in its possession or control is an illegitimate product as defined at section 581(8) of FD&C Act, must notify the Food and Drug Administration (FDA or Agency) and certain immediate trading partners under section 582 of

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<sup>1</sup> This guidance has been prepared by the Office of Compliance in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Office of Regulatory Affairs at the Food and Drug Administration.

<sup>2</sup> Insofar as section IV.B of this guidance sets forth the process by which trading partners must terminate notifications of illegitimate product and products with a high risk of illegitimacy in consultation with FDA, it has binding effect. This is discussed further in the Introduction.

<sup>3</sup> For this guidance, *trading partner* is defined in section 581(23)(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 30eee(23)(A)), and refers to a manufacturer, repackager, wholesale distributor, or dispenser. For purposes of this guidance, *trading partner* does not refer to a third-party logistics provider (3PL) as defined in section 581(23)(B) of the FD&C Act (21 U.S.C. 360eee(23)(B)), though FDA encourages 3PLs to follow the recommendations in this guidance to the extent relevant to the 3PL’s operations.

<sup>4</sup> Trading partners must be authorized as defined in FD&C Act section 581(2) and required under FD&C Act section 582(b)(3), (c)(3), (d)(3) and (e)(3).

the FD&C Act (21 U.S.C. 360eee-1), as added by the Drug Supply Chain Security Act (DSCSA). Manufacturers are additionally required under section 582 to notify FDA and certain immediate trading partners after the manufacturer determines or is notified by FDA or a trading partner that there is a high risk that a product is illegitimate.<sup>5</sup> This guidance identifies specific scenarios that could significantly increase the risk of a suspect product entering the pharmaceutical distribution supply chain; provides recommendations on how trading partners can identify a product and determine whether a product is a suspect product as soon as practicable; and sets forth the process by which trading partners should notify FDA of illegitimate product or products with a high risk of illegitimacy, and how they must terminate the notifications, in consultation with FDA.

This guidance does not address all provisions of the DSCSA related to suspect and illegitimate products. As FDA works to implement other provisions of the DSCSA, the Agency intends to issue additional information to support efforts to develop standards, issue guidance and regulations, establish pilot programs, and conduct public meetings.

FDA's guidance documents, in general, 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. Insofar as section IV.B of this guidance sets forth the process by which trading partners must terminate notifications of illegitimate product and products with a high risk of illegitimacy in consultation with FDA, it has binding effect.<sup>6</sup>

## **II. BACKGROUND**

### **A. Drug Supply Chain Security Act**

On November 27, 2013, the DSCSA (Title II of Public Law 113-54) was signed into law. Section 203 of the DSCSA added section 582(h)(2) to the FD&C Act, which requires FDA to issue guidance to aid trading partners in identifying a suspect product and terminating notifications. *Suspect product* is defined in section 581(21) of the FD&C Act as a product for which there is reason to believe it (A) is potentially counterfeit, diverted, or stolen; (B) is potentially intentionally adulterated such that the product would result in serious adverse health consequences or death to humans; (C) is potentially the subject of a fraudulent transaction; or (D) appears otherwise unfit for distribution such that the product would result in serious adverse health consequences or death to humans. Section 582 of the FD&C Act requires trading partners, upon determining that a product in their possession or control is a suspect product, to quarantine the product while they promptly conduct an investigation to determine whether the product is an illegitimate product. *Illegitimate product* is defined in section 581(8) of the FD&C

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<sup>5</sup> The portion of this guidance that describes when manufacturers should notify FDA of a high risk that a product is illegitimate is shaded in gray and is being distributed for comment purposes only.

<sup>6</sup> See section 582(h)(2)(A) of the FD&C Act.



Act as a product for which credible evidence shows that it is (A) counterfeit, diverted, or stolen; (B) intentionally adulterated such that the product would result in serious adverse health consequences or death to humans; (C) is the subject of a fraudulent transaction; or (D) appears otherwise unfit for distribution such that the product would be reasonably likely to result in serious adverse health consequences or death to humans.<sup>7</sup>

Section 582 of the FD&C Act requires trading partners, upon determining that a product in their possession or control is illegitimate, to notify FDA and all immediate trading partners (that they have reason to believe may have received the illegitimate product) not later than 24 hours after making the determination. Manufacturers are additionally required under section 582(b)(4)(B)(ii)(II) to notify FDA and immediate trading partners (that the manufacturer has reason to believe may possess a product manufactured by or purported to be manufactured by the manufacturer) not later than 24 hours after the manufacturer determines or is notified by FDA or a trading partner that there is a high risk that the product is illegitimate.

The DSCSA outlines critical steps to build an electronic, interoperable system over the next 10 years that will identify and trace certain prescription drugs as they are distributed within the United States. For many years, FDA has been engaged in efforts to improve the security of the drug supply chain to protect U.S. patients from unsafe, ineffective, and poor quality drugs. Since at least the formation of the first FDA Counterfeit Drug Task Force in 2003, FDA has strongly advocated for a multilayered approach to securing the supply chain. A key component of that approach has been to encourage heightened vigilance and awareness among supply chain partners. The electronic, interoperable system that will be established under the DSCSA will enhance FDA's ability to help protect U.S. consumers by improving detection and removal of potentially dangerous drugs from the drug supply chain.

## **B. Scope of This Guidance**

Pursuant to section 582(h)(2) of the FD&C Act, this guidance identifies specific scenarios that could significantly increase the risk of a suspect product entering the pharmaceutical distribution supply chain; provides recommendations on how trading partners can identify such product and determine whether a product is a suspect product as soon as practicable; describes when manufacturers should notify FDA of a high risk that a product is illegitimate; and sets forth the process by which trading partners must terminate notifications in consultation with FDA regarding illegitimate product under section 582(b)(4)(B)(iv), (c)(4)(B)(iv), (d)(4)(B)(iv), and (e)(4)(B)(iv) of the FD&C Act and the process for terminating notifications in consultation with FDA regarding products with a high risk of illegitimacy under section 582(b)(4)(B)(iv). This guidance also addresses how trading partners should notify FDA when they determine that a product in their possession or control is an illegitimate product under section 582(b)(4)(B)(ii)(I), (c)(4)(B)(ii), (d)(4)(B)(ii), and (e)(4)(B)(ii) of the FD&C Act, and how manufacturers should notify FDA regarding products with a high risk of illegitimacy under section 582(b)(4)(B)(ii)(II).

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<sup>7</sup> For additional definitions applicable to this guidance, please refer to section 581 of the FD&C Act.

### **III. IDENTIFICATION OF SUSPECT PRODUCT AND, FOR MANUFACTURERS, PRODUCT WITH A HIGH RISK OF ILLEGITIMACY**

Trading partners, upon determining that a product in their possession or control is suspect or upon receiving a request for verification from the FDA (whereby FDA has made a determination that a product within the possession or control of the trading partner is a suspect product), must have systems in place that enable them to quarantine suspect product and promptly conduct an investigation, in coordination with other trading partners, as applicable, to determine whether a suspect product is illegitimate.

As trading partners conduct business on a daily basis, they should exercise vigilance, maintain awareness about suspicious activity or potential threats to their supply chain, and devote attention and effort to detecting suspect product.

The next two sections of this guidance (A.) identify some specific scenarios that could significantly increase the risk of suspect products entering the pharmaceutical distribution supply chain and (B.) make recommendations to assist trading partners in identifying suspect product and making determinations about whether a product is suspect as soon as practicable. The scenarios contained in this guidance are based on Agency experience with suspect product in the drug supply chain. These examples are illustrative and should not be viewed as an exhaustive list of all potential scenarios that increase the likelihood that a suspect product could enter the pharmaceutical distribution supply chain. Trading partners should consider the surrounding circumstances of any particular scenario they may encounter in determining whether or not a product is suspect, including whether multiple scenarios are present in any given transaction.

#### **A. Specific Scenarios That Could Significantly Increase the Risk of a Suspect Product Entering the Pharmaceutical Distribution Supply Chain**

There may be situations involving trading partners where heightened vigilance would be appropriate. In addition, there could be identifiable characteristics of products that might increase the likelihood that they are suspect products. The following are examples of some specific scenarios that could significantly increase the risk of a suspect product entering the drug supply chain. Thus, trading partners should be particularly diligent when engaging in transactions that involve:

##### *1. Trading Partners and Product Sourcing*

- Purchasing from a source new to the trading partner.
- Receiving an unsolicited sales offer from an unknown source. Trading partners might receive unsolicited offers or advertisements through an email, a fax, a telephone call, or an in-person sales call from a person or entity with whom they do not have an established business relationship.
- Purchasing on the Internet from an unknown source. Trading partners might be searching for a better price on the Internet or for a product that they cannot obtain

*Contains Nonbinding Recommendations and Binding Provisions*

from their usual source, and might be tempted to turn to a person or entity with whom they do not have an established business relationship.

- Purchasing from a source that a trading partner knows or has reason to believe has engaged in questionable or suspicious business practices that could increase the risk of suspect product entering the supply chain, such as:
  - A trading partner that has been involved in business transactions where they sold or delivered illegitimate product.
  - A trading partner that has a history of problematic or potentially false transaction histories or pedigrees, such as those that contain misspelled words or incomplete information.
  - A trading partner that is reluctant to provide a transaction history associated with the product being purchased, or does not do so in a timely manner.
  - A trading partner that provides transaction information, a transaction statement, and/or transaction history that appears to be incomplete or suspicious.

2. *Supply, Demand, History, and Value of the Product*

- Product that is generally in high demand in the U.S. market.
- Product that is in higher demand because of its potential or perceived relationship to a public health or other emergency (e.g., antiviral drugs).
- Product that has a high sales volume or price in the United States.
- Product offered at a price that is “too good to be true.”
- Product that has been previously or is currently being counterfeited or diverted (e.g., HIV, antipsychotic, or cancer drugs).
- Product that has been previously or is currently the subject of a drug shortage (see a list of current drugs in shortage at <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/default.htm> and <http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm> for more information).
- Product that has been or is the subject of an illegitimate product notification under the DSCSA or other alert or announcement related to drug quality.
- Product that has been or is the subject of an FDA counterfeit or cargo theft alert

(See <http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/co-unterfeitmedicine/default.htm> and <http://www.fda.gov/iceci/criminalinvestigations/ucm182888.htm> for more information).

3. *Appearance of the Product*

- Appearance of a package or a container used for transport (e.g., case or tote) that seems suspicious (e.g., it has a label that contains misspellings or appears different from the standard label for that product in color, font, images, or otherwise).
- Package that exhibits unusual or excessive adhesive residue.
- Package that contains foreign identification features (such as a different drug identification number where a National Drug Code (NDC) number would be expected).
- Package that is missing information, such as the lot number or other lot identification, or the expiration date.
- Package that is missing security or anti-counterfeiting technologies normally featured on the FDA-approved product that are easily visible to the eye, such as holograms, color shifting inks, neckbands, or watermarks.
- Finished dosage form that seems suspicious (e.g., it has a different shape or color from the FDA-approved product, a different or unusual imprint, an unusual odor, or there are signs of poor quality like chips or cracks in tablet coatings or smeared or unclear ink imprints).

**B. Recommendations on How Trading Partners Might Identify Suspect Product and Determine Whether the Product Is a Suspect Product as Soon as Practicable**

The following are recommendations for trading partners on ways that they can expeditiously identify suspect product and determine whether the product is suspect (and, after investigation, whether it is illegitimate). In general, trading partners should exercise due diligence when conducting business and should confirm that all trading partners are authorized. Trading partners should discuss with each other any observations, questions, or concerns they have related to the status of a drug as a suspect product to aid them in determining whether the drug should be considered a suspect product. Trading partners should also contact regulatory authorities, law enforcement, the drug's manufacturer, or other available resources to aid in that determination when additional expertise is called for to make an accurate assessment of the status of a drug as a suspect product. If a trading partner receives a product in a secured transport container or sealed homogenous case, trading partners should examine the appearance of that container as

### *Contains Nonbinding Recommendations and Binding Provisions*

recommended below. If trading partners observe anything suspicious, they should take steps to ascertain whether the product inside the transport container is suspect. Strategies to identify suspect product include, but are not limited to, the following recommendations:

- Be alert for offers of product for sale at a very low price or one that is “too good to be true.”
- Closely examine the package and the transport container (such as the case or tote):
  - To look for signs that it has been compromised (e.g., opened, broken seal, damaged, repaired, or otherwise altered). If a trading partner receives a product in a secured transport container or sealed homogenous case, trading partners should examine the appearance of that container to see if anything about that appearance seems suspicious, such as shrink wrap that has unexpected markings, or a seal that is broken, torn, or repaired.
  - To see if the package or the transport container has changed since the last shipment of the same product type was received for an unexplained reason (e.g., a notification about the change from the manufacturer has not been received).
  - To see if product inserts are missing, do not correspond to the product, or are suspicious in some way.
  - For shipping addresses, postmarks, or other materials indicating that the product came from an unexpected foreign entity or source.
- Closely examine the label on the package, and the label on the individual retail unit, if applicable, for:
  - Any missing information, such as the lot number or other lot identification, NDC, or strength of the drug.
  - Any altered product information, such as smudged print or print that is very difficult to read.
  - Misspelled words.
  - Bubbling in the surface of a label.
  - Lack of an “Rx only” symbol.<sup>8</sup>
  - Foreign language with little or no English provided.<sup>9</sup>
  - Foreign language that is used to describe the lot number.<sup>10</sup>

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<sup>8</sup> Or, for products distributed solely in the Commonwealth of Puerto Rico or any other territory where the predominant language is Spanish, “Solamente Rx” (21 CFR 201.16).

<sup>9</sup> Except for products distributed solely in the Commonwealth of Puerto Rico or any other territory where the predominant language is one other than English (21 CFR 201.15 (c)(1)).

<sup>10</sup> Except for products distributed solely in the Commonwealth of Puerto Rico or any other territory where the predominant language is one other than English (21 CFR 201.15(c)(1)).

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- A product name that differs from the name that appears on the FDA-approved drug label or labeling.
- A product name that is the product name for a foreign version of the drug.
- A product that is transported in a case or tote, when not expected under the circumstances.
- Lot numbers and expiration dates on product that do not match the lot numbers and expiration dates of its outer container.

Again, under section 582 of the FD&C Act, trading partners must have systems in place that enable them, upon determining that a product in their possession or control is suspect or upon receiving a request for verification from the FDA that has made a determination that a product within the possession or control of the trading partner is a suspect product, to quarantine suspect product and promptly conduct an investigation, in coordination with other trading partners, as applicable, to determine whether a suspect product is illegitimate. In addition, trading partners must, as applicable, make the notifications described in section 582(b)(4)(B)(ii)(I), (c)(4)(B)(ii), (d)(4)(B)(ii), and (e)(4)(B) of the FD&C Act related to illegitimate product determinations, and, for manufacturers, the notification of a high risk of illegitimacy described in section 582(b)(4)(B)(ii)(II).

#### **C. For Manufacturers: High Risk of Illegitimacy Notifications<sup>11</sup>**

Section 582(b)(4)(B)(ii)(II) of the FD&C Act requires manufacturers to make notifications in certain circumstances for products that pose a high risk of illegitimacy. The provision states as follows:

*(II) HIGH RISK OF ILLEGITIMACY.--A manufacturer shall notify the Secretary and immediate trading partners that the manufacturer has reason to believe may have in the trading partner's possession a product manufactured by, or purported to be a product manufactured by, the manufacturer not later than 24 hours after determining or being notified by the Secretary or a trading partner that there is a high risk that such product is an illegitimate product. For purposes of this subclause, a 'high risk' may include a specific high risk that could increase the likelihood that illegitimate product will enter the pharmaceutical distribution supply chain and other high risks as determined by the Secretary in guidance pursuant to subsection (h).*

FDA interprets this provision to require manufacturers to notify (1) FDA and (2) the manufacturer's immediate trading partners (that the manufacturer has reason to believe may have in the trading partner's possession a product manufactured by, or purported to be a product manufactured by, the manufacturer) in three general scenarios:

- (1) Within 24 hours after determining or being notified by FDA or a trading partner that there is a high risk that a product that the manufacturer has reason to believe is in an immediate trading partner's possession is an illegitimate product.

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<sup>11</sup> This section of the guidance is being distributed for comment purposes only.

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- (2) Within 24 hours after determining or being notified by FDA or a trading partner that there is a specific high risk that could increase the likelihood that illegitimate product will enter the U.S. pharmaceutical distribution supply chain.
- (3) Within 24 hours after determining or being notified by FDA or a trading partner that there exists an “other high risk” as determined by FDA in guidance pursuant to subsection 582(h).

FDA believes that Congress intended section 582(b)(4)(B)(ii)(II) to leverage the surveillance systems that many manufacturers already have in place to detect counterfeit and otherwise violative versions of their products. Manufacturers could learn about products with a high risk of illegitimacy from a variety of sources, including from within their own company, from their trading partners, from the FDA, or from other domestic and/or foreign regulatory authorities—even when a product may not be in the manufacturer’s possession or control.

Below are scenarios and examples in which a manufacturer should make a notification under section 582(b)(4)(B)(ii)(II).

1. *High Risk of Illegitimacy Notification for Products That the Manufacturer Has Reason to Believe Are in an Immediate Trading Partner’s Possession*

The first general scenario, described above, involves notifications for products that the manufacturer has reason to believe are in an immediate trading partner’s possession.

An example of this scenario might occur when the manufacturer is asked to coordinate a suspect product investigation by an immediate trading partner under section 582(c)(4)(B), 582(d)(4)(B), or 582(e)(4)(B), and the manufacturer determines that there is a high risk that the product is illegitimate. Some sample scenarios involving high risks of illegitimacy, in which a manufacturer should make a notification, include:

- A manufacturer learns from a trading partner that a suspect product purporting to be one produced by that manufacturer has been found in the U.S. pharmaceutical distribution supply chain. The manufacturer examines the suspect product and believes the product could be illegitimate but wants to take additional steps before determining that it is illegitimate. The manufacturer has reason to believe that additional illegitimate products are in the possession of immediate trading partners. For example, a wholesale distributor informs a manufacturer that it believes it has a counterfeit of that manufacturer’s product. The wholesale distributor sends the product to the manufacturer. The manufacturer examines the product and believes it could be counterfeit, but wants to perform a laboratory analysis or other analysis for confirmation.
- A manufacturer learns that its product has been stolen or diverted in the United States while not in its possession or control, and the manufacturer has reason to believe that an immediate trading partner might have the stolen or diverted product in its possession.

2. *Specific High Risks That Could Increase the Likelihood of an Illegitimate Product Entering the U.S. Pharmaceutical Distribution Supply Chain*

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Section 582(b)(4)(B)(ii)(II) states that a high risk of illegitimacy may include a “specific high risk” that could increase the likelihood that illegitimate product will enter the pharmaceutical distribution supply chain. In such cases, the product has not yet entered the pharmaceutical distribution supply chain, so no immediate trading partners would have it in their possession. Section 582(b)(4)(B)(ii)(II) thus would require the manufacturer to make a notification to FDA, but the manufacturer would not be required to notify immediate trading partners. To help ensure the integrity of the supply chain, however, FDA recommends that a manufacturer notify its immediate trading partners of such “specific high risk[s]” even if that manufacturer does not have reason to believe that its immediate trading partners may have the high risk product in their possession. Some examples involving specific high risks include:

- A manufacturer learns that a product with a high risk of illegitimacy (purporting to be one produced by that manufacturer) has been found in another country, and that such product is likely destined for a trading partner in the United States. For instance, the manufacturer learns from a foreign regulatory authority that one of its products has been counterfeited in another country, and that some of that product is on a cargo ship destined for the United States for delivery to a wholesale distributor.
- A manufacturer learns that its product was stolen or diverted in another country, and that such product is destined for the United States in a manner that leads the manufacturer to believe the product will likely enter the U.S. pharmaceutical distribution supply chain. For instance, the manufacturer learns from a foreign law enforcement agency that its product was stolen during transport in another country and is on a plane destined for the United States for delivery to a dispenser.
- A manufacturer learns that there is a high risk that its product has been intentionally adulterated in another country such that the product would result in serious adverse health consequences or death to humans, and that such product is likely destined for the United States in a manner that leads the manufacturer to believe the product will enter the pharmaceutical distribution supply chain. For instance, the manufacturer learns from its own investigation that there is a high risk that a contaminant that would result in serious adverse health consequences or death to humans was added to a product in another country and sent to a repackager in the United States.

As noted above, the scenarios given in sections 1 and 2 are examples, rather than an exhaustive list of circumstances in which trading partners should make notifications under section 582(b)(4)(B)(ii)(II).

### *3. Other High Risks as Determined by FDA: High Risk of Illegitimacy Notification Where a Manufacturer Has Reason to Believe the Product Has Entered the Pharmaceutical Distribution Supply Chain*

Section 582(b)(4)(B)(ii)(II) of the FD&C Act permits FDA to determine, through guidance pursuant to section 582(h), “other high risks” that would trigger a notification under this provision. FDA believes that one “other high risk” not covered by the two general scenarios described above is when a manufacturer has reason to believe that an illegitimate product has



entered the pharmaceutical distribution supply chain, even though the manufacturer does not have reason to believe that an immediate trading partner possesses the high risk product.<sup>12</sup> As with the second general scenario, described above, section 582(b)(4)(B)(ii)(II) would require the manufacturer to make a notification to FDA, but the manufacturer would not be required to notify immediate trading partners. To help ensure the integrity of the supply chain, however, FDA recommends that a manufacturer notify its immediate trading partners of this “other high risk,” even if that manufacturer does not have reason to believe that its immediate trading partners may have the high risk product in their possession.

A manufacturer could learn that a product with a high risk of illegitimacy that was manufactured by (or purported to be manufactured by) that manufacturer, may be in the possession of a trading partner, but that trading partner is not an immediate trading partner of the manufacturer. Some examples that involve this other high risk include:

- A manufacturer learns that a licensed health care practitioner is administering an oncology drug to patients that purports to have been manufactured by that manufacturer but the manufacturer determines that there is a high risk that the drug is a counterfeit. The licensed health care practitioner purchased the drug from a wholesale distributor, so he/she is not an immediate trading partner of the manufacturer. However, the manufacturer believes that the product has entered the pharmaceutical distribution supply chain.
- A manufacturer learns that its product has been stolen or diverted in the United States, and the manufacturer learns that a patient filled a prescription and received some of the stolen or diverted product. The patient suffers an adverse event, and FDA and the manufacturer are notified of that situation. Because the dispenser did not purchase the product from the manufacturer, it is not an immediate trading partner of the manufacturer. However, the product has entered the pharmaceutical distribution supply chain.
- A manufacturer learns that wholesale distributor B received product and transaction history going back to the manufacturer from wholesale distributor A, but the listed dosage form of the product on the transaction history is not one that has ever been used by the manufacturer. Wholesale distributor B provided a copy of the transaction history it received from wholesale distributor A to the manufacturer, and the manufacturer concluded, after reviewing the copy and receiving similar reports from other trading partners, that a fraudulent transaction had occurred. Because wholesale distributor B did not purchase the product from the manufacturer, it is not an immediate trading partner of the manufacturer. However, the product has entered the pharmaceutical distribution supply chain.

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<sup>12</sup> FDA reserves authority to articulate additional “other high risk[s]” in subsequent guidance(s).

#### **IV. NOTIFICATION OF ILLEGITIMATE PRODUCTS AND PRODUCTS WITH A HIGH RISK OF ILLEGITIMACY**

##### **A. Notification to FDA**

As discussed above, trading partners must, as applicable, make the notifications described in section 582(b)(4)(B)(ii)(I), (c)(4)(B)(ii), (d)(4)(B)(ii), and (e)(4)(B)(ii) of the FD&C Act related to illegitimate product determinations, and, for manufacturers, the notification of a high risk of illegitimacy described in section 582(b)(4)(B)(ii)(II). This section of the guidance addresses the process by which trading partners should notify FDA and other trading partners regarding illegitimate products under section 582. After review of the circumstances surrounding the event, if FDA determines that notification is not required under section 582(b)(4)(B)(ii)(I), (c)(4)(B)(ii), (d)(4)(B)(ii), (e)(4)(B)(ii), or (b)(4)(B)(ii)(II) of the FD&C Act, FDA intends to inform the submitting entity.

##### *1. Process to Notify FDA of Illegitimate Products*

The following process should be used to notify FDA of illegitimate products:

- (1) Trading partners should access FDA's Web page at <http://www.accessdata.fda.gov/scripts/cder/email/drugnotification.cfm> for notifications.
- (2) Trading partners should follow the instructions on the Web page for accessing Form FDA 3911 (Appendix 1). Using this form, trading partners should provide information about the person or entity initiating the notification, the product determined to be illegitimate that is the subject of the notification to FDA, and a description of the circumstances surrounding the event that prompted the notification.
- (3) Form FDA 3911 should be submitted using the method provided in the form or on the Web page.
- (4) FDA will acknowledge receipt of the notification and assign an incident number. This number should be referenced in all future correspondence about the illegitimate product, including any request for termination.
- (5) In addition to notifying FDA, the trading partner that determines it has an illegitimate product in its possession or control must notify all immediate trading partners that it has reason to believe may also possess the drug. Trading partners may notify other trading partners of an illegitimate product using existing systems and processes used for similar types of communications to those partners, which might include, but are not limited to, posting of notifications on a company Web site, telephoning, sending an email, or mailing or faxing a notification.

##### *2. Process used by manufacturers to Notify FDA of a Product With a High Risk of Illegitimacy*

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The following process should be used by manufacturers to notify FDA of a product with a high risk of illegitimacy: under section 582(b)(4)(B)(ii)(II):

- (1) Manufacturers should access FDA's Web page at:  
<http://www.accessdata.fda.gov/scripts/cder/email/drugnotification.cfm>
- (2) Manufacturers should follow the instructions on the Web page for accessing Form FDA 3911 (Appendix 1). Using this form, manufacturers should provide information about the person or entity initiating the notification, the product determined to have a high risk of illegitimacy that is the subject of the notification to FDA, and a description of the circumstances surrounding the event that prompted the notification.
- (3) FDA will acknowledge receipt of the notification and assign an incident number. This number should be documented in all future correspondence about the product with the high risk of illegitimacy, including any request for termination.
- (4) In addition to notifying FDA, the manufacturer that determines that a product has a high risk of illegitimacy must notify all immediate trading partners that it believes may possess the drug. Manufacturers may notify other trading partners of a product with a high risk of illegitimacy using existing systems and processes used for similar types of communications to those partners, which might include, but are not limited to, posting of notifications on a company Web site, telephoning, sending an email, or mailing or faxing a notification.
- (5) If a product with a high risk of illegitimacy is found to be an illegitimate product, manufacturers should submit a follow-up notification that explains the updated classification and references the incident number of the original notification of high risk of illegitimacy.
- (6) If it is determined that a product that was subject to a high risk of illegitimacy notification is not an illegitimate product, manufacturers must submit a request for termination of the high risk of illegitimacy notification to the FDA according to the process in Section B below.

**B. Process for Termination of Notification in Consultation With FDA<sup>13</sup>**

Section 582(h)(2)(A) of the FD&C Act directs FDA to issue guidance setting forth the process that trading partners shall follow for terminating notifications regarding illegitimate product, or for manufacturers, terminating notification of a high risk of illegitimacy, in consultation with FDA, under section 582(b)(4)(B), (c)(4)(B), (d)(4)(B), and (e)(4)(B). Section 582(b)(4)(B), (c)(4)(B), (d)(4)(B), and (e)(4)(B) require trading partners to have in place systems to enable them to terminate notifications, in consultation with FDA. This section of the guidance addresses

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<sup>13</sup> Insofar as section IV.B. of this guidance sets forth the process by which trading partners should terminate notifications of an illegitimate product or products with a high risk of illegitimacy in consultation with FDA, it has binding effect.

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the process by which trading partners must terminate such notifications in consultation with FDA. This process must be used when trading partners believe that a notification they made to FDA regarding illegitimate product, or for a manufacturer, a notification of a high risk of illegitimacy, is no longer necessary.

The process for terminating notifications in consultation with FDA is as follows:

- (1) The trading partner making a notification to the FDA shall be responsible for making the request for termination.
- (2) Trading partners must access FDA's Web page at <http://www.accessdata.fda.gov/scripts/cder/email/drugnotification.cfm> for termination of notifications.
- (3) Trading partners must follow the instructions on the Web page for accessing Form FDA 3911 (Appendix 1). Using this form, trading partners must provide to FDA information about the person or entity initiating the request for termination, the illegitimate product or the product with a high risk of illegitimacy, the notification that was issued, and an explanation about what actions have taken place or what information has become available that makes the notification no longer necessary. Trading partners should include the FDA-assigned incident number associated with the notification in the request for termination.
- (4) This form must be submitted by using the method provided in the form or on the Web page. The trading partner's submission of a request for termination of a notification will be viewed as a request for consultation with FDA, as required in section 582 of the FD&C Act. FDA may request any additional information it determines necessary to complete the consultation.
- (5) FDA will review the request and consult with the trading partner. The response time will depend on the number of requests for termination and the circumstances surrounding the requests for termination that are received by FDA.

FDA interprets the DSCSA's requirement for trading partners to "mak[e] a determination, in consultation with the Secretary, that a notification is no longer necessary"<sup>14</sup> to require that trading partners provide the Agency with an opportunity to provide its expert views and advice on proposed terminations of notifications. Therefore, a trading partner must wait until FDA responds to the termination request before the trading partner notifies other trading partners that a notification is terminated. FDA intends to respond to requests for termination within 10 business days of submission. In some cases, FDA may contact a trading partner to notify the partner that additional time is needed to respond to the request for termination. If a trading partner believes that exigent circumstances require expedited consideration of a termination request (e.g., a potential drug shortage), the trading partner must describe those circumstances to FDA in the termination request on the FDA Form 3911 when making the request for termination.

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<sup>14</sup> Section 582(b)(4)(iv), (c)(4)(B)(iv), (d)(4)(B)(iv), and (e)(4)(B)(iv) of the FD&C Act.

Under section 582(b)(4)(B), (c)(4)(B), (d)(4)(B), and (e)(4)(B) of the FD&C Act, after FDA provides its consultation response, and the trading partner determines that the notification is no longer necessary, the trading partner that made the request for termination must promptly notify immediate trading partners that the notification has been terminated. Trading partners may notify their trading partners of a termination using existing systems and processes used for similar types of communications to those partners, which might include, but are not limited to, posting of notifications on a company Web site, telephoning, sending an email, or mailing or faxing a letter or notification.

## **V. PAPERWORK REDUCTION ACT OF 1995**

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The time required to complete this information collection is estimated to average as follows.

### *Notify FDA of an Illegitimate Product:*

- 1 hour for manufacturers and repackagers
- 1 hour for wholesale distributors
- 1 hour for dispensers

### *Notify Trading Partners of an Illegitimate Product or a Product With a High Risk of Illegitimacy:*

- 0.20 hour (12 minutes) for manufacturers and repackagers
- 0.20 hour (12 minutes) for wholesale distributors
- 0.20 hour (12 minutes) for dispensers

### *Consult With FDA and Terminate Notification:*

- 1 hour for manufacturers and repackagers
- 1 hour for wholesale distributors
- 1 hour for dispensers

### *Notify Trading Partners That a Termination Has Been Terminated:*

- 0.20 hour (12 minutes) for manufacturers and repackagers
- 0.20 hour (12 minutes) for wholesale distributors
- 0.20 hour (12 minutes) for dispensers

These estimates include the time to review instructions, gather the data needed, and complete and review the information collection and transmit to FDA. It also includes the time to notify trading

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partners. Send comments regarding this burden estimate or suggestions for reducing this burden to: Office of Regulatory Policy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0806 (expires 12/31/2018).

**APPENDIX 1: FORM FDA 3911**

FORM FDA 3911 and the FORM FDA 3911 Instructions Supplement are available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/HumanDrugForms/default.htm>

If you are experiencing difficulties accessing the form, please contact the FDA forms manager at [FormsManager@OC.FDA.GOV](mailto:FormsManager@OC.FDA.GOV) for assistance.

# **Attachment**



Compounded By: CSJ PROVIDENCE ST JOSEPH MEDICAL CENTER  
501 S Buena Vista ST, Burbank CA 91505-4809 818-843-5111

**CSJ NEUROTEL-2405-01**  
78 yrs [10/17/1938] [REDACTED] Ord# [REDACTED]  
**levETIRacetam (KEPPRA) 750 mg in sodium chloride**

**0.9% 100 mL IVPB Intravenous**  
Vol: 107.5 mL Freq: Q12H Rate: 430 mL/hr  
Inf Over: 15 Minutes Due: [ ] [REDIS] AG  
Prep Date: 11/29/16  
**Do not refrigerate.**

**Do Not Start After:**  This originally said "Exp:"



Tech: RPh:



# **Attachment**

## Why GAO Did This Study

Drug compounding is the process of combining, mixing, or altering ingredients to create a drug tailored to the needs of an individual patient. An outbreak of fungal meningitis in 2012 linked to contaminated compounded drugs raised concerns about state and federal oversight of drug compounding. The Drug Quality and Security Act, enacted in 2013, helped clarify FDA's authority and included a provision for GAO to report on drug compounding.

This report examines (1) the settings in which drugs are compounded, and the extent of drug compounding; (2) state laws and policies governing drug compounding, and how they are enforced; (3) communication between states and FDA, as well as among states, regarding drug compounding, and the associated challenges; and (4) steps FDA has taken to implement its responsibilities to oversee drug compounding, and challenges that have been reported with these efforts.

GAO surveyed state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands (all but 4 completed the survey); reviewed documents and interviewed officials from FDA, 25 stakeholder organizations (including national pharmacy and medical associations), and agencies in 3 states selected for having differing laws and policies; reviewed relevant laws; and examined FDA data on drug compounding inspections and actions taken.

HHS provided general comments on a draft of this report, as well as technical comments, which were incorporated as appropriate.

View [GAO-17-64](#). For more information, contact Marcia Crosse at (202) 512-7114 or [crossesem@gao.gov](mailto:crossesem@gao.gov).

## DRUG COMPOUNDING

### FDA Has Taken Steps to Implement Compounding Law, but Some States and Stakeholders Reported Challenges

#### What GAO Found

GAO's survey of state pharmacy regulatory bodies found that drugs are compounded in a variety of health care settings, and some data are collected on the number of entities that compound drugs (drug compounders), but not the volume of compounded drugs. In addition to pharmacies, drug compounding settings include physicians' offices and outsourcing facilities—a new type of facility established by law in 2013, which can compound sterile drugs without patient-specific prescriptions and register with and are inspected by the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS). While FDA and some states collect data on drug compounders, only one state reported collecting data on the number of prescriptions or the volume of compounded drugs. In addition, states GAO surveyed and stakeholders GAO interviewed did not collect data specific to the extent of compounding performed by nonpharmacists, such as physicians.

Nearly all of the states GAO surveyed reported having drug compounding laws, regulations, or policies, though few apply to nonpharmacists, and states conduct inspections and can take actions to enforce them. Less than 20 percent of states reported having laws, regulations, or policies specific to compounding by nonpharmacists (e.g., physicians), and these state laws varied. To help ensure compliance, most states reported inspecting drug compounders, such as pharmacies and outsourcing facilities, and most states can take several types of actions against pharmacies, including monetary fines, and suspension and revocation of a license or registration.

Most states reported being satisfied with their communication with FDA and other states, although some reported challenges. About three quarters of the states reported participating in FDA-sponsored activities, such as intergovernmental meetings, and obtaining information from FDA's website. Some states reported challenges with this communication, such as getting FDA to respond to requests for information. In terms of communication between states, most survey respondents reported that they are satisfied with this communication, which occurs through conferences and other activities.

FDA has taken steps to implement its regulatory responsibilities to oversee drug compounding, but states and stakeholder organizations have cited challenges and concerns. FDA has issued numerous draft and final guidance documents related to drug compounding, and conducted more than 300 inspections of drug compounders, which resulted in actions such as FDA issuing warning letters and voluntary recalls of potentially contaminated compounded drugs. Some stakeholder organizations said the amount of time it takes FDA to finalize the guidance and other documents—including those required by the 2013 law—is challenging. FDA officials noted that reviewing the large number of comments received has contributed to the time the agency has taken to finalize them. States and stakeholder organizations also cited concerns related to access to compounded drugs and differences between states and FDA on the appropriate inspection protocols to use when inspecting drug compounders. In August 2016, FDA changed its procedures to address concerns about the appropriate protocols to use for these inspections.



November 2016

# DRUG COMPOUNDING

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to Implement  
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# GAO Highlights

Highlights of [GAO-17-64](#), a report to congressional committees

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Figure

Figure 1: Percentage of States Reporting each Level of Satisfaction with Food and Drug Administration (FDA) Communication Regarding Drug Compounding

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**Abbreviations**

CGMP	current good manufacturing practice
DQSA	Drug Quality and Security Act
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
HHS	Department of Health and Human Services
MOU	memorandum of understanding
USP	U.S. Pharmacopeial Convention

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November 17, 2016

The Honorable Lamar Alexander  
Chairman  
The Honorable Patty Murray  
Ranking Member  
Committee on Health, Education, Labor, and Pensions  
United States Senate

The Honorable Fred Upton  
Chairman  
The Honorable Frank Pallone, Jr.  
Ranking Member  
Committee on Energy and Commerce  
House of Representatives

Drug compounding is the process of combining, mixing, or altering ingredients to create a medication tailored to the needs of an individual patient. Compounding is typically used to prepare medications that are not commercially available, such as medication for a patient who is allergic to an ingredient in a mass-produced pharmaceutical product. At the state level, drug compounding has traditionally been overseen by state pharmacy regulatory bodies (e.g., boards of pharmacy). In addition to pharmacists, other health care practitioners, such as physicians, may prepare compounded drugs, and these practitioners are generally overseen by their respective state licensing agencies (e.g., state medical boards). At the federal level, the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), is responsible for overseeing the safety and quality of domestic and imported pharmaceutical products under the Federal Food, Drug, and Cosmetic Act (FDCA).<sup>1</sup>

Concerns have been raised that some pharmacies were going beyond traditional drug compounding for individual patients by compounding and selling large quantities of drugs to facilities in multiple states without meeting federal safety and other requirements applicable to new drugs.

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<sup>1</sup>See 21 U.S.C. §§ 301 *et seq.*

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Further, an outbreak of fungal meningitis in 2012 linked to contaminated compounded steroid injections, which resulted in over 60 deaths and hundreds of people getting ill, raised questions about the safety and quality of compounded drugs and concerns about state and federal oversight of drug compounding. In July 2013, we reported that FDA's oversight authority was unclear and recommended that Congress consider clarifying FDA's authority to oversee drug compounding.<sup>2</sup> The Drug Quality and Security Act (DQSA), enacted in November 2013, helped clarify FDA's authority to oversee drug compounding nationally and created a new category of compounders called outsourcing facilities—facilities that meet certain FDA requirements, including compounding sterile drugs, that register with and are inspected by FDA, and are allowed to compound drugs without patient-specific prescriptions. The act also included a provision for GAO to review drug compounding.<sup>3</sup> This report examines

1. the settings in which drugs are compounded, and the extent of drug compounding in each state;
2. state laws, regulations, and policies governing drug compounding, and how they are enforced;
3. how communication is conducted between states and FDA, as well as among states, regarding compounding, and any associated challenges; and
4. steps FDA has taken to implement its responsibilities to oversee drug compounding since enactment of the DQSA, and any challenges that have been reported with these efforts.

This report also includes an appendix that describes information about the safety and quality of compounded drugs that is available to purchasers of these drugs (e.g., hospitals, health systems, and patients). (See app. I.)

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<sup>2</sup>See GAO, *Drug Compounding: Clear Authority and More Reliable Data Needed to Strengthen FDA Oversight*, [GAO-13-702](#) (Washington, D.C.: July 31, 2013). We also reported on drug compounding in 2003; see GAO, *Prescription Drugs: State and Federal Oversight of Drug Compounding by Pharmacies*, [GAO-04-195T](#) (Washington, D.C.: Oct. 23, 2003).

<sup>3</sup>Pub. L. No. 113-54, tit. I, 127 Stat. 587 (2013).

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To address our objectives, we administered a web-based survey to the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands.<sup>4</sup> We achieved a survey response rate of 93 percent: 50 of the 54 states completed the survey. The survey collected information from the states on the settings in which drug compounding occurs; available data on drug compounding in each state; state laws, regulations, and policies related to drug compounding; activities states have participated in related to drug compounding with FDA and other states; states' perspectives on communication with FDA and other states; and their perspectives on FDA's implementation of the DQSA, among other things.<sup>5</sup>

In addition, we interviewed officials from 25 stakeholder organizations that have a stake or an interest in drug compounding to obtain information on topics such as state laws, regulations, and policies on drug compounding; their perspectives on any challenges in communication between FDA and states, as well as among states, related to drug compounding; and their perspectives on FDA's implementation of the DQSA. We selected these stakeholder organizations to include national organizations representing (1) pharmacies and pharmacists, including those that compound drugs; (2) physicians, including those in medical specialties identified as compounding drugs; and (3) state boards of pharmacy and state medical boards; as well as experts in drug compounding, and an organization that conducted research related to drug compounding. We reviewed relevant documents provided by these stakeholder organizations, including comments submitted to FDA regarding FDA's compounding-related activities. In addition to officials from the 25 stakeholder organizations, we interviewed state officials, including officials from the boards of pharmacy, medical boards, and the agencies that have oversight responsibility for outsourcing facilities in three selected states—North Carolina, Minnesota, and Texas. We selected these states because they reported differing laws, regulations, or policies related to drug compounding (such as oversight of outsourcing facilities) in their responses to the survey, among other reasons. We obtained information on state laws, regulations, and policies related to drug compounding in each selected state, and we

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<sup>4</sup>We refer to all of the state pharmacy regulatory bodies that we surveyed as states in this report.

<sup>5</sup>Not all of the 50 respondents that completed the survey answered every survey question.

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obtained additional details for certain survey responses from the board of pharmacy officials. In addition, we interviewed officials from two pharmacy benefit managers—third-party administrators of prescription drug programs for certain health plans and federal and state government employee plans—to obtain information related to drug compounding, including how these entities determine the safety and quality of compounded drugs. We used information collected from our survey and obtained from the interviews and related documents to describe the information about the safety and quality of compounded drugs that is available to purchasers of these drugs. The perspectives of the officials from the 25 stakeholder organizations, three selected states, and two pharmacy benefit managers are not generalizable, but provided us with valuable insight on these issues.

We interviewed FDA officials to obtain information on steps FDA has taken to implement its regulatory responsibilities to oversee drug compounding since enactment of the DQSA, and we reviewed relevant laws and regulations related to drug compounding. In addition, we reviewed relevant documents from FDA, including FDA's draft memorandum of understanding (MOU) with states regarding distribution of compounded human drug products, and FDA's draft and final guidance related to drug compounding and implementation of the DQSA, such as FDA's final guidance on registration of outsourcing facilities. We also analyzed FDA data on inspections of drug compounders, and data on actions taken, such as the issuance of warning letters related to drug compounding.<sup>6</sup> We determined that the data we used from FDA on inspections and actions taken related to drug compounding were sufficiently reliable for purposes of this study by discussing data collection processes and limitations of the data with agency officials, and comparing the data against other published sources. See appendix II for more detailed information on our objectives, scope, and methodology.

We conducted this performance audit from May 2015 to November 2016 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our

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<sup>6</sup>An FDA warning letter is a correspondence that notifies a responsible individual or firm that the agency considers one or more products, practices, processes, or other activities to be in violation of the FDCA, its implementing regulations, and other federal statutes.

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findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

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## Background

Traditionally, drug compounding is the process of combining, mixing, or altering ingredients to create a customized medication for an individual patient. For example, a pharmacist may tailor a medication for a patient who is allergic to an ingredient in a conventionally manufactured drug or prepare a liquid formulation for a patient who has difficulty swallowing pills. Pharmacies sometimes compound drugs in advance of receiving individual patient prescriptions in anticipation of receiving prescriptions based on historical prescribing patterns—a practice referred to as anticipatory compounding. Drugs are also sometimes compounded to be kept in stock by a hospital, clinic, or physician’s office to administer to patients, such as patients with an immediate need for the compounded drug—a practice referred to as office-use compounding. In addition to pharmacists, other health care practitioners, such as physicians, may also compound drugs. Compounded drugs include nonsterile preparations—such as capsules, ointments, creams, gels, and suppositories—and sterile preparations, including intravenously administered fluids, ophthalmic products, and other injectable drugs. Compounded sterile drugs pose special risks of contamination if not made properly, and require special safeguards to prevent injury or death to patients receiving them. In addition, nonsterile drugs that are compounded improperly (e.g., if they contain too much active ingredient) can also cause serious harm.

An outbreak of fungal meningitis in 2012 linked to contaminated compounded drugs led to questions about the safety and quality of compounded drugs, and raised concerns about state and federal oversight of drug compounding. At the time, concerns were raised by FDA and others—including members of Congress and public health advocates—that some pharmacies were going beyond traditional drug compounding by producing large quantities of compounded drugs without prescriptions for individual patients, and selling those compounded drugs to facilities in multiple states. Many believed that these types of pharmacies were engaging in conventional manufacturing under the guise of compounding without meeting safety and other requirements with which conventional drug manufacturers must comply. In July 2013, we

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found that the authority of FDA to oversee drug compounding was unclear and this lack of clarity had resulted in gaps in oversight of drug compounding.<sup>7</sup> Specifically, two federal circuit court decisions had resulted in differing FDA authority in different parts of the country, and these inconsistent decisions contributed to challenges in FDA's ability to inspect and take enforcement action against entities engaging in drug compounding.

In November 2013, the DQSA was enacted to help clarify FDA's authority to oversee drug compounding. The act established a new type of facility, an outsourcing facility, that prepares sterile compounded drugs and which may compound drugs without patient-specific prescriptions.<sup>8</sup> These outsourcing facilities differ from drug compounders operating under section 503A of the FDCA, which exempts drugs compounded by a licensed pharmacist or licensed physician based on the receipt of a valid prescription, for an identified individual patient, and in accordance with certain other conditions, from three key provisions of the FDCA that are otherwise applicable.<sup>9</sup> The DQSA also removed certain provisions from section 503A of the FDCA that were found to be unconstitutional by the U.S. Supreme Court in 2002, and affirmed the validity of the remaining

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<sup>7</sup>See [GAO-13-702](#).

<sup>8</sup>Section 503B of the FDCA, as added by the DQSA, 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. Outsourcing facilities must comply with current good manufacturing practice (CGMP) requirements and will be inspected by FDA according to a risk-based schedule. In addition, outsourcing facilities must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the drug products they compound.

<sup>9</sup>Compounded drug products meeting the requirements of section 503A are exempt from the following three requirements in the FDCA: the requirements to comply with CGMP requirements, label drugs with adequate directions for use, and have an FDA-approved new drug or abbreviated new drug application. References to sections 503A and 503B in this report are to sections 503A and 503B of the FDCA, as codified at 21 U.S.C. §§ 353a, 353b.

provisions in section 503A.<sup>10</sup> Table 1 outlines some of the requirements under section 503A, applicable to 503A compounders, and section 503B, applicable to outsourcing facilities.<sup>11</sup>

**Table 1: Requirements Applicable to Drug Compounders under Sections 503A and 503B of the FDCA**

	<b>503A compounder<sup>a</sup></b>	<b>503B outsourcing facility</b>
Who may compound	Licensed pharmacist in a state-licensed pharmacy or federal facility, or licensed physician.	Licensed pharmacist or individual under the direct supervision of a licensed pharmacist in an outsourcing facility.
Type of drugs compounded	May compound nonsterile drugs or sterile drugs.	Must compound sterile drugs and may also compound nonsterile drugs.
Prescriptions	Compounding must be based on receipt of a valid prescription for an identified individual patient. <sup>b</sup>	Compounding may or may not be based on receipt of prescriptions for identified individual patients.
Registration with the Food and Drug Administration (FDA)	No registration requirement.	Must register with FDA and reregister annually.
Inspections	No requirement for FDA to inspect; while FDA may choose to inspect, a pharmacy's or physician's records may be exempt from inspection in certain cases. <sup>c</sup>	Inspected by FDA according to a risk-based schedule, based on the known safety risks of such outsourcing facilities.
Quality standards	Exempt from current good manufacturing practice (CGMP) requirements, but not from other quality requirements, such as the prohibition on preparing, packing, or holding drugs under insanitary conditions. <sup>d</sup>	Must comply with CGMP requirements, in addition to other quality requirements, such as the prohibition on preparing, packing, or holding drugs under insanitary conditions. <sup>d</sup>

<sup>10</sup>In 2001, the United States Court of Appeals for the Ninth Circuit struck down all of the advertising, promotion, and solicitation provisions of section 503A of the FDCA because those provisions violated the Free Speech Clause of the First Amendment. The court also held that, because these provisions could not be severed from the remainder of section 503A, all of section 503A was invalid. In 2002, the United States Supreme Court struck down the law's advertising, promotion, and solicitation restrictions without addressing whether the rest of section 503A remained law. See *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002). For additional information on the history of FDA's authority over drug compounding and approach to oversight before enactment of the DQSA, see [GAO-13-702](#).

<sup>11</sup>For purposes of this report, we use the term 503A compounder to refer to individuals or entities that are not outsourcing facilities that qualify for the exemptions under section 503A of the FDCA, including pharmacies, physicians, and federal facilities. Drug compounders that do not qualify for the exemptions under section 503A, and are not outsourcing facilities under section 503B, are regulated as conventional manufacturers and are subject to the provisions of the FDCA applicable to such manufacturers.

	<b>503A compounder<sup>a</sup></b>	<b>503B outsourcing facility</b>
Labeling <sup>e</sup>	No labeling requirements.	Compounded medications must have a label that includes, among other things <ul style="list-style-type: none"> <li>the statement, "This is a compounded drug";</li> <li>the date that the drug was compounded and the expiration date;</li> <li>the statement "Not for resale" and, where applicable, "Office Use Only";</li> <li>a list of active and inactive ingredients; and</li> <li>the name, address, and phone number of the outsourcing facility.</li> </ul>
Reporting of drugs compounded	No reporting requirements.	Must submit a report to FDA upon initial registration and twice per year, identifying the drugs compounded by the facility during the previous 6 months. For each drug, the report must include the following information <ul style="list-style-type: none"> <li>the active ingredient and its source;</li> <li>the strength of the active ingredient per unit;</li> <li>the dosage form and route of administration;</li> <li>the package description;</li> <li>the number of units produced; and</li> <li>the National Drug Code number of the source drug or bulk active ingredient, if available.</li> </ul>
Reporting of adverse events	No reporting requirements.	Must submit adverse event reports to FDA.
Fees	No fee requirements.	Must pay annual establishment fees and any applicable reinspection fees.
Compounded drugs that are essentially copies of commercial drugs	Must not compound regularly or in inordinate amounts drug products that are essentially a copy of a commercially available drug product.	Compounded drugs must not be essentially a copy of one or more approved drugs.
Bulk substances	Product is compounded using bulk drug substances that are (1) components of FDA-approved human drugs; (2) the subject of an applicable monograph; or (3) appear on a list developed by FDA.	Product is compounded using bulk drug substances that either appear on a list developed by FDA or are used to compound drugs that appear on FDA's drug shortage list at the time of compounding, distribution, and dispensing.
Drugs that may not be compounded <sup>f</sup>	Must not compound a drug product that (1) appears on a list developed by FDA of drug products withdrawn or removed from the market for safety or efficacy reasons, or (2) appears on a list developed by FDA of drug products that present demonstrable difficulties for compounding.	Must not compound a drug product that (1) appears on a list developed by FDA of drug products withdrawn or removed from the market for safety or efficacy reasons or (2) appears on a list of drugs or categories of drugs that present demonstrable difficulties for compounding.

Source: GAO analysis of the Federal Food, Drug, and Cosmetic Act (FDCA). | GAO-17-64

Notes: Drug compounders may also be subject to additional requirements under the FDCA.

<sup>a</sup>503A compounders are individuals or entities that are not outsourcing facilities that qualify for the exemptions under section 503A of the FDCA, including pharmacies, physicians, and federal facilities. Drug compounders that do not qualify for the exemptions under section 503A, and are not outsourcing facilities under section 503B, are regulated as conventional manufacturers and are subject to the provisions of the FDCA applicable to such manufacturers.



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<sup>b</sup>Compounding can take place after the 503A compounder receives the prescription, or in limited quantities before the 503A compounder receives a prescription, provided the compounding is based on a history of receiving valid prescription orders for the product.

<sup>c</sup>A pharmacy's records are exempt from FDA's inspection authority if the pharmacy is in compliance with any applicable local laws regulating the practice of pharmacy and medicine, regularly engages in dispensing drugs upon a prescription from a licensed practitioner, and does not manufacture, prepare or compound drugs for sale other than during the regular course of their business of dispensing or selling drugs at retail. Even if a pharmacy or physician is exempt from a records inspection, FDA has general inspection authority to inspect any facility in which drugs are manufactured, processed, packed, or held. 21 U.S.C. § 374.

<sup>d</sup>CGMP requirements provide a framework for a manufacturer to follow to produce safe, pure, and high-quality drugs. See 21 C.F.R. pts. 210-211.

<sup>e</sup>Compounded drugs remain subject to labeling requirements in section 503(b) of the FDCA concerning dispensed prescription drugs, regardless of whether they are compounded by 503A compounders or 503B outsourcing facilities. 21 U.S.C. § 352(b).

<sup>f</sup>FDA is required to establish lists for each of these categories for 503A compounders and 503B outsourcing facilities.

While FDA is required to inspect outsourcing facilities, it does not routinely inspect 503A compounders, although it may in certain instances (e.g., in response to complaints).<sup>12</sup> In general, states regulate compounding as part of the practice of pharmacy and the state pharmacy regulatory bodies (e.g., boards of pharmacy) are responsible for oversight of the practice of pharmacy, which may include inspections of pharmacies that are 503A compounders. For example, a state board of pharmacy

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<sup>12</sup>FDA inspections may result in FDA issuing inspection observation reports, which are called FDA form 483 inspection observation reports, and, in some cases, warning letters or other regulatory actions. An FDA form 483 inspection observation report is a report that is issued at the conclusion of an inspection when FDA investigators have observed conditions that, in their judgment, may constitute violations of the FDCA and related acts.

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may inspect pharmacies that compound drugs for compliance with the U.S. Pharmacopeial Convention's (USP) compounding standards.<sup>13</sup>

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## Drugs Are Compounded in a Variety of Settings; FDA and Some States Collect Data on the Number of Drug Compounders, but Not the Volume of Compounded Drugs

Our survey of state pharmacy regulatory bodies found that drugs are compounded in a variety of pharmacy and other health care settings, including outsourcing facilities. While FDA and some states collect data on drug compounders, nearly all of the states reported that they did not collect data on the volume of compounded drugs.

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## Drugs Are Compounded in a Variety of Pharmacy and Other Health Care Settings

Our survey of state pharmacy regulatory bodies found that drugs, including sterile drugs, are compounded in a variety of pharmacy and other health care settings. Respondents in almost all of the states we surveyed reported that different types of pharmacies, such as retail and hospital pharmacies, were authorized to prepare sterile compounded drugs in their state. Respondents in most states also reported that FDA-registered outsourcing facilities were authorized to compound sterile drugs in their states; however, respondents in 5 states reported that these

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<sup>13</sup>USP is a scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements. USP's current suite of General Chapters for compounding includes: Chapter <797> *Pharmaceutical Compounding—Sterile Preparations*, which provides procedures and requirements for compounding sterile preparations; Chapter <795> *Pharmaceutical Compounding—Nonsterile Preparations*, which provides guidance on applying good compounding practices in the preparation of nonsterile compounded formulations for dispensing and/or administration to humans or animals; and Chapter <1160>—*Pharmaceutical Calculations in Prescription Compounding*, among others. According to USP officials, USP's compounding chapters reference over 40 additional USP chapters. In addition to setting standards that affect compounding, USP—through the United States Pharmacopeia-National Formulary, a compendium of public pharmacopeial standards—provides monographs for drug articles, including ingredients used in compounded preparations, and monographs for the compounded preparations themselves, comprising standards of identity, quality, purity, strength, packaging, and labeling.

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entities were not authorized to do so for reasons including that the state was still in the process of developing a state license for these entities. In addition, respondents in over half of the states reported that physicians' offices—both general practitioners' offices and medical specialty offices (e.g., dermatologists and pediatricians)—were authorized to prepare sterile compounded drugs in their states; however, respondents in several other states reported that they did not know if certain medical settings were authorized to do so. For example, respondents in 18 states reported that they did not know if general practitioners' offices were authorized. See table 2 for information on the types of entities authorized to prepare sterile compounded drugs.

**Table 2: Types of Entities Authorized to Prepare Sterile Compounded Drugs, by Number of Reporting States**

Type of entity	Number of states (%)			
	Yes, authorized	No, not authorized	Don't know	No response
Corporate chain pharmacies (e.g., Walgreens, CVS)	42 (84)	5 (10)	1 (2)	2 (4)
Retail pharmacies (e.g., independently owned pharmacies, community pharmacies, and compounding pharmacies that fill walk-in patient prescriptions)	45 (90)	2 (4)	0 (0)	3 (6)
Compounding pharmacies (e.g., large-scale pharmacies that do not fill walk-in patient prescriptions, and licensed in multiple states)	46 (92)	1 (2)	1 (2)	2 (4)
FDA-registered outsourcing facilities	39 (78)	5 (10)	4 (8)	2 (4)
Outsourcing facility (licensed or registered by state)	29 (58)	9 (18)	8 (16)	4 (8)
Hospital pharmacies	48 (96)	0 (0)	0 (0)	2 (4)
Outpatient clinics	33 (66)	4 (8)	11 (22)	2 (4)
Home infusion pharmacies	46 (92)	0 (0)	2 (4)	2 (4)
General practitioners' offices	26 (52)	4 (8)	18 (36)	2 (4)
Medical specialty offices (e.g., dermatologists, pediatricians)	26 (52)	5 (10)	18 (36)	1 (2)
Home health care agencies	15 (30)	11 (22)	22 (44)	2 (4)
Hospice and palliative care agencies	14 (28)	10 (20)	22 (44)	4 (8)

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Note: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

Respondents in several states reported that any licensed or registered pharmacy could potentially compound nonsterile drugs. For example, respondents in two states commented that almost all pharmacies compound or have the potential to compound nonsterile drugs, such as simple creams. A respondent in one state commented that they are under the assumption that any licensed pharmacy can perform nonsterile compounding without a special authorization to do so, and a respondent in another state reported that nearly all community and hospital pharmacies do at least some nonsterile compounding.

In addition, officials from some of the stakeholder organizations we interviewed said that certain medical specialists, such as dermatologists, pediatricians, and allergists, prepare compound drugs. They explained that, for example, some medical specialists mix nonsterile topical creams

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or sterile preparations, such as lidocaine (a local anesthetic agent that can be administered by injection), as part of their medical practice. However, some of these officials said that whether health care practitioners compounded drugs depended on what was considered compounding, and that some medical specialists generally use compounded drugs provided by a pharmacy or outsourcing facility and do not compound the drugs themselves.

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### FDA and Some States Collect Data on Drug Compounders, but Only One State Reported Collecting Data on the Volume of Compounded Drugs

According to FDA officials, there is no good source for data on the extent of drug compounding and who is doing it except for data on outsourcing facilities. Although outsourcing facilities are required to provide FDA with a report of the drugs they compounded during the previous 6-month period, including the number of units they produced, aggregate data on the listed drugs were not available at the time of our review. According to FDA officials, not all outsourcing facilities provided these reports and the data provided were not yet collected and maintained in a standard format. Therefore, the officials said that FDA does not input the data into a single database, but instead maintains this information on the individual spreadsheets that the outsourcing facilities provided. According to FDA, the agency plans to make necessary modifications to its electronic reporting system to accommodate the information outsourcing facilities must provide in the future so that outsourcing facilities will be able to electronically submit drug product reports into a single standardized format.<sup>14</sup> In addition, even though the compounded drugs are reported—and some outsourcing facilities report thousands of compounded drugs—FDA has not received data on the quantity of each drug listed in the reports in some cases, according to the officials. Further, while all outsourcing facilities are required to submit drug product reports to FDA, the officials we interviewed said that there are some facilities that have not provided it. As of April 22, 2016, 40 of the 59 outsourcing facilities had not provided some or all required reports. One FDA official said that to date, FDA has not taken regulatory action against outsourcing facilities

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<sup>14</sup>FDA issued revised draft guidance on drug product reporting for outsourcing facilities in November 2014, and when this guidance is finalized it will prescribe the form and manner in which outsourcing facilities are required to submit drug reporting information to FDA. See Food and Drug Administration, *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (Rockville, Md.: Nov. 2014).

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that have not provided the reports of the drugs they compounded unless FDA was already taking steps to address some other violation of statute by the outsourcing facility, including through the issuance of a warning letter. According to the FDA officials, this is because addressing all of the firm's violations that FDA has identified in a single action is a more effective mechanism to bring the firm into compliance and a more efficient use of agency resources than pursuing separate actions for discrete violations of the FDCA.

While respondents in almost all of the states we surveyed reported having license categories for resident and nonresident pharmacies, respondents in some states reported having other license categories, including those specific to sterile drug compounding.<sup>15</sup> For example, 12 states reported having a separate license category for resident pharmacies that compound sterile drugs and 12 states reported having a sterile compounding license category for nonresident pharmacies. Other respondents reported licensing categories for pharmacies that included nuclear pharmacies, home infusion pharmacies, and Internet/mail order pharmacies; and entities that distribute compounded drugs.<sup>16</sup> (See table 3.) In addition, respondents in some states reported that they do not have separate license categories for specific types of practice settings; however, they are aware of pharmacies and other entities in their state that engage in certain practice areas (e.g., pharmacies that engage in sterile compounding).

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<sup>15</sup>Resident pharmacies are those located within the state. Nonresident pharmacies are those located outside of the state.

<sup>16</sup>For example, a licensed wholesale distributor may distribute compounded drugs.

**Table 3: State-Reported Categories of Licenses, Permits, or Registrations for Pharmacies and Other Entities, by State**

Category of license, permit, or registration	Number of states (%)		
	Yes	No	No response
Resident pharmacies	50 (100)	0 (0)	0 (0)
Nonresident pharmacies	48 (96)	2 (4) <sup>a</sup>	0 (0)
Resident sterile compounding pharmacies	12 (24)	38 (76)	0 (0)
Nonresident sterile compounding pharmacies	12 (24)	38 (76)	0 (0)
Resident community pharmacy	22 (44)	27 (54)	1 (2)
Resident nuclear pharmacy	17 (34)	30 (60)	3 (6)
Resident long-term-care pharmacy	11 (22)	38 (76)	1 (2)
Resident hospital pharmacy	25 (50)	23 (46)	2 (4)
Resident home infusion pharmacy	7 (14)	41 (82)	2 (4)
Resident specialty pharmacy	8 (16)	40 (80)	2 (4)
Resident Internet or mail-order pharmacy	5 (10)	41 (82)	4 (8)
Nonresident Internet or mail-order pharmacy	11 (22)	35 (70)	4 (8)
Resident wholesale distributor <sup>b</sup>	41 (82)	7 (14)	2 (4)
Nonresident wholesale distributor <sup>b</sup>	36 (72)	10 (20)	4 (8)
Resident outsourcing facility	18 (36)	30 (60)	2 (4)
Nonresident outsourcing facility	15 (30)	31 (62)	4 (8)

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

<sup>a</sup>Two states reported that they have a pharmacy license, but not separate licenses for resident and nonresident pharmacies.

<sup>b</sup>Some states reported that they do not differentiate between resident and nonresident wholesale distributors, and some states reported that other state agencies, such as the department of health, oversee these entities.

In addition, respondents in half of the states we surveyed reported collecting data on licensed or registered pharmacies that compound sterile drugs, but not all of these states reported data.<sup>17</sup> For example, 16 states reported data for 2015, ranging from 31 pharmacies in Nevada to

<sup>17</sup>Thirty-two states reported that they did not differentiate data on pharmacies on drug compounding for human use versus drug compounding for animal (i.e., veterinary) use, 15 states reported they could differentiate some or all of the data, and 3 states did not respond to this survey question. Therefore, some of the data reported could include drug compounding for human and animal use.

1,024 in California. Respondents in most of the states that reported data on pharmacies that compound sterile drugs reported collecting this information yearly. (See table 4.)

**Table 4: States That Reported Data on the Number of Licensed or Registered Resident and Nonresident Pharmacies That Compound Sterile Drugs, Calendar Year 2015**

State	Number of pharmacies that compound sterile drugs			Frequency in which state collects this data
	All licensed or registered pharmacies	Resident pharmacies	Nonresident pharmacies	
California	1,024	935	89	Continuously updated <sup>a</sup>
Florida	581	456	125	Yearly <sup>b</sup>
Iowa	385	157	228	Yearly
Kansas <sup>c</sup>	269	109	160	Yearly
Kentucky	354	184	170	Yearly
Minnesota <sup>c</sup>	140	100	40	Not specified
Nevada <sup>c</sup>	31	31	— <sup>d</sup>	Not specified
New Jersey <sup>c</sup>	376	175	201	Yearly
North Carolina	448	263	185	Continuously updated
Ohio	352	94	258	Yearly
Oklahoma <sup>c</sup>	313	280	33	Yearly
South Carolina <sup>c</sup>	336	123	213	Yearly
South Dakota <sup>c</sup>	35	35	— <sup>d</sup>	Yearly
Texas	928	780	148	Yearly <sup>e</sup>
Virginia	321	162	159	Yearly <sup>f</sup>
Wyoming	146	5	141	Yearly

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

<sup>a</sup>California requires a special license for sterile compounding and reported the number of pharmacies with that license as of January 1, 2015.

<sup>b</sup>Florida reported 2015 data for the state's fiscal year, July 1, 2014, through June 30, 2015.

<sup>c</sup>These states reported estimated counts.

<sup>d</sup>Nevada and South Dakota reported that their states do not collect these data.

<sup>e</sup>Texas reported 2015 data as of September 8, 2015.

<sup>f</sup>Virginia reported 2015 data as of July 2, 2015.

National data on the extent of drug compounding, as measured by the number of prescriptions or the volume of compounded drugs (e.g., number of units), were not available from our survey, as only one state reported collecting these data, and its data were limited to sterile



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compounded drugs. That state reported that 658,128 total prescriptions for sterile compounded drugs were dispensed by pharmacies in the state in 2014, and 708,142 total prescriptions were dispensed in 2015.<sup>18</sup> In addition, the state reported that close to 2.5 million units of sterile compounded drugs were dispensed by pharmacies in the state in 2014, and almost 2 million units were dispensed in 2015.<sup>19</sup> Staff from the state's board of pharmacy said that the state does not collect data on the total number of all prescriptions dispensed by pharmacies; therefore, they could not calculate the percentage of prescriptions for sterile compounded drugs to all prescription drugs. Board staff also noted that the source of the state's data was based on self-reporting from pharmacies; as such, pharmacies' methods for identifying and reporting numbers of prescriptions and units of sterile compounded drugs may differ, and the state cannot confirm the validity or accuracy of the data.

When asked if collecting data on the number of prescriptions for compounded drugs or the volume of compounded drugs would have any effect on their oversight of drug compounding activities, officials from the state boards of pharmacy in our three selected states said that collecting such data could be burdensome and costly. For example, the official from Texas said that because they have thousands of licensed pharmacies in their state, the volume of such data would be overwhelming and they do not know what they would do with all of that data. The official from North Carolina said that there would be a significant cost to collecting these data and the ultimate benefit is unclear. In addition, the official from Minnesota said that it seemed like there could be a sizable amount of data to collect, and the pharmacy board would have to work out details, including whether the data would be collected in aggregate or much more specifically by patient, how the data would be collated and stored (such as in a database), and how the board would pay for such data collection and management.

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<sup>18</sup>According to staff from the state's board of pharmacy, these data only include sterile compounded drugs dispensed by a pharmacy, and do not include sterile compounded drugs dispensed by other health care practitioners, such as physicians, or nonsterile compounded drugs.

<sup>19</sup>This state defines a unit of compounded drug dispensed as a single dosage vial or package.

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Officials in almost all of the stakeholder organizations we interviewed had not conducted or were not aware of any studies or reviews on the extent of drug compounding or the settings in which compounding occurs in each state. However, one stakeholder organization, the Pew Charitable Trusts, conducted a survey of the state boards of pharmacy in the 50 states and the District of Columbia (43 of the 51 states responded) on state oversight of sterile drug compounding.<sup>20</sup> Among its findings, the Pew Charitable Trusts reported that from 3 percent to 24 percent of pharmacies in the 43 responding states were performing sterile compounding. In June 2016, HHS's Office of Inspector General reviewed spending for compounded drugs under Part D, the Medicare program's prescription drug benefit.<sup>21</sup> This review found that Medicare Part D spending for compounded drugs rose from \$70.2 million in 2006 to \$508.7 million in 2015, particularly for topical compounded drugs which include creams and ointments. The HHS Office of Inspector General attributed this increase to both an increase in the average cost of prescriptions and an increase in the number of beneficiaries receiving these compounded drugs.

While respondents in 26 states reported that providers in general practitioners' and medical specialty offices were authorized to compound drugs in their state, we did not find any sources of data specific to the extent to which this occurs. In one of our selected states, the state medical board official said that the extent of drug compounding by physicians and nonpharmacist health care practitioners is likely minimal because their board has not heard about it; however, because the board is complaint driven (i.e., they only inspect or investigate practitioners if a complaint has been submitted) it could be that such compounding activity has not led to any complaints. Another state's medical board official told us that it is not known whether the scale of compounding by physicians is small and specific to certain medical specialties, or whether it is widespread. This official speculated that it is not widespread, except

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<sup>20</sup>The Pew Charitable Trusts, *National Assessment of State Oversight of Sterile Drug Compounding* (Washington D.C.: February 2016). The Pew Charitable Trusts also reported on best practices related to drug compounding; see The Pew Charitable Trusts, *Best Practices for State Oversight of Drug Compounding* (Washington D.C.: March 2016).

<sup>21</sup>Department of Health and Human Services, Office of Inspector General, *High Part D Spending on Opioids and Substantial Growth in Compounded Drugs Raise Concerns* (Washington D.C.: June 2016).

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within particular medical specialties. Further, officials from one stakeholder organization—a national medical association—said that they were not sure how extensive compounding by physicians is or the amount of compounding that is being conducted; and officials from another stakeholder organization—a different national medical association—told us that they would not know how to go about gathering information on the extent of compounding by physicians. Finally, an official from another stakeholder organization—a national pharmacy association—told us the extent of physician compounding varies dramatically depending on the practice environment or physician specialty, in that almost every patient receives compounded drugs from physicians in outpatient surgery and cancer centers, but general practitioners do not usually perform much compounding otherwise.

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### Nearly All States Reported Having Drug Compounding Laws, Though Few Apply to Nonpharmacists, and States Conduct Inspections and Can Take Actions to Enforce These Laws

Respondents in almost all of the states we surveyed reported having laws, regulations, or policies specific to the practice of drug compounding. However, few apply to physicians and other nonpharmacists. To help ensure compliance with state laws, regulations, or policies specific to drug compounding, respondents in most states reported inspecting pharmacies and other drug compounders, and most reported their state can take several types of actions against noncompliant pharmacies or other drug compounders.

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### Almost All States Reported Having Laws, Regulations, or Policies Specific to Drug Compounding

Respondents in 48 of the states we surveyed reported having laws, regulations, or policies specific to the practice of drug compounding; however, these generally only apply to pharmacies and pharmacists. A respondent in one of the remaining states—Pennsylvania—reported that its state had proposed rules and regulations governing compounding

practices.<sup>22</sup> The respondent in the other remaining state—New York—reported that the state did not have any laws specific to compounding; however, the state had laws regarding outsourcing facilities operating under section 503B of the FDCA. Respondents in over half the states (26) reported enacting laws or adopting regulations or policies specific to drug compounding in response to the DQSA. Table 5 shows the number of states that reported having laws, regulations, or policies specific to drug compounding, including pending or proposed laws, regulations, or policies, and those specific to nonpharmacist health care practitioners and FDA-registered outsourcing facilities.

**Table 5: Laws, Regulations, or Policies Related to Drug Compounding, by Number of Reporting States, as of January 1, 2016**

State law, regulation, or policy	Number of states with law, regulation, or policy (%)			
	Yes	No	Don't know	No response
Laws, regulations, or policies specific to the practice of drug compounding	48 (96)	2 (4)	0 (0)	0 (0)
Laws enacted, or regulations or policies adopted, related to drug compounding in response to the federal Drug Quality and Security Act (Pub. L. No. 113-54) enacted in November 2013	26 (52)	24 (48)	0 (0)	0 (0)
Additional legislation, regulations, or policies related to drug compounding under consideration	30 (60)	12 (24)	6 (12)	2 (4)
Laws, regulations, or policies specific to drug compounding by physicians or other nonpharmacist health care practitioners	9 (18)	23 (46)	17 (34)	1 (2)
Pending or proposed laws, regulations, or policies specific to drug compounding by physicians or other nonpharmacist health care practitioners	3 (6)	23 (46)	22 (44)	2 (4)
Laws, regulations, or policies specific to Food and Drug Administration (FDA) registered outsourcing facilities	17 (34)	27 (54)	4 (8)	2 (4)
Pending or proposed legislation specific to FDA-registered outsourcing facilities	13 (26)	28 (56)	7 (14)	2 (4)

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Note: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

<sup>22</sup>The board of pharmacy official in Pennsylvania said that while Pennsylvania did not have any laws specific to the practice of drug compounding at the time of our review, the state does have a provision in state law regarding pharmacy supplies and preparing prescriptions that their inspectors can use when they encounter pharmacies that compound drugs, and that their inspectors are trained in USP chapters 795 and 797 compounding standards.

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In addition, respondents in 39 states reported that anticipatory compounding for both sterile and nonsterile compounded drugs is authorized or allowed in their state, and respondents in 27 states reported that compounding for office use is authorized or allowed in their state. However, respondents in 4 of the 27 states commented that only FDA-registered outsourcing facilities may compound drugs for office use and a respondent in 1 state reported that their state was working on regulations to prohibit this practice to align with federal restrictions on pharmacies under section 503A.<sup>23</sup> In our three selected states, compounding for office use is allowed in Texas, but not in North Carolina or Minnesota. The Texas board of pharmacy official said that the state enacted legislation to allow compounding for office use in 2005, but noted that the volume of office-use compounding in pharmacies appears to have dropped dramatically because outsourcing facilities registered with FDA are now providing this service. The North Carolina board of pharmacy official told us that North Carolina revised its laws regarding compounding for office use following enactment of the DQSA and this practice is no longer allowed in the state. This official said that there is no such thing as office-use compounding in North Carolina unless a facility is registered with FDA as an outsourcing facility. According to the Minnesota board of pharmacy official, compounding by licensed pharmacies for office use has not been allowed in the state for decades, and an exemption that had been provided for some large health care systems and specialty pharmacies to compound products to use within their system is no longer available.

State laws, regulations, and policies related to licensing for sterile drug compounding, labeling and testing of compounded drugs, compounding qualifications and standards, and reporting of compounded drug products

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<sup>23</sup>Anticipatory compounding is the creation of a drug product prior to receipt of an individual patient prescription in anticipation of receiving prescriptions based on historical prescribing patterns. Drug compounding for office use is the compounding of a drug product, without an individual patient prescription, to be kept as stock in a doctor's office, hospital, or other health care facility. To qualify for exemption from the requirement to follow CGMP requirements and other FDCA provisions under section 503A of the FDCA, 503A compounders may only compound based on (1) the prescription order for an individual patient, or (2) in limited quantities before the receipt of a valid prescription order for such individual patient, and based on a history of valid prescription orders for the compounded drug product. 21 U.S.C. § 353a(a). Under section 503B of the FDCA, outsourcing facilities may compound drugs with or without a patient-specific prescription. 21 U.S.C. § 353b(d)(4)(C).

varied across states. For example, respondents in 12 states reported requiring a license or registration for sterile compounding facilities, and respondents in 24 states reported requiring labeling for compounded drugs, as of January 1, 2016. Table 6 provides a summary of select provisions related to drug compounding and the number of states that reported having each provision.

**Table 6: Provisions Related to Drug Compounding, by Number of Reporting States, as of January 1, 2016**

Provisions related to drug compounding	Number of states (%)
<b>Licensing for sterile compounding</b>	
License or registration for sterile compounding facilities	12 (24)
License or registration for pharmacists who prepare sterile compounded drugs	5 (10)
License or registration for physicians or other nonpharmacist health care practitioners who prepare sterile compounded drugs	3 (6)
<b>Labeling and testing of compounded drugs</b>	
Compounded drug products are required to have labeling that indicates that the drug is a compounded drug	24 (48)
Sterile compounded drugs are subject to random or routine sampling for potency, purity, and sterility	25 (50)
<b>Compounding qualifications and standards</b>	
Pharmacy staff are required to demonstrate competence in sterile compounding	33 (66)
Compliance with the U.S. Pharmacopeial Convention (USP) Chapter 797 Pharmaceutical Compounding-Sterile Preparations (in part or whole)	33 (66)
Sterile compounding continuing education for licensed pharmacists and/or pharmacy technician	12 (24)
State inspectors must have competence in sterile compounding	22 (44)
<b>Reporting of compounded drugs</b>	
Adverse drug events are reported to the state pharmacy board or other state entity, or FDA's MedWatch program <sup>a</sup>	19 (38)
Nonresident states report to resident state board of pharmacy on any actions taken against resident entities	28 (56)
Complaints filed by another state are reported to the state pharmacy board or other state entity	32 (64)

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

<sup>a</sup>MedWatch is the Food and Drug Administration's (FDA) adverse event reporting system.

Further, respondents in 40 states reported that they require FDA-registered outsourcing facilities that conduct business within their state to have a license in their state, and some states require more than one license type for FDA-registered outsourcing facilities. (See table 7.) For example, one state reported that an FDA-registered outsourcing facility is required to register with the state as a manufacturer, but if the facility is also providing compounded drugs for patient-specific prescriptions the facility must also register as a pharmacy.

**Table 7: State Licensing Requirements for FDA-Registered Outsourcing Facilities, by Number of Reporting States**

State licensing requirement	Number of states <sup>a</sup>
Pharmacy	20
Wholesale distributor	19
Manufacturer	10
Outsourcing facility (licensed or registered by the state)	12

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

In addition, one state reported requiring Food and Drug Administration (FDA) registered outsourcing facilities to be licensed as sterile compounding pharmacies.

<sup>a</sup>Total numbers exceed 40 because of states that require registration for more than one license type.

Some states also have different licensing categories for resident (in-state) and nonresident (out-of-state) FDA-registered outsourcing facilities, and oversight of these facilities varies by state. For example, in our three selected states:

- **Minnesota.** The Minnesota Board of Pharmacy has oversight responsibility for outsourcing facilities in Minnesota. The board of pharmacy official said that under Minnesota law, outsourcing facilities are considered to be a subtype of manufacturer and are required to follow CGMP requirements.<sup>24</sup> This law also specifies that no license shall be issued or renewed for an outsourcing facility unless the applicant provides proof of registration with FDA as an outsourcing facility, according to the official.
- **North Carolina.** The North Carolina Department of Agriculture and Consumer Services, Food and Drug Protection Division, has oversight responsibility for outsourcing facilities in North Carolina. According to an official from this department, a state statute specifically refers to outsourcing facilities and applies the same requirements applicable to conventional drug manufacturers to these facilities, including the requirement to register with the department.<sup>25</sup> As with conventional drug manufacturers, the department has oversight responsibility for

<sup>24</sup>Minn. Stat. § 151.252, subd. 1a.

<sup>25</sup>N.C. Gen. Stat. § 106-140.1.

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the storage and distribution of outsourcing facilities' finished products.<sup>26</sup>

- **Texas.** The Texas Department of State Health Services, Drugs and Medical Devices Group, has oversight responsibility for outsourcing facilities in Texas. Officials from this department told us that in-state facilities are licensed as manufacturers of prescription drugs, and out-of-state facilities are licensed as prescription drug distributors. The officials said that Texas law does not specifically address outsourcing facilities; therefore, they regulate these entities as manufacturers and apply federal regulations and FDA guidelines and policies in their oversight of these entities, including inspecting them under CGMP requirements.

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### Few States Reported Having Laws or Policies Specific to Drug Compounding by Physicians and Other Nonpharmacist Health Care Practitioners

Respondents in less than 20 percent of states (9 states) reported having laws, regulations, or policies specific to compounding by physicians or other nonpharmacist health care practitioners (e.g., physician assistants), and these laws varied by state. For example, one state reported that its state statute requires pharmacy board licensure of all entities that compound drugs and possess compounded drugs, including physicians; and another state reported having a law that specifically allows a medical practitioner to compound drugs for patients under the practitioner's care.

Officials in one of our three selected states—Minnesota—reported having a law specific to compounding by physicians and other nonpharmacist health care practitioners. Officials in the two other states reported that they did not have any laws, regulations, or policies specific to such compounding.

- **Minnesota.** Minnesota's statute on compounding applies to both health care practitioners and pharmacies.<sup>27</sup> The Minnesota statute requires practitioners and pharmacists to comply with USP compounding standards, among other things. However, an official

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<sup>26</sup>The North Carolina official reported that there were two outsourcing facilities in North Carolina. One of these facilities is a dual-purpose facility in that it is a compounding pharmacy (compounding drugs for specific patients in accordance with a prescription) and an outsourcing facility registered with FDA, and the other facility is also a dual-purpose facility licensed as a drug manufacturer and an outsourcing facility registered with FDA.

<sup>27</sup>Minn. Stat. § 151.253. subd. 2.



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from the Minnesota Board of Pharmacy told us that the pharmacy board relies on the state's Board of Medical Practice to inform physicians that compounding by physicians should be compliant with the USP chapters related to nonsterile and sterile compounding (USP chapters 795 and 797, respectively) depending on what they are compounding. This official said that the board of pharmacy does not know which physicians may be compounding, and while the pharmacy board has the authority to inspect any place in the state in which drugs are held to be distributed, they need to give advance notice of inspection to physicians. An official from the Minnesota Board of Medical Practice said that the medical board has a complaint-driven process and that if there are allegations that a physician has violated medical or pharmacy statutes that regulate the practice of medicine, including compounding, the board has the authority to investigate.

- **North Carolina.** A state statute in North Carolina requires that a physician who dispenses prescription drugs, for a fee or other charge, register with the board of pharmacy and comply with relevant laws and regulations governing distribution of drugs that apply to pharmacists; however, this statute does not specifically address compounding by physicians.<sup>28</sup> According to the board of pharmacy official we interviewed, disciplinary authority over these physicians lies solely with the state's medical board. The North Carolina Medical Board official explained that the board has the authority to discipline a physician for violating any law involving the practice of medicine and that compounding drugs is included in the practice of medicine. This official further explained that the board's role in overseeing physicians has historically been complaint driven and the board had not had any complaints or issues brought to its attention related to compounding by physicians until a recent case referred to them by the board of pharmacy. This official said that the board is currently developing its role in overseeing compounding by physicians.
- **Texas.** The Texas medical board official told us that there was no specific mention of compounding by physicians in the Texas state statute. The official said, however, that if the medical board received a complaint that involved one of their licensees (i.e., practitioner) violating the state's drug compounding laws, then the board could take enforcement actions.

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<sup>28</sup>N.C. Gen. Stat. § 90-85.21(b).

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Respondents in 21 states reported that their office had heard concerns about the practice of compounding by physicians and other nonpharmacists. Some of the concerns respondents in these states reported were about a lack of regulation and oversight of compounding by physicians and other nonpharmacists, and whether physicians were complying with compounding standards, such as USP standards. Further, respondents in some states were unsure which entity, if any, in their state had oversight responsibility for compounding by physicians and other nonpharmacists. For example, respondents in 17 states reported that they did not know if their state had any laws, regulations, or policies specific to drug compounding by nonpharmacists. A respondent in one state commented that they do not believe that the medical, nursing, and naturopath practitioners are subject to any laws, regulations, or policies related to compounding.

Some of the stakeholder organizations we interviewed also expressed concerns about compounding by physicians and other nonpharmacists. Officials from one stakeholder organization said that drug compounding conducted in standalone physician practices does not generally fall under medical licensing requirements of state medical boards; therefore, there are gaps in oversight of compounding by physicians. Officials from another stakeholder organization told us that there are an increasing number of companies that are targeting physicians, offering to establish compounding labs within the physicians' offices. The officials said that the market has been responding to DQSA by targeting physicians because FDA's oversight of drug compounding has focused on pharmacists, and the market sees an opportunity for physicians to profit off of compounding rather than see the prescriptions they write leave their offices. An official from another stakeholder organization said that there is an enormous amount of compounding in physician offices, but few state boards of pharmacy have oversight over this practice. This official said that boards of pharmacy oversee pharmacists and pharmacies, but do not oversee compounding by physicians. According to this official, the state boards of pharmacy have tried to bring physician-compounded drugs under their oversight, but it has been difficult. Officials from one stakeholder organization, the Federation of State Medical Boards, told us that they conducted an informal review of state laws regarding compounding by physicians (i.e., state medical practice acts) and found that few states have laws specifically regulating compounding by physicians; however,

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most medical boards consider compounding as part of the practice of medicine. The officials said that they plan to further study this issue to determine whether to develop guidelines for their members.<sup>29</sup> In addition, FDA officials told us that the agency has not taken a proactive role in compounding by physicians and there is not much oversight of physician compounding by state medical boards. FDA officials noted that they did inspect one physician who was compounding after receiving complaints, and that they planned to discuss oversight of physician compounding at FDA's intergovernmental meeting with state officials in September 2016.

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### Most States Reported Inspecting Resident Pharmacies and Can Take a Variety of Enforcement Actions to Enforce Drug Compounding Laws

To help ensure compliance with state laws, regulations, or policies related to drug compounding, respondents in most states reported inspecting resident pharmacies and relying on inspections by the home state of nonresident pharmacies. Specifically, respondents in 42 states reported inspecting all licensed resident pharmacies, respondents in 6 states reported inspecting some of these pharmacies, and respondents in 29 states reported relying on a home state's inspection report for nonresident pharmacy inspections.<sup>30</sup> Specific to entities that compound or distribute sterile compounded drugs, table 8 shows the number of states that

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<sup>29</sup>Officials from the Federation of State Medical Boards told us that they introduced a draft position statement to their House of Delegates on the compounding of medications by physicians in April 2016; however, after receiving comments from stakeholder organizations, the officials said that their Committee on Ethics and Professionalism will continue to study the issue of compounding by physicians, and that they are in discussions with FDA and USP officials regarding this issue.

<sup>30</sup>For the 2 remaining states that did not report inspecting all or some licensed resident pharmacies, the respondent in 1 state reported that their state does not inspect resident pharmacies and the other state did not respond to this question. For the 21 remaining states that did not report relying on home state inspections for licensed nonresident pharmacies, respondents in 6 states reported inspecting some or all nonresident pharmacies, 14 states reported that their states do not inspect nonresident pharmacies, and 1 state did not respond to this question.

According to officials from the National Association of Boards of Pharmacy, in most cases, states do not have the capacity to inspect pharmacies in other states and, therefore, must rely on information from either the pharmacy's home state, a third party, or both in order to make informed licensing decisions. The officials said the association has been working to develop and implement an inspection blueprint to achieve consistency, quality, and reliability of inspections across states, so that a nonresident state can be comfortable accepting an inspection report from a home state that uses the blueprint.

reported conducting inspections for sterile compounding pharmacies, wholesale distributors, and outsourcing facilities.

**Table 8: Number of States That Reported Inspecting Resident and Nonresident Sterile Compounding Pharmacies, Wholesale Distributors, and Outsourcing Facilities**

Type of entity	Number of states (%)					
	Yes, all	Yes, some	No	State does not have this type of entity	Rely on home state inspection (nonresident only)	No response
Resident sterile compounding pharmacy <sup>a</sup>	36 (72)	3 (6)	2 (4)	8 (16)	N/A	1 (2)
Nonresident sterile compounding pharmacy <sup>a</sup>	5 (10)	3 (6)	11 (22)	5 (10)	25 (50)	1 (2)
Resident wholesale distributor	33 (66)	9 (18)	5 (10)	1 (2)	N/A	2 (4)
Nonresident wholesale distributor	1 (2)	2 (4)	19 (38)	0 (0)	26 (52)	2 (4)
Resident outsourcing facility	24 (48)	2 (4)	11 (22)	12 (24)	N/A	1 (2)
Nonresident outsourcing facility	3 (6)	2 (4)	17 (34)	8 (16)	19 (38)	1 (2)

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

<sup>a</sup>Twelve states reported having a separate state license category for resident sterile compounding pharmacies, and 12 states reported having a category for nonresident sterile compounding pharmacies; however, some states reported that they inspect pharmacies they know are compounding sterile drugs even if their state does not have a specific license category for these entities.

Types of state inspections include prelicensure, for cause (e.g., in response to a complaint), and recurring (e.g., every 1 to 2 years). Respondents in most states reported conducting these types of inspections for resident pharmacies, resident sterile compounding pharmacies, and resident wholesale distributors; however, few states reported conducting any of these types of inspections for nonresident entities. In addition, the number of full-time equivalent pharmacy inspectors authorized to inspect either resident or nonresident pharmacies, or both, ranged from zero to 138. A respondent in one state that did not have any pharmacy inspectors reported that the five pharmacy board members conducted these inspections.

Survey respondents also reported their states required certain qualifications for pharmacy inspectors. For example, most respondents reported that their state required inspectors to have a current pharmacist's license and almost half the states required inspectors to have practiced pharmacy for a minimum number of years. Specific to

inspections of compounding facilities, respondents in 21 states reported requiring inspectors to complete a specialized training program in sterile compounding, respondents in 15 states reported requiring inspectors to complete a specialized training program in nonsterile compounding, and respondents in 4 states reported requiring inspectors to have prior experience in compounding.

Time frames for recurring inspections of pharmacies and other drug compounders, as well as entities that distribute compounded drugs, vary by state, and respondents in some states reported challenges in meeting their inspection time frames. Respondents reported state inspection time frames ranging from at least once a year to every 5 years or more, and they also varied by type of entity being inspected. (See table 9.) Respondents in 21 states reported that they have challenges in meeting their state’s required inspection time frames, citing reasons such as limited resources and the time required to conduct inspections. For example, a respondent in one state commented that there are over 1,000 sterile compounding pharmacies in their state that are supposed to be inspected each year, which is challenging for the 46 inspectors who conduct these inspections. A respondent in another state commented that they have a small staff responsible for inspections and investigations, so the priority goes to sterile compounding facilities.

**Table 9: Frequency of Recurring Inspections, by the Number of States That Reported Conducting Them**

Type of entity inspected	Number of states				
	At least once a year	1 – up to 2 years	2 – up to 3 years	3 – up to 5 years	5 or more years
Resident pharmacy	13	16	9	2	1
Nonresident pharmacy	0	2	0	0	0
Resident sterile compounding pharmacy <sup>a</sup>	21	11	4	2	0
Nonresident sterile compounding pharmacy <sup>a</sup>	1	3	0	0	0
Resident wholesale distributor	5	13	4	4	1
Nonresident wholesale distributor	0	1	0	0	0
Resident outsourcing facility	11	9	1	2	0
Nonresident outsourcing facility	1	2	0	0	0

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

<sup>a</sup>Twelve states reported having a separate state license category for resident sterile compounding pharmacies, and 12 states reported having a category for nonresident sterile compounding

pharmacies; however, some states reported that they inspect pharmacies they know are compounding sterile drugs even if their state does not have a specific license category for these entities.

To enforce drug compounding laws, regulations, or policies, respondents in most states reported they can take several types of actions against pharmacies or other compounding entities, including suspension and revocation of a license or registration, monetary fines, or a cease and desist order. For example, respondents in 45 states reported they can suspend a pharmacy or pharmacist’s license and respondents in 41 states reported they can impose monetary fines. (See table 10.) Other types of actions that respondents reported included nondisciplinary administrative letters of warning, restricting a license (e.g., restricting a pharmacist from engaging in sterile compounding), and reprimands.

**Table 10: Types of Enforcement Actions That Can Be Taken Against Licensed or Registered Pharmacists or Pharmacies, by the Number of States That Reported They May Take this Action**

Type of enforcement action	Number of states
Suspension of pharmacist/pharmacy license	45
Voluntary relinquishment or surrender of pharmacist/pharmacy license	42
Probation of licensed pharmacist/pharmacy	42
Revocation of pharmacist/pharmacy license	41
Monetary fine	41
Cease and desist order	34
Prosecution under state or federal law	25
Mandatory recall of compounded drugs	19

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Note: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

While respondents in several states reported data on the number of actions taken against pharmacies for cases involving compounded drugs, respondents in some states reported that they do not track such data specific to cases involving compounded drugs. Of the respondents in the 41 states that reported they can impose a monetary fine, 13 states reported imposing monetary fines on pharmacies or pharmacists for cases involving compounded drugs in 2014, and 12 states reported taking this action in 2015. The number of pharmacies or pharmacists that states reported receiving these fines in 2015 ranged from 1 pharmacy or pharmacist in 1 state to 73 in another state. In addition, respondents in 8 states reported suspending pharmacy or pharmacist licenses in 2014 and

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respondents in 6 states reported taking this action in 2015. Of the respondents in the 19 states that reported they can conduct a mandatory recall of compounded drugs, 2 states reported taking this action in 2014 and 3 states reported doing so in 2015. Respondents in 4 states reported revoking 1 or 2 pharmacy or pharmacist licenses in 2015 for cases involving compounded drugs.

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### Most States Are Satisfied With Their Communication with FDA and Other States, although Some States Reported Challenges

Most states reported overall satisfaction with their communication with FDA on compounding issues through events such as FDA-sponsored activities, but some states reported challenges with this communication. Similarly, most states reported overall satisfaction with communication among states at conferences and meetings, but some states noted challenges.

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### About Three Quarters of States Reported Participating in FDA-Sponsored Activities and Obtaining FDA Drug Compounding Information; Some States Reported Challenges with This Communication

FDA has communicated with states on compounding issues in a variety of ways, including FDA-sponsored activities, such as intergovernmental meetings; most states reported this communication was helpful. In 2014 and 2015, FDA held three intergovernmental working meetings on pharmacy compounding with pharmacy board representatives from states and U.S. territories.<sup>31</sup> Survey respondents in about three quarters of the states reported participating in FDA's intergovernmental meetings on drug compounding, and most participating states reported these activities were very or moderately helpful; however, a number of participating states reported that the activities were slightly or not at all helpful. For example, respondents in 41 states reported participating in FDA's March 2014 Intergovernmental Working Meeting on Pharmacy Compounding, and of those states that reported participating in this meeting, respondents in 33 states, or about 80 percent, reported that the meeting was very or moderately helpful. However, respondents in 4 states that reported participating in the March 2014 meeting reported that the meeting was

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<sup>31</sup>FDA held its fourth intergovernmental working meeting on pharmacy compounding since enactment of the DQSA on September 20 and 21, 2016.

slightly or not at all helpful. See table 11 for the number of states that reported participating in FDA-sponsored activities and how the participating states rated the helpfulness of the activities.

**Table 11: States That Reported Participating in FDA-Sponsored Activities Related to Drug Compounding and How These States Rated the Helpfulness of Each Activity**

Food and Drug Administration (FDA) sponsored activity	Number of states that reported participating in activity (%)				How states that reported participating in FDA-sponsored activities rated the helpfulness of each activity			
	Yes	No	Don't know	No response	Very or moderately helpful	Slightly or not at all helpful	Don't know	No response
FDA's March 2014 Intergovernmental Working Meeting on Pharmacy Compounding	41 (82)	2 (4)	4 (8)	3 (6)	33	4	2	2
FDA's March 2015 Intergovernmental Working Meeting on Pharmacy Compounding	37 (74)	7 (14)	4 (8)	2 (4)	28	5	3	1
FDA's November 2015 Intergovernmental Working Meeting on Pharmacy Compounding	35 (70)	11 (22)	1 (2)	3 (6)	25	6	2	2
FDA's Pharmacy Compounding Advisory Committee meeting, February 2015 <sup>a</sup>	8 (16)	31 (62)	9 (18)	2 (4)	6	2	0	0
FDA's Pharmacy Compounding Advisory Committee meeting, June 2015 <sup>a</sup>	7 (14)	34 (68)	5 (10)	4 (8)	5	2	0	0

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

<sup>a</sup>The Drug Quality and Security Act, enacted in November 2013, required FDA to convene and consult with a Pharmacy Compounding Advisory Committee before issuing certain regulations.

Respondents from most states reported obtaining compounding-related information from FDA's website, and in general, states found this information helpful. For example, respondents in 38 states reported obtaining a list of FDA-registered outsourcing facilities from FDA's website, and 32 of them found the information very or moderately helpful. See table 12 for the number of states that reported obtaining information related to drug compounding from FDA's website and how these states rated the helpfulness of the information.



**Table 12: The Number of States That Reported Obtaining Information Related to Drug Compounding from FDA’s Website and How These States Rated the Helpfulness of This Information**

Information on the Food and Drug Administration’s (FDA) website	Number of states that reported obtaining the information (%)			How states that reported obtaining the information rated the helpfulness of the information			
	Yes	No	No response	Very or moderately helpful	Slightly or not at all helpful	Don’t know	No response
List of FDA-registered outsourcing facilities	38 (76)	10 (20)	2 (4)	32	3	0	3
Names of compounding pharmacies that were inspected by FDA	33 (66)	15 (30)	2 (4)	29	3	0	1
FDA Form 483 inspection observation reports to determine violations found during inspections of compounding pharmacies	35 (70)	13 (26)	2 (4)	25	7	1	2
FDA Form 483 inspection observation reports to determine violations found during inspections of FDA-registered outsourcing facilities	33 (66)	15 (30)	2 (4)	23	6	1	3
FDA warning letters issued to compounding pharmacies	35 (70)	13 (26)	2 (4)	27	6	1	1
FDA warning letters issued to FDA-registered outsourcing facilities	32 (64)	16 (32)	2 (4)	26	4	1	1
Information on recalls of compounded drugs	36 (72)	12 (24)	2 (4)	30	3	1	2

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

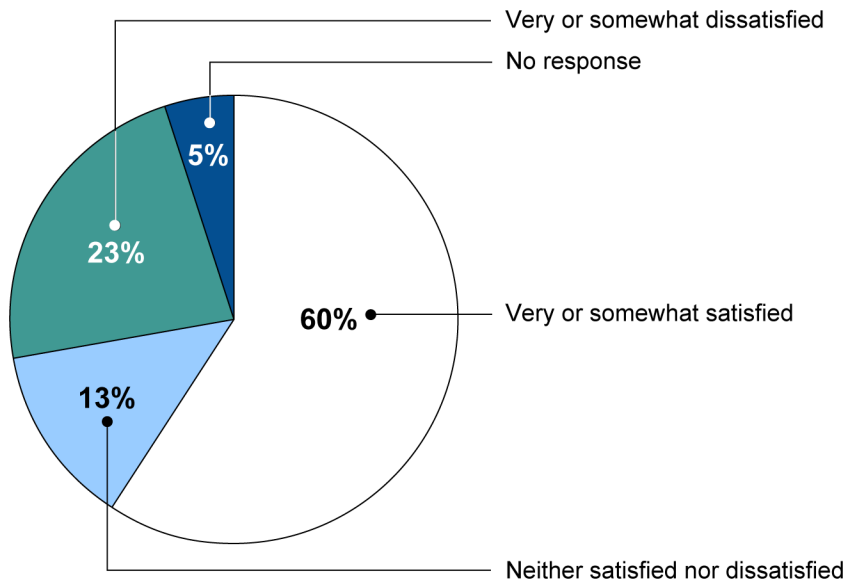
Note: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

Of the respondents in the 40 states that reported having had communication with FDA regarding drug compounding issues, 24 states (60 percent) reported that, overall, they were very or somewhat satisfied with this communication; however, 9 states (23 percent) reported they were very or somewhat dissatisfied. (See fig. 1.) The respondent in one state that reported being satisfied with their communication with FDA said “It has been very helpful to have ongoing meetings and discussion with FDA at FDA-sponsored events and other meetings. The emphasis on state communication is noted and appreciated.” However, the respondent in another state that indicated dissatisfaction with their communication with FDA commented that “there seems to be no real progress in

providing guidance as to what regulatory approaches FDA intends to take—it seems like FDA is burdened by red tape that prevents it from sharing information with the states on common issues.”

**Figure 1: Percentage of States Reporting each Level of Satisfaction with Food and Drug Administration (FDA) Communication Regarding Drug Compounding**

Forty states that reported having had communication or interactions with FDA related to drug compounding issues were asked about their overall satisfaction with that communication or interaction.



Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

Percentages exceed 100 percent because of rounding.

Respondents in 25 states reported that they have not experienced specific challenges in their communication or interactions with FDA related to drug compounding issues, but respondents in 15 states reported experiencing one or more communication challenge with FDA. Fourteen of them reported that getting FDA to respond to their requests for information was very or moderately challenging; and 10 of them reported that getting FDA to provide responses to their questions related to oversight of drug compounding was very or moderately challenging. Finally, respondents in several states elaborated on their states' communication or interactions with FDA. For example, one respondent reported that “it has taken years for the FDA to respond or even acknowledge the Board’s communication in some instances. Timeliness

is a significant issue.” Another respondent reported that when they work with FDA, FDA requests a variety of information from the board, but will not provide any information to the board. See table 13 for how 15 states—the states that reported experiencing one or more communication challenges with FDA—rated these challenges.

**Table 13: States Reporting Challenges in Communication or Other Interactions with FDA**

Types of communication or interactions with the Food and Drug Administration (FDA) that posed a challenge	Significance of challenges in communication or other interactions with FDA reported by 15 states reporting challenges				
	Number of states				
	Very challenging	Moderately challenging	Slightly challenging	Not at all challenging	Not applicable
Getting FDA to respond to our requests for information	7	7	1	0	0
Scheduling an individual meeting with FDA	2	2	5	3	3
Getting FDA to provide responses to our questions related to oversight of drug compounding	4	6	3	0	2
Getting notification of pharmacy inspections conducted by FDA in our state	2	4	2	6	1
Getting complete information from FDA in Form 483 inspection observation reports on pharmacy inspections conducted by FDA in our state	5	2	3	3	2
Getting FDA approval of our requests for joint inspections of licensed or registered pharmacies in our state <sup>a</sup>	2	1	3	1	7
Getting notification from FDA when FDA determines a licensed or registered pharmacy in our state is acting contrary to section 503A of the Federal Food, Drug, and Cosmetic Act	5	3	0	3	4
Getting notification from FDA of FDA enforcement actions taken against licensed or registered pharmacies in our state	3	5	0	3	4

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

<sup>a</sup>One of the 15 states did not indicate a significance of the challenge related to this type of communication or interaction with FDA.

FDA officials noted that federal law prohibits FDA from sharing certain nonpublic information with state officials that have not provided

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confidentiality commitments to FDA. According to FDA officials, the agency has encouraged and worked with states and individual state officials to provide such commitments through FDA commissioning or information sharing agreements.<sup>32</sup> Survey respondents in 27 states reported having commissioned officers with FDA; 16 of them reported that having commissioned officers for sharing information and conducting activities related to drug compounding was very or somewhat effective, and 5 of them reported having commissioned officers was very or somewhat ineffective.<sup>33</sup> A respondent in one state reported that having commissioned officers “has expedited the sharing of information,” while a respondent in another state reported “the inability to share information with other staff, the board, or to use the information obtained through commissioner status in disciplinary actions against the subject licensee makes this process ineffective and inefficient.” In addition, 11 states reported having an information sharing agreement with FDA; 8 of them reported this agreement was very or somewhat effective for sharing information related to drug compounding, and 2 of them reported the agreement was neither effective nor ineffective.<sup>34</sup> A respondent in one state reported “information sharing [with FDA] has improved greatly in the past two years.” However, a respondent in another state reported “the process still feels like the state needs to pry information from the FDA.”

We also asked the stakeholder organizations about FDA’s communication with the states related to drug compounding. Seven of the 25 stakeholder organizations we interviewed said that, overall, communication between the states and FDA has improved since the DQSA was enacted;

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<sup>32</sup>A state official may be commissioned as an officer of FDA and, by virtue of this status, be eligible to receive FDA-owned nonpublic information. 21 U.S.C. § 372. FDA may also share certain nonpublic information, such as deliberative and confidential commercial information, with state officials under a written confidentiality agreement. 21 C.F.R. § 20.88. For example, FDA created a 5-year, single signature “Long-Term Drug Compounding Information Sharing Agreement” to improve communications and facilitate oversight of compounding pharmacies.

<sup>33</sup>For the six remaining states, respondents in five states reported that they did not know how effective having commissioned officers was for sharing information related to drug compounding and one state did not provide a response.

<sup>34</sup>The remaining state did not respond to the effectiveness of the information sharing agreement.

however, 2 stakeholder organizations commented that FDA only has one-way communication with states.

**Communication among States Occurs through Several Venues and Activities; Most States are Satisfied with this Communication, but Some Reported Challenges**

Respondents in 42 states reported communicating with other states regarding issues related to drug compounding using venues such as national association meetings, e-mails, phone calls, and informal networking at FDA-sponsored events. Respondents in 35 states reported that they were very or somewhat satisfied with their communication and interactions with other state pharmacy regulatory bodies related to drug compounding issues. See table 14 for the number of states reporting having various types of communications or interactions with other state regulatory bodies, and how these states rated the helpfulness of the communication or interaction.

**Table 14: Helpfulness of Communication and Interactions with Other State Pharmacy Regulatory Bodies, by States That Reported Having Communication and Interactions**

Type of communication or interaction with other state pharmacy regulatory bodies	Number of states			
	States reporting having communication or interaction	Helpfulness of communication or interaction		
		Very or moderately helpful	Slightly or not at all helpful	Don't know
National associations (e.g., National Association of Boards of Pharmacy conferences, annual national association meetings)	39 <sup>a</sup>	34	3	1
Regional associations (e.g., conferences or regional meetings)	26	22	4	0
State-to-state direct communication (e.g., in-person meetings, phone calls and/or emails with other state boards of pharmacy)	34	33	1	0
Conduct joint inspections with other state boards of pharmacy or other state pharmacy regulatory bodies	9	8	1	0
Informal networking with other states that takes place at events sponsored by the Food and Drug Administration or industry	33	32	1	0
Other types of interactions (e.g., meetings with state boards of pharmacy and state associations)	6	6	0	0

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

<sup>a</sup>One of the 39 states did not indicate a level of helpfulness of national association meetings.

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Respondents in 35 states reported that they had not experienced challenges regarding their communication or interactions with other state pharmacy regulatory bodies related to drug compounding issues, but respondents in 5 states did report challenges. One of the 5 that reported challenges commented that some states do not return phone calls, and other states have little or no resources. Another respondent that reported challenges commented that there needs to be a single national model regarding the regulation and licensure of compounding pharmacies.

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## **FDA Has Taken Steps to Implement Its Drug Compounding Responsibilities, but States and Stakeholder Organizations have Cited Challenges and Concerns**

FDA has taken steps to implement its drug compounding responsibilities since enactment of the DQSA, but states and stakeholder organizations have cited a number of challenges and concerns. FDA has issued numerous guidance documents related to drug compounding, and conducted more than 300 inspections of drug compounders. However, some stakeholder organizations said the amount of time it takes FDA to finalize guidance and other key documents is challenging. States and stakeholder organizations also cited concerns regarding FDA's implementation of its drug compounding responsibilities.

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## **FDA Has Released Final and Draft Documents Related to Drug Compounding, and Conducted More than 300 Inspections of Drug Compounders**

FDA has issued numerous documents related to compounding since the DQSA was enacted; most of these are draft documents. FDA has released final guidance on adverse event reporting requirements, the process and fees related to registering with FDA as an outsourcing facility, and pharmacy compounding under section 503A, among others. The remaining guidance and other documents that are still in draft include documents that, according to many stakeholder organizations we interviewed, are key to FDA's implementation of its drug compounding responsibilities. See table 15 for final guidance, draft guidance, and other draft documents issued by FDA.

**Table 15: Final and Draft Documents Related to FDA’s Drug Compounding Regulatory Responsibilities**

<b>Date issued</b>	<b>Type</b>	<b>Title</b>
<b>Documents issued in final</b>		
11/24/2014	Final guidance	Fees for Human Drug Compounding Outsourcing Facilities Under Sections 503B and 744K of the FD&C Act <sup>a</sup>
11/24/2014	Final guidance	Registration of Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act <sup>a</sup>
8/12/2015	Final guidance	Guidance For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act
10/8/2015	Final guidance	Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act
7/2/2014 (amended 10/26/2015 and 6/9/2016)	Final guidance	Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act
6/9/2016	Final guidance	Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act
6/9/2016	Final guidance	Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act
10/7/2016	Final rule	Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness
<b>Documents issued in draft</b>		
7/2/2014	Draft guidance	Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act <sup>a</sup>
11/24/2014	Draft guidance	Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act
2/13/2015	Draft guidance	Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities
2/13/2015	Draft guidance	Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application
2/13/2015	Draft memorandum of understanding <sup>b</sup>	Draft Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the State of [insert STATE] and the U.S. Food and Drug Administration
4/15/2016	Draft guidance	Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act
4/15/2016	Draft guidance	Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act
4/15/2016	Draft guidance	Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act
7/7/2016	Draft guidance	Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act
7/7/2016	Draft guidance	Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act
8/3/2016	Draft guidance	Insanitary Conditions at Compounding Facilities

Date issued	Type	Title
10/18/2016	Proposed rule	Amendments to the Regulation Regarding the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness

Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-17-64

<sup>a</sup>The FD&C Act is an alternative abbreviation for the Federal Food, Drug, and Cosmetic Act.

<sup>b</sup>Under section 503A, FDA is required to develop, in consultation with the National Association of Boards of Pharmacy, a standard memorandum of understanding between states and FDA that addresses distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a state agency of complaints relating to drug products compounded in that state that are distributed outside the state.

According to our review of FDA data, FDA has also inspected drug compounders, including outsourcing facilities, and issued FDA form 483 inspection observation reports. FDA has also taken action, including issuing warning letters, when issues have been identified in these inspections. From May 2012 through April 22, 2016, FDA completed 265 inspections of 503A compounders and other drug compounders that were not outsourcing facilities. As of April 22, 2016, FDA had completed 75 inspections of outsourcing facilities. These 75 inspections were at 59 of the 91 facilities that had registered with FDA as an outsourcing facility. FDA officials noted that many of the entities that registered as outsourcing facilities withdrew their outsourcing facility registration submission before the agency scheduled an inspection, and others were not yet operating when the agency attempted to inspect them.

In general, FDA conducts three types of inspections: for-cause, follow-up, and surveillance. See table 16 for a description of FDA inspection types and the number of each type of inspection conducted by FDA for drug compounders as of April 22, 2016.



**Table 16: Types of Food and Drug Administration (FDA) Inspections, and the Number of Inspections of Drug Compounders**

Inspection type	Description	FDA inspections of 503A compounders (from May 2012 through April 22, 2016) <sup>a</sup>	FDA inspections of 503B outsourcing facilities (through April 22, 2016) <sup>b</sup>
For cause	FDA conducts for-cause inspections usually in response to a complaint, such as a report of a serious adverse event or product quality problem (e.g., contamination).	121	6
Follow-up	FDA conducts inspections to follow up on earlier inspection findings and/or FDA regulatory actions. For example, if FDA inspected the drug compounder in the past and found concerning practices or if FDA took regulatory action, such as issuing a warning letter, FDA conducts a follow-up inspection to check whether the drug compounder has implemented adequate corrective actions.	40	15
Surveillance	<p>FDA conducts surveillance inspections of some drug compounders that are not outsourcing facilities, including 503A compounders. These inspections are not in response to an immediate adverse event or complaint, but instead are meant to check on drug compounders of which FDA is aware (e.g., because of prior inspections or complaints).</p> <p>FDA is required to inspect outsourcing facilities on a risk-based schedule. According to agency officials, the agency's goal is to inspect outsourcing facilities within 2 months of their initial registration with FDA if they had not been recently inspected prior to registration, and then every 12-18 months thereafter.</p>	104	54
<b>Total</b>		<b>265</b>	<b>75</b>

Source: GAO analysis of FDA information. | GAO-17-64

<sup>a</sup>This includes inspections of 503A compounders and other drug compounders that are not outsourcing facilities. The 503A compounders are individuals or entities that are not outsourcing facilities that qualify for the exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA), including pharmacies, physicians, and federal facilities. Drug compounders that do not qualify for the exemptions under section 503A, and are not outsourcing facilities under section 503B, are regulated as conventional manufacturers and are subject to the provisions of the FDCA applicable to such manufacturers.

<sup>b</sup>The Drug Quality and Security Act, enacted in November 2013, created the category of outsourcing facility, and FDA conducted its first inspection of an outsourcing facility on March 5, 2014.

According to agency officials, FDA's Center for Drug Evaluation and Research issues all inspection assignments for 503A compounders and outsourcing facilities. FDA officials told us that, in an effort to focus the

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agency's resources efficiently, the center and the agency's Office of Regulatory Affairs approach the coordination and scheduling of drug-compounding-related inspection assignments from a national perspective.<sup>35</sup> Unlike outsourcing facilities or conventional manufacturers, 503A compounders are not required to register with FDA. As such, FDA is only aware of a small percentage of the thousands of pharmacies that compound drugs, and FDA does not inspect all 503A compounders, according to FDA officials.<sup>36</sup> For outsourcing facilities, which register with FDA, the agency is required to inspect them on a risk-based schedule.<sup>37</sup> As of May 23, 2016, 91 facilities had registered with FDA as outsourcing facilities at some point in time, and as of July 2016, FDA had inspected 46 of the 60 establishments with active outsourcing facility registrations at least once.<sup>38</sup>

According to agency officials, FDA's risk models—which are used to determine which facilities to inspect—use information from a number of sources, including FDA's Field Accomplishment and Compliance Tracking System. However, as we reported in 2013, this database does not consistently indicate the final inspection classification—that is, it does not always include accurate information about whether the agency's final determination was that an official action was indicated, voluntary action was indicated, or if no action was indicated from the results of the

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<sup>35</sup>According to the officials, certain geographic areas seem to have a higher concentration of drug compounders that the agency has reason to inspect. Therefore, the officials said the center works closely with FDA's Office of Regulatory Affairs to assist FDA district offices that may become overwhelmed with the volume of compounding inspections. For example, FDA may order an inspection of a pharmacy in one district, but assign it to investigators from another district that has a lower inspection workload at that time.

<sup>36</sup>According to FDA officials, FDA uses a risk-based model, using factors such as prior regulatory actions, recall history, adverse event history, the history of complaints, and findings from prior inspections, to prioritize and make inspection assignments for 503A compounders and other drug compounders that are not outsourcing facilities.

<sup>37</sup>See 21 U.S.C. § 353b(b)(4).

<sup>38</sup>According to agency officials, FDA's goal is to conduct the initial inspections of outsourcing facilities within 2 months of the facility's registration, and to conduct surveillance inspections on each outsourcing facility every 12 to 18 months thereafter. Agency officials reported that in some cases, a facility may have registered as an outsourcing facility before the facility was operational; in these circumstances FDA would wait to inspect the facility until it is operational.

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inspection.<sup>39</sup> We recommended that FDA address this shortcoming by taking steps to consistently collect reliable and timely information in FDA's databases on inspections and enforcement actions associated with compounded drugs; however, as of June 2016, FDA officials reported the agency's database did not consistently include final inspection classifications. According to FDA officials, the agency's database includes recommendations from the district office, which may differ from the final inspection classifications after the case has undergone further review by officials in the Center for Drug Evaluation and Research and the Office of Regulatory Affairs. FDA officials told us that the agency took steps in June 2016 to make sure the final inspection classifications in its database are accurate by (1) including a section on data entry—including updating the inspection classification in the database—in a June 2016 training on compounding for center and Office of Regulatory Affairs staff, and (2) discussing the inspection classification during the joint assessment call for compounding inspections in order to decide on a final inspection classification and to make sure this classification is updated in the database. The officials said that FDA plans to update the final classifications for inspections FDA has already conducted and for all inspections moving forward.<sup>40</sup>

According to agency officials, FDA invites the relevant state regulatory authority (generally the state board of pharmacy, state department of health, or both) to accompany FDA on inspections of drug compounders. During the inspection, FDA investigators collect evidence relating to

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<sup>39</sup>See [GAO-13-702](#). FDA classifies an inspection as "official action indicated" if objectionable conditions were found that warrant regulatory action by the agency. A classification of "voluntary action indicated" means that objectionable conditions that do not meet the threshold for regulatory action were identified and any corrective actions are left to the establishment to take voluntarily. A classification of "no action indicated" means that no objectionable conditions or practices were found during the inspection (i.e., conditions or practices that violate CGMP requirements), or if the significance of the documented objectionable conditions found does not justify further FDA action.

<sup>40</sup>For each inspection of a drug compounder, FDA conducts a joint assessment call involving officials from the Center for Drug Evaluation and Research and Office of Regulatory Affairs to conduct a more formal evaluation of the inspection results, including any violations, according to agency officials. At the conclusion of this call, the officials produce a document of findings and a recommended action with respect to that case. Recommended actions could include issuing a warning letter, pursuing an injunction, or sending a state referral letter. FDA could also recommend closing the case with no further actions as a result of the joint assessment call.

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whether the drug compounder meets certain conditions of sections 503A or 503B, as applicable, and to conditions and practices that, if deficient, raise safety concerns for public health. The inspections typically focus on identifying any insanitary conditions that could cause a drug product to be contaminated with filth or rendered injurious to health in violation of the FDCA, and review practices that, if deficient, could lead to potency problems or labeling mix ups.<sup>41</sup>

From May 11, 2012, through April 22, 2016, FDA conducted 265 inspections of 210 different establishments of drug compounders that are not outsourcing facilities, including 503A compounders. As a result of these inspections, the agency issued 228 FDA form 483 inspection observation reports (finding problems such as dead insects in ceilings and other insanitary conditions), and has taken a number of actions.<sup>42</sup> (See table 17.)

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<sup>41</sup>See 21 U.S.C. § 351(a)(2)(A).

<sup>42</sup>An FDA form 483 inspection observation report is issued to firm management at the conclusion of an inspection when FDA investigators have observed conditions that, in their judgment, may constitute violations of the FDCA and related acts.

While FDA provided data on inspections of 503A compounders and other drug compounders that are not outsourcing facilities from May 2012 through April 22, 2016, the agency provided data on the actions taken related to these inspections through June 28, 2016.

**Table 17: The Number and Type of Actions Taken from May 2012 to June 28, 2016 Related to Food and Drug Administration (FDA) Inspections of Drug Compounders That are Not Outsourcing Facilities**

Action	Number
Warning letter (to notify the compounder of significant violations of FDA regulations)	81 <sup>a</sup>
Voluntary recall	72 <sup>b</sup>
State referral letter (refers inspection findings to the applicable state regulatory agency)	31
Regulatory meeting (requested by FDA management to inform responsible individuals or firms about one or more practices, products, or other activities considered to be in violation of the law, and to discuss violations that would not be handled by other means)	1

Source: GAO analysis of FDA data. | GAO-17-64

Notes: This table includes actions related to inspections of 503A compounders and other drug compounders that are not outsourcing facilities. The 503A compounders are individuals or entities that are not outsourcing facilities that qualify for the exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA), including pharmacies, physicians, and federal facilities. Drug compounders that do not qualify for the exemptions under section 503A, and are not outsourcing facilities under section 503B, are regulated as conventional manufacturers and are subject to the provisions of the FDCA applicable to such manufacturers.

The actions are related to inspections conducted from May 2012 through April 22, 2016.

In addition, the agency sought and obtained two warrants to inspect pharmacies that refused inspection during this time period and obtained nine injunctions against drug compounders that were not outsourcing facilities. FDA also took criminal enforcement actions against three drug compounders that were not outsourcing facilities related to inspections during this time period.

<sup>a</sup>This number represents the number of drug compounders that are not outsourcing facilities that received warning letters; a drug compounder may have had more than one inspection associated with a warning letter.

<sup>b</sup>In addition, two inspections resulted in FDA requests for recalls but no recalls occurred.

As of April 2016, FDA had conducted 75 inspections of 59 different outsourcing facilities. Actions related to its inspections of outsourcing facilities included 24 FDA warning letters and 15 voluntary recalls.<sup>43</sup> (See table 18.)

<sup>43</sup>While FDA provided data on inspections of outsourcing facilities from March 5, 2014, through April 22, 2016, the agency provided data on the actions taken related to these inspections through June 28, 2016.

**Table 18: The Number and Type of Actions Taken from March 5, 2014, to June 28, 2016 Related to Food and Drug Administration (FDA) Inspections of Outsourcing Facilities**

Action	Number
Warning letter (to notify an outsourcing facility of significant violations of FDA regulations)	24 <sup>a</sup>
Voluntary recall	15
Untitled letter (to notify an outsourcing facility of violations that do not meet the threshold of regulatory significance of a warning letter)	1

Source: GAO analysis of FDA data. | GAO-17-64

Notes: The Drug Quality and Security Act, enacted in November 2013, created the category of outsourcing facility, and FDA conducted its first inspection of an outsourcing facility on March 5, 2014. The actions are related to inspections conducted from March 5, 2014, through April 22, 2016. In addition, the agency also obtained two injunctions against outsourcing facilities during this time period.

<sup>a</sup>This number represents the number of outsourcing facilities that received warning letters; an outsourcing facility may have had more than one inspection associated with a warning letter.

### Some Stakeholder Organizations said the Amount of Time it Takes FDA to Finalize Draft Documents Related to Drug Compounding is Challenging

Officials from 6 of the 25 stakeholder organizations we interviewed said the amount of time it takes FDA to finalize guidance and other relevant documents, including the list of drugs that are difficult to compound, is challenging. For example, officials from one of these stakeholder organizations told us that, as a result, they were uncertain regarding how to move forward under the DQSA; they did not know how to advise their members without final guidance from FDA regarding the list of drugs that are difficult to compound.

In addition, FDA has not finalized the standard memorandum of understanding (MOU) under section 503A between FDA and states that choose to sign it. Under section 503A, unless a drug is compounded in a state that has entered into an MOU with FDA, a pharmacist, pharmacy, or physician cannot distribute, or cause to be distributed, compounded drug products outside the state in which they are compounded in quantities that exceed 5 percent of the total prescription orders dispensed or distributed by that pharmacy or physician. These restrictions and the terms of the MOU will apply, once the standard MOU is finalized and made available to the states for their consideration and signature, to drugs compounded under section 503A, and will not apply to drugs compounded by outsourcing facilities. The law requires the standard MOU, which FDA is to develop in consultation with the National Association of Boards of Pharmacy, to address the interstate distribution of inordinate amounts of compounded drug products and to provide for appropriate investigation by a state of complaints related to compounded

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drug products distributed outside of the state.<sup>44</sup> Officials from two stakeholder organizations we talked to expressed concern regarding the time it is taking FDA to finalize the standard MOU. Specifically, they are concerned with the potential implications that the MOU may have on how they do business.

In particular, the draft MOU that FDA published for comment in February 2015, would restrict interstate distribution of compounded products under section 503A to less than 30 percent of the number of compounded and noncompounded drug products that a pharmacy, pharmacist, or physician in a state that has entered into the MOU distributes or dispenses both intrastate and interstate in a calendar month. Pharmacists, pharmacies, and physicians in states that have not entered into the MOU would be limited to distributing compounded drug products in quantities that do not exceed 5 percent of all prescription orders they dispense or distribute.<sup>45</sup>

Officials from five stakeholder organizations that we talked to said they were concerned that, in the draft MOU, FDA's proposed definition of distribution includes dispensing. Representatives from one pharmacist stakeholder organization stated that, if the MOU defines distribution interchangeably with dispensing, compounded drugs dispensed will be included in the 30 percent calculation for interstate distribution of compounded drugs. As a result, they are concerned that pharmacies that regularly dispense compounded drugs across state lines, such as pharmacies in the metropolitan Washington D.C. area, where the borders of the District of Columbia, Maryland, and Virginia are in close proximity, will be limited in the number of compounded drugs they can dispense to patients, even though some of these patients may only live a short distance from the pharmacy.<sup>46</sup>

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<sup>44</sup>21 U.S.C. § 353a(b)(3)(B).

<sup>45</sup>Food and Drug Administration, *Addressing Certain Distributions of Compounded Human Drug Products Between the State of [insert STATE] and the Food and Drug Administration*, Draft Memorandum of Understanding, 80 Fed. Reg. 8874 (Feb. 19, 2015).

<sup>46</sup>The draft MOU includes a statement that FDA does not intend to include "prescriptions dispensed to a patient (or patient's agent), if the patient (or patient's agent) to whom the drug is dispensed carries the drug across State lines after it has been dispensed to the patients (or patient's agent) at the facility in which the drug was compounded" in the percentage of compounded drug products that a drug compounding may distribute interstate.

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FDA officials cited a number of reasons for the time it has taken the agency to finalize the agency's draft drug compounding documents, including the time and steps required to solicit and evaluate comments and issue guidance. For example, FDA officials attributed the time it has taken to finalize the draft MOU and other documents to a number of factors, including the time needed to review public comments and to conduct public meetings with state boards of pharmacy; FDA has received over 3,000 comments on the agency's draft MOU alone, many of which raise complex policy issues that need to be resolved, according to agency officials. In addition, according to the officials, these documents must go through FDA's internal clearance process along with numerous other requirements before being finalized.

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### States and Stakeholder Organizations Cited Concerns Regarding FDA's Implementation of Its Drug Compounding Responsibilities

States and stakeholder organizations reported a number of concerns related to FDA's implementation of its drug compounding responsibilities. These concerns included the availability of compounded drugs for use in physicians' offices, a potential loss in patient access to needed medications, and conflicting federal and state inspection protocols.

In response to our survey of state pharmacy regulatory bodies, respondents from 30 states reported that they had heard concerns that FDA's implementation of DQSA would affect the availability of compounded drugs for use in physicians' offices, generally referred to as office-use compounding. FDA's April 15, 2016, draft guidance on the prescription requirement for drugs compounded under section 503A states that the agency interprets section 503A to require a valid prescription for an individual patient before a pharmacy may provide a compounded drug to a provider.<sup>47</sup> Therefore, the draft guidance indicates that compounding of a drug product to be kept as stock in a doctor's office, hospital, or other health care facilities without an individual patient prescription is not permitted by any pharmacy that is not an outsourcing facility. Officials from some of the stakeholder organizations we talked to have raised concerns that FDA's draft guidance is inconsistent with laws

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<sup>47</sup>Department of Health and Human Services, Food and Drug Administration, *Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act, Guidance for Industry, Draft Guidance*, (Silver Spring, Md.: April 2016). See <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf>, accessed April 18, 2016.



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in states that allow compounding for office use, and respondents in 27 states reported that their state laws currently allow office-use compounding.<sup>48</sup>

FDA officials noted that the agency's policies with respect to the prescription requirement in section 503A are intended to protect patients from poor quality compounded drugs that could cause serious harm while preserving access to drugs compounded for office-use for patients who need them. They stated that the prescription requirement in section 503A is critical to differentiate compounding by pharmacies and physicians under section 503A from conventional manufacturing and compounding by outsourcing facilities, which are subject to routine FDA oversight. FDA officials also said that stakeholders should advise the agency if instances arise in which a health care facility that orders compounded drugs for office use to meet patients' medical needs is unable to obtain these drugs from outsourcing facilities.

Respondents in 23 states reported concerns about access to certain compounded drugs for patients with a medical need for these drugs. For example, for compounded drugs for which there is not a great demand, there is concern that outsourcing facilities would choose not to compound these drugs. Therefore, according to these respondents, there is a concern that if 503A compounders are not allowed to compound these drugs for office use, patients could lose access to needed medications.

Some states and stakeholder organizations reported differences between the protocols that some states and FDA use when inspecting pharmacies engaged in drug compounding that are not outsourcing facilities. Specifically, officials in the states noted that their states inspect pharmacies to assess their compliance with state pharmacy practice rules, which are often based on the standards in USP chapters 795 (nonsterile compounding) and 797 (sterile compounding). These officials said that although pharmacies meeting the requirements of section 503A are exempt from FDA's CGMP requirements, FDA's publicly available form 483 inspection observation reports have included observations related to CGMP requirements, even for those 503A compounders. FDA

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<sup>48</sup>Respondents in 4 of the 27 states commented that only outsourcing facilities registered with FDA may compound drugs for office use.

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officials indicated they were aware of concerns about this practice, and on July 13, 2016, FDA announced a change in the agency's procedures that took effect on August 1, 2016. Under the new procedures, FDA investigators first make a preliminary assessment of whether a compounder's drugs are exempt from CGMP requirements under section 503A. If the preliminary assessment is that the compounder's drugs are exempt, the investigator will not issue an inspection observation report showing observations solely related to noncompliance with CGMP requirements. Instead, the FDA form 483 inspection observation report will only include observations that do not relate solely to CGMP requirements. However, if the preliminary assessment is that the compounder's drugs are not exempt under section 503A, the agency may cite CGMP-related observations in the inspection observation report.<sup>49</sup>

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## Agency Comments

We provided a draft of this report to the Secretary of Health and Human Services. HHS provided written comments, which are reproduced in appendix III. HHS also provided technical comments, which we incorporated as appropriate.

In its comments, HHS stated that FDA has prioritized efforts to increase collaboration between FDA and states regarding oversight of drug compounding, and cited examples of FDA's efforts to do so. HHS also stated that FDA is committed to working with states to further improve communication, noting FDA's efforts to improve communications while

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<sup>49</sup>According to agency officials, when FDA's post-inspection review differs from the FDA investigators' preliminary assessment and reveals that a facility does not produce drugs in accordance with the conditions of section 503A, FDA intends to consider citing CGMP violations in any regulatory action it decides to pursue. FDA's notice indicates that, although drug products compounded in accordance with the conditions of section 503A are exempt from certain requirements in the FDCA, they remain subject to all other provisions of the FDCA that apply to conventional drug manufacturers, including, but not limited to, the prohibition on preparing, packing, or holding drugs under insanitary conditions. FDA will continue to include observations on FDA form 483 inspection observation report that appear to constitute insanitary conditions or to violate other requirements from which 503A does not provide an exemption without regard to the investigator's preliminary assessment of a firm's status under section 503A. Department of Health and Human Services, Food and Drug Administration, *Insanitary Conditions at Compounding Facilities, Guidance for Industry, Draft Guidance*, (Silver Spring, Md.: August 2016). See <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf>, accessed August 26, 2016.

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commenting that, in some cases, federal law prohibits the agency from sharing certain information. HHS also acknowledged some of the concerns of states and stakeholders that we noted in our report, including compounding by physicians and access to compounded drugs, and provided information on steps FDA has taken or plans to take regarding these issues.

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We are sending copies of this report to the Secretary of Health and Human Services, appropriate congressional committees, and other interested parties. In addition, the report will be available at no charge on the GAO Web site at <http://www.gao.gov>.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or [crossem@gao.gov](mailto:crossem@gao.gov). Contact points for our Offices of Congressional Relations and Public Affairs are on the last page of this report. GAO staff who made major contributions to this report are listed in appendix IV.



Marcia Crosse  
Director, Health Care

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# Appendix I: Information for Purchasers Regarding the Safety and Quality of Compounded Drugs

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Representatives of stakeholder organizations we interviewed and states we surveyed identified a number of tools available to purchasers of compounded drugs, including institutional purchasers (e.g., hospitals), health care practitioners (e.g., physicians), and individual patients, that are available for use to determine whether drug compounders are maintaining the appropriate standards for the safety and quality of these drugs.

Examples of tools identified include the following:

- **Food and Drug Administration's (FDA) compounding website:** Purchasers can review FDA's compounding website, which includes information on FDA inspections and actions taken by FDA related to deficiencies found during an inspection. In response to our survey of state pharmacy regulatory bodies, respondents in 13 states reported that they would direct purchasers of compounded drugs to use FDA's compounding website, or other FDA information, in order to determine the safety and quality of compounded drugs.
- **State board of pharmacy websites:** Purchasers can contact their state board of pharmacy or search their state board of pharmacy's website to determine whether the state has inspected a pharmacy, and if so, whether the state had found shortcomings in its compounding operations (for those states that make this information available on their website). Fourteen states reported that they would direct purchasers of compounded drugs to state websites.
- **Pharmacy accreditation organizations:** Purchasers can determine whether a pharmacy was accredited for compounding by an organization, such as the Accreditation Commission for Health Care's Pharmacy Compounding Accreditation Board, or identify whether a pharmacy has met the requirements of other national associations' programs, such as the National Association of Boards of Pharmacy's Verified Pharmacy Program.<sup>1</sup> Six of the 25 stakeholder organizations we talked to indicated that pharmacy accreditation for compounding

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<sup>1</sup>As of August 2016, the Accreditation Commission for Health Care's Pharmacy Compounding Accreditation Board had accredited 445 pharmacies. According to officials from the National Association of Boards of Pharmacy, as of August 2016, users from at least 44 jurisdictions utilized information from the Verified Pharmacy Program database, which was developed to enable states to make decisions regarding licensing nonresident pharmacies.

by an organization, such as the Accreditation Commission for Health Care's accreditation board, is a tool that purchasers of compounded drugs can use to assess the safety and quality of compounded drugs.

However, our review found that there were few drug compounders with clean inspections, and relatively few compounders were accredited.<sup>2</sup> Therefore, many purchasers of compounded drugs may rely on information from state and federal regulatory bodies on the safety and quality of compounded drugs, including deficiencies found during inspections.

Institutional purchasers and health care practitioners have additional tools available to identify and evaluate drug compounders as they seek sources to provide compounded drugs for their operations.

- **The American Society of Health-System Pharmacists' assessment tool:** Nine of the 25 stakeholder organizations we talked to referenced the American Society of Health-System Pharmacists' assessment tool, which is intended to help purchasers that choose to outsource the preparation of compounded drugs to evaluate proposals in order to select a drug compounder to supply those drugs.
- **The International Academy of Compounding Pharmacists' Compounding Pharmacy Assessment Questionnaire:** Three of the 25 stakeholder organizations we talked to referenced the International Academy of Compounding Pharmacists' compounding pharmacy assessment questionnaire checklist. This tool was developed based on the U.S. Pharmacopeial Convention's compounding standards, to provide purchasers with a checklist of what to look for in a pharmacy compounding practice.

Other organizations involved in the purchase of prescription drugs—specifically pharmacy benefit managers—may utilize their own tools to help determine whether drug compounders are maintaining the

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<sup>2</sup>Of the 75 inspections of outsourcing facilities that FDA conducted from March 5, 2014, through April 22, 2016, FDA issued FDA form 483 inspection observation reports to 85 percent of them. An FDA form 483 inspection observation report is issued to firm management at the conclusion of an inspection when FDA investigators have observed conditions that, in their judgment, may constitute violations of the FDCA and related acts. Of the inspections that did not result in FDA issuing an FDA form 483 inspection observation report, one facility was not yet operational at the time of the inspection.

appropriate standards for the safety and quality of these drugs.<sup>3</sup> For example, officials from one pharmacy benefit manager told us that their organization has developed a credentialing process to evaluate compounding pharmacies for inclusion in their network and to determine the type of compounded drugs these pharmacies may sell in the pharmacy benefit manager's network. The officials said that this process consists of a questionnaire that covers items such as the pharmacy's quality procedures for each compounded dosage form (i.e., it determines whether the pharmacy is capable of accurately making capsules, complex suspensions, and other dosage forms), and the pharmacy's quality practices and procedures. In addition, the officials said they also review the findings from inspections conducted by a state or FDA. At the end of the credentialing process, the organization will establish an agreement with the pharmacy that allows it conduct either "complex nonsterile compounding" or "limited scope nonsterile compounding."<sup>4</sup>

Ten of the 25 stakeholder organizations we talked to indicated that the drug's label is also a tool for patients to use to determine whether the drug is a compounded drug. Outsourcing facilities are required to include a statement on compounded drugs indicating that it is a compounded drug, as well as the drug's expiration date and ingredients.<sup>5</sup> In addition, 24 states reported requiring labeling for compounded drugs, as of January 1, 2016. Therefore, for drugs with such labeling, the patient (if the drug is dispensed directly to a patient) or the provider (if administered in the office or medical facility) could know it was a compounded drug and the expiration date and the ingredients. Section 503A of the Federal Food, Drug, and Cosmetic Act does not require 503A compounders to include a statement that it is a compounded drug on the drugs they

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<sup>3</sup>A pharmacy benefit manager is a third-party administrator of prescription drug programs for certain health plans and federal and state government employee plans responsible for developing and maintaining the drug formulary, contracting with pharmacies, negotiating discounts and rebates with drug manufacturers, and processing and paying prescription drug claims.

<sup>4</sup>A complex nonsterile compounding agreement would allow the pharmacy to compound drugs, such as creams with multiple ingredients, and the limited scope nonsterile compounding agreement would allow the pharmacy to compound drugs such as shake lotions (i.e., a lotion that separates into parts with time so it needs to be shaken before use).

<sup>5</sup>21 U.S.C. § 353b(a)(10).

compound. One stakeholder organization pointed out that most labeling is not consistent and that certain drugs may not have a label, such as compounded drugs for hospital patients, or compounded drugs in nuclear pharmacies; another stakeholder organization stated that unless a state requires pharmacies to label compounded drugs as such, patients likely won't know whether the drug was compounded. FDA officials also noted that the agency has heard from stakeholders that physicians and patients may not be aware that the drugs that they are administering or receiving were compounded, or that they are not approved by FDA.

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# Appendix II: Objectives, Scope, and Methodology

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The Drug Quality and Security Act (DQSA), enacted in November 2013, included a provision for GAO to review drug compounding. We examined (1) the settings in which drugs are compounded, and the extent of drug compounding in each state; (2) state laws, regulations, and policies governing drug compounding, and how they are enforced; (3) how communication is conducted between states and FDA, as well as among states, regarding compounding, and any associated challenges; and (4) steps FDA has taken to implement its responsibilities to oversee drug compounding since enactment of the DQSA, and any challenges that have been reported with these efforts. We also examined available information for purchasers of compounded drugs (e.g., hospitals, health systems, and patients) to determine the safety and quality of those drugs.

To address our reporting objectives and obtain information about purchasers of compounded drugs, we administered a web-based survey to the state pharmacy regulatory bodies (e.g., boards of pharmacy) in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands. We interviewed officials at 25 national associations and other stakeholder organizations, government officials in 3 states (Minnesota, North Carolina, and Texas), officials at two pharmacy benefit manager organizations, and officials from the Food and Drug Administration (FDA); and we reviewed relevant documents from FDA and the organizations we interviewed. Finally, to address steps FDA has taken to implement its regulatory responsibilities to oversee drug compounding and related challenges, we reviewed relevant laws and analyzed FDA data on inspections of drug compounders and actions taken related to its inspections of these entities.

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## 2016 Survey of State Pharmacy Regulatory Bodies on Drug Compounding

We administered a web-based survey to the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands. We surveyed state pharmacy regulatory bodies (states) because these are the entities that regulate pharmacy practice, including drug compounding activities, through state laws and regulations. To collect information on drug compounding across the country, we surveyed all 50 states and the District of Columbia. We also included selected U.S. territories in our survey population—Guam, Puerto Rico, and the U.S. Virgin Islands—because these are the three most populous territories, all have boards of pharmacy, and all are members of the



National Association of Boards of Pharmacy.<sup>1</sup> We primarily obtained contact information for the states from information on boards of pharmacy on the National Association of Boards of Pharmacy's website, and we tested the survey by conducting three pretests of draft versions with officials from a state board of pharmacy in a rural state, officials from a state board of pharmacy in a populous state, and a national pharmacy association.

Our survey was administered from February 8, 2016, through April 15, 2016. We collected information from survey respondents on the settings in which drug compounding occurs and data on drug compounding in each state, state laws, regulations, and policies related to drug compounding, activities states have participated in related to drug compounding with FDA and other states, states' perspectives on communication with FDA and other states, states' perspectives on FDA's implementation of the DQSA, and information on how states would notify purchasers of compounded drugs that a compounded drug was found to be of questionable safety or quality, among other things.

We had a survey response rate of 93 percent; 50 of the 54 states completed the survey. Two states, Alaska and Indiana, responded to some of the survey questions but did not complete the survey; therefore, their responses were not included in our survey analyses. Two of the territories, Puerto Rico and the U.S. Virgin Islands, did not respond to any of the survey questions.

We analyzed the survey responses from the 50 completed surveys and conducted follow up with respondents, as needed, to clarify certain survey responses or obtain additional information.<sup>2</sup> We conducted data checks on the survey responses, including checking for skip patterns and invalid responses, to ensure the reliability of the data.

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<sup>1</sup>We refer to all of the state pharmacy regulatory bodies that we surveyed as states in this report.

<sup>2</sup>We relied on state reporting of, and did not independently review, all 50 states' laws, regulations, and policies applicable to drug compounding.

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Interviews with Officials in Stakeholder Organizations, State Government Agencies, and FDA

To further address our objectives, we interviewed officials from 25 stakeholder organizations that have a stake or an interest in drug compounding to obtain information such as reviews on the extent of drug compounding; reviews of state laws, regulations, and policies on drug compounding; their perspectives on any challenges in communication between FDA and states, as well as among states, related to drug compounding; and their perspectives on FDA's implementation of the DQSA. We selected these stakeholder organizations to include national organizations representing (1) pharmacies and pharmacists, including those that compound drugs; (2) physicians, including those in medical specialties identified as compounding drugs; and (3) state boards of pharmacy, state medical boards, and state health officials; as well as experts in drug compounding, and an organization that conducted research related to drug compounding.<sup>3</sup> We reviewed relevant documents provided by these stakeholder organizations, including comments submitted to FDA regarding FDA's compounding-related activities.

We also interviewed state agency officials from the boards of pharmacy, medical boards, and the state agencies that have oversight responsibility for outsourcing facilities, in three selected states—North Carolina, Minnesota, and Texas.<sup>4</sup> We selected these states because they reported differing laws, regulations, or policies related to drug compounding in their responses to the survey, which included having different types of state

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<sup>3</sup>We interviewed officials from the following 25 national associations and other stakeholder organizations: the Accreditation Commission for Health Care, American Academy of Dermatology, American Academy of Ophthalmology, American Hospital Association, American Medical Association, American Pharmacists Association, American Society of Clinical Oncology, American Society of Consultant Pharmacists, American Society of Health-System Pharmacists, Association of State and Territorial Health Officials, Clinical IQ, Dr. Loyd Allen Jr., Federation of State Medical Boards, Institute for Safe Medication Practices, International Academy of Compounding Pharmacists, the Joint Commission, National Alliance of State Pharmacy Associations, National Association of Boards of Pharmacy, National Association of Chain Drug Stores, National Community Pharmacists Association, National Conference of State Legislatures, National Home Infusion Association, Pew Charitable Trusts, Professional Compounding Centers of America, and the U.S. Pharmacopeial Convention.

<sup>4</sup>Licensed outsourcing facilities are overseen by the North Carolina Department of Agriculture and Consumer Services, Food and Drug Protection Division, in North Carolina, and by the Texas Department of State Health Services, Drugs and Medical Devices Group, in Texas. The Minnesota Board of Pharmacy has oversight responsibilities for licensed outsourcing facilities in Minnesota.

agencies or departments with oversight responsibilities for outsourcing facilities, and variation in their oversight responsibilities of physicians or other nonpharmacists. Through the interviews with the board of pharmacy officials, we obtained additional information on state laws and policies related to drug compounding, as well as additional details for certain survey responses. In our interviews with state medical board officials, we obtained information on the medical board's role in the oversight of drug compounding and other information, as available, related to compounding by physicians in each state. Two of our three selected states—North Carolina and Texas—had a separate state agency responsible for overseeing FDA-registered outsourcing facilities licensed in the state; therefore, we obtained information in these interviews specific to their oversight responsibilities for these facilities. In addition, we interviewed officials from two pharmacy benefit managers—third-party administrators of prescription drug programs for certain health plans and federal and state government employee plans—to obtain information related to drug compounding, including how these entities determine the safety and quality of compounded drugs.<sup>5</sup> The perspectives of the officials from the 25 stakeholder organizations, three selected states, and two pharmacy benefit managers are not generalizable, but provided us with valuable insight on these issues.

We reviewed relevant documents from FDA, including FDA's draft memorandum of understanding (MOU) for use with states regarding distribution of compounded human drug products, and FDA's draft and final guidance related to drug compounding, such as FDA's final guidance on registration of outsourcing facilities. We also reviewed relevant federal laws and regulations related to drug compounding, including sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act. In addition, we interviewed FDA officials and reviewed information on FDA's compounding website to determine steps FDA has taken to implement its regulatory responsibilities to oversee drug compounding since enactment of the DQSA.

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<sup>5</sup>The two pharmacy benefit manager organizations that we interviewed were Express Scripts and CVS Caremark. We selected these organizations because they were two of the largest pharmacy benefit managers in the country.

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## Analysis of FDA Inspections Data

To further address our objective on steps FDA has taken to implement its regulatory responsibilities to oversee drug compounding since enactment of the DQSA, we analyzed FDA data from May 2012 through April 22, 2016, on the number of inspections that FDA has conducted on drug compounders, and data on actions that FDA has taken related to these inspections from May 2012 through June 28, 2016.<sup>6</sup> Actions included FDA issuing an FDA form 483 inspection observation report or a warning letter to an entity.<sup>7</sup> We also obtained FDA data on outsourcing facilities that were currently registered with FDA or have ever been registered with FDA (i.e., facilities that were registered as an outsourcing facility at some point with FDA but are no longer registered) as of April 22, 2016. We determined that the data we used from FDA on inspections and actions related to drug compounding were sufficiently reliable for our purposes by discussing data collection processes and limitations of the data with agency officials, and comparing the data against other published sources.

We conducted this performance audit from May 2015 to November 2016 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

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<sup>6</sup>FDA provided inspection data for 503A compounders and outsourcing facilities from May 2012 through April 22, 2016, and data on actions taken from May 2012 through June 28, 2016. We requested FDA inspection data starting in May 2012 because our prior report on drug compounding analyzed this data on 503A compounders up to May 2012, see [GAO-13-702](#). The inspection data we examined on outsourcing facilities started in March 2014 because outsourcing facilities were not created until enactment of the Drug Quality and Security Act in November 2013, and FDA conducted its first inspection in March 2014.

<sup>7</sup>An FDA form 483 is an inspection observation report that is issued at the conclusion of an inspection when FDA investigators have observed conditions that, in their judgment, may constitute violations of the FDCA and related acts. An FDA warning letter is a correspondence that notifies a responsible individual or firm that the agency considers one or more products, practices, processes, or other activities to be in violation of the FDCA, its implementing regulations, and other federal statutes.

# Appendix III: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation  
Washington, DC 20201

OCT 19 2016

Marcia Crosse  
Director, Health Care  
U.S. Government Accountability Office  
441 G Street NW  
Washington, DC 20548

Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, *"DRUG COMPOUNDING: FDA Has Taken Steps to Implement Compounding Law, But Some States and Stakeholders Reported Challenges"* (GAO-17-64).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

A handwritten signature in black ink, appearing to read "Jim R. Esquea".

Jim R. Esquea  
Assistant Secretary for Legislation

Attachment

**GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: DRUG COMPOUNDING: FDA HAS TAKEN STEPS TO IMPLEMENT COMPOUNDING LAW, BUT SOME STATES AND STAKEHOLDERS REPORTED CHALLENGES (GAO-17-64)**

The U.S. Department of Health and Human Services (HHS) appreciates the opportunity to review and comment on this draft report. We also appreciate the Government Accountability Office's (GAO) in-depth analysis of the U.S. Food and Drug Administration's (FDA) implementation of the compounding provisions of the law and its interactions with stakeholders, including States, on matters pertaining to drug compounding. While GAO noted some challenges that we address below, we believe that the draft report reflects the significant efforts of FDA over the past several years to develop policies, conduct inspections and take regulatory action, and collaborate with stakeholders to mitigate the risks to the public health from compounded drug products.

FDA believes that effective oversight of human drug compounding requires close collaboration between FDA and the States, and, since 2012, the Agency has prioritized efforts to increase such collaboration. Examples of these efforts include: inviting States to accompany FDA on inspections of State-licensed pharmacies; holding teleconferences with States on various topics, such as to discuss FDA recommendations that a State-licensed pharmacy initiate a recall due to lack of sterility assurance, or to address questions from State officials regarding policy or enforcement matters; and holding monthly meetings with the National Association of Boards of Pharmacy to discuss matters of mutual concern. FDA also holds annual Intergovernmental Working Meetings, most recently on September 21-22, 2016, after GAO's State survey concluded. In response to feedback from prior meetings, FDA changed the format of this meeting to facilitate increased discussion (e.g., through breakout sessions). We received positive feedback from States regarding this most recent meeting.

FDA is pleased that many States provided GAO with positive feedback regarding FDA/State communication, and we are committed to working with States on further improvement. We note that, in some cases, Federal law prohibits FDA from sharing certain information requested by State officials who have not entered into information-sharing agreements with FDA. FDA has encouraged and worked with States and individual State officials to provide such commitments through FDA commissioning pursuant to section 702(a)(1) of the Food, Drug, and Cosmetic Act (FD&C Act or Act) [21 U.S.C. § 372] or information-sharing agreements pursuant to 21 CFR 20.88. For example, FDA created a 5 year, single signature "Long-Term Drug Compounding Information Sharing Agreement," to improve communications and facilitate oversight of compounding pharmacies. FDA also created a chart, "Compounding Domestic Inspection Information Sharing Chart," to describe categories of information that are gathered during or after an FDA inspection, the types of non-public information that might be included in the various categories of information, and the conditions under which such non-public information can be shared with a State. Both documents are available on FDA's website.

FDA is aware of the concerns identified in GAO's report associated with physician compounding, including the lack of State oversight over this activity in many cases. FDA is engaging in discussions with the Federation of State Medical Boards and other organizations concerning physician compounding, and, in the future, we intend to offer guidance and educational outreach concerning provisions of Federal law that apply to physician compounding. For example, FDA's August 2016 draft guidance, *Insanitary Conditions at Compounding*

**GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: HIGH-CONTAINMENT LABORATORIES: IMPROVED OVERSIGHT OF DANGEROUS PATHOGENS NEEDED TO MITIGATE RISK (GAO-16-642)**

*Facilities*, provides examples of conditions that FDA considers to be “insanitary.” This draft guidance clarifies that compounded drugs, including drugs compounded by physicians, are adulterated in violation of Federal law if they are prepared, packed, or held under insanitary conditions whereby they may become contaminated with filth or rendered injurious to health. In addition, FDA held a session during its most recent Intergovernmental Working Meeting in September 2016, concerning challenges associated with oversight of physician compounding.

FDA also recognizes the concerns raised by representatives from certain States and stakeholder organizations concerning access to compounded drugs. As FDA implements the compounding provisions of the FD&C Act, we are committed to establishing policies that preserve access to compounded drugs for patients who need them, while protecting patients from receiving poor quality compounded drugs that could cause serious harm. After the 2012 fungal meningitis outbreak that resulted in over 60 deaths and over 750 cases of infection in patients in 20 States, Congress passed the Drug Quality and Security Act, establishing a new category of compounders called “outsourcing facilities” that may compound and distribute drugs without first receiving patient-specific prescriptions, but that are subject to increased Federal oversight and quality standards. Outsourcing facilities engage in compounding of sterile and non-sterile drugs, small and large batches, and with and without first receiving patient-specific prescriptions. Health care facilities that need non-patient specific compounded drugs to meet patients’ medical needs should obtain those drugs from outsourcing facilities.

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# Appendix IV: GAO Contact and Staff Acknowledgments

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## GAO Contact

Marcia Crosse (202) 512-7114 or [crossem@gao.gov](mailto:crossem@gao.gov)

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## Staff Acknowledgments

In addition to the contact above, Kim Yamane (Assistant Director), Lisa A. Lusk (Analyst-in-Charge), Matthew Byer, Julie Flowers, Sandra George, and Drew Long made key contributions to this report.



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Please Print on Recycled Paper.

# **Attachment**

# FDA proposes six bulk drug substances for inclusion on the 503A bulks list

*Proposed rule also addresses criteria for evaluating bulk drug substances and four bulk drug substances not proposed for inclusion on the 503A bulks list*

**[12/15/2016]** Today FDA issued a proposed rule, **List of Bulk Drug Substances that can be used to Compound Drug Products** (<https://www.federalregister.gov/documents/2016/12/16/2016-30109/list-of-bulk-drug-substances-that-can-be-used-to-compound-drug-products>), addressing six bulk drug substances the agency has evaluated and is proposing for inclusion on a list of bulk drug substances that can be used in compounding under section 503A of the Food, Drug, and Cosmetic Act. The proposed rule also proposes that four other bulk drug substances that FDA evaluated not be included on the 503A bulks list.

If the proposed rule is finalized, the six bulk drug substances proposed for inclusion will be the first ones included on the 503A bulks list.

FDA also proposes to use the following criteria when evaluating nominated substances for inclusion on the list:

1. The physical and chemical characterization of the substance;
2. Any safety issues raised by the use of the substance in compounded drug products;
3. The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and
4. 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.

FDA proposes to consider each criterion in the context of the others and balance them, on a substance-by-substance basis, to decide whether a particular substance is appropriate for inclusion on the 503A bulks list. The **Federal Register notice** (<https://www.federalregister.gov/documents/2016/12/16/2016-30109/list-of-bulk-drug-substances-that-can-be-used-to-compound-drug-products>) announcing the proposed rule provides additional details about the kind of information proposed to be considered for each criterion and how FDA proposes to weigh the information.

Substances proposed for inclusion on the 503A bulks list

The FDA applied the proposed criteria for evaluating bulk drug substances for the 503A bulks list. Based on its evaluation, as well as consultation with the Pharmacy Compounding Advisory Committee, FDA is proposing to include six bulk drug substances on the list:

- **[Brilliant Blue G \(/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf#page=193\)](#)**, also known as Coomassie Brilliant Blue G-250
- **[cantharidin \(/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM433804.pdf#page=752\)](#)** (for topical use only)
- **[diphenylcyclopropanone \(/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM433804.pdf#page=636\)](#)** (for topical use only)
- **[N-acetyl-D-glucosamine \(/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf#page=276\)](#)** (for topical use only)
- **[squaric acid dibutyl ester \(/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM433804.pdf#page=595\)](#)** (for topical use only)
- **[thymol iodide \(/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM433804.pdf#page=509\)](#)** (for topical use only)

Substances not proposed for inclusion on the 503A bulks list

FDA is proposing that the following four substances not be included on the list:

- **[oxitriptan \(/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf#page=302\)](#)**
- **[piracetam \(/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM433804.pdf#page=792\)](#)**
- **[silver protein \(/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM433804.pdf#page=542\)](#)** mild
- **[tranilast \(/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf#page=231\)](#)**

The public comment period on the proposed rule closes in 90 days. The **Federal Register notice** (<https://www.federalregister.gov/documents/2016/12/16/2016-30109/list-of-bulk-drug-substances-that-can-be-used-to-compound-drug-products>) has information on how to submit comments.

**[More in Drug Safety and Availability \(/Drugs/DrugSafety/default.htm\)](#)**

**[Drug Alerts and Statements \(/Drugs/DrugSafety/ucm215175.htm\)](#)**

**[Medication Guides \(/Drugs/DrugSafety/ucm085729.htm\)](#)**

**[Drug Safety Communications \(/Drugs/DrugSafety/ucm199082.htm\)](#)**

[Drug Shortages \(/Drugs/DrugSafety/DrugShortages/default.htm\)](#) ▼

[Postmarket Drug Safety Information for Patients and Providers \(/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm\)](#) ▼

**[Information by Drug Class \(/Drugs/DrugSafety/InformationbyDrugClass/default.htm\)](#)**

**[Medication Errors \(/Drugs/DrugSafety/MedicationErrors/default.htm\)](#)**

[Drug Safety Podcasts \(/Drugs/DrugSafety/DrugSafetyPodcasts/default.htm\)](#) ▼

[Safe Use Initiative \(/Drugs/DrugSafety/SafeUseInitiative/default.htm\)](#) ▼

**[Drug Recalls \(/Drugs/DrugSafety/DrugRecalls/default.htm\)](#)**

[Drug Supply Chain Integrity \(/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/default.htm\)](#) ▼

Report SE-623, Issue 16"). Accomplishing the revision required by this paragraph terminates the requirements of paragraph (g) of this AD. Accomplishing the revision required by this paragraph also terminates the requirements of paragraph (g) of AD 2012-12-07.

(1) The initial compliance times for the tasks specified in Fokker Services B.V. Engineering Report SE-623, Issue 16, are at the later of the applicable compliance times specified in Fokker Services B.V. Engineering Report SE-623, Issue 16, or within 30 days after the effective date of this AD, whichever is later.

(2) If any discrepancy is found, before further flight, repair using a method approved by the Manager, International Branch, ANM-116, Transport Airplane Directorate, FAA; or the EASA; or Fokker B.V. Service's EASA DOA.

**(l) No Alternative Actions or Intervals**

After the maintenance or inspection program, as applicable, has been revised as required by paragraph (k) of this AD, no alternative actions (e.g., inspections) or intervals may be used unless the actions or intervals are approved as an AMOC in accordance with the procedures specified in paragraph (m)(1) of this AD.

**(m) Other FAA AD Provisions**

The following provisions also apply to this AD:

(1) *Alternative Methods of Compliance (AMOCs)*: The Manager, International Branch, ANM-116, Transport Airplane Directorate, FAA, has the authority to approve AMOCs for this AD, if requested using the procedures found in 14 CFR 39.19. In accordance with 14 CFR 39.19, send your request to your principal inspector or local Flight Standards District Office, as appropriate. If sending information directly to the International Branch, send it to ATTN: Tom Rodriguez, Aerospace Engineer, International Branch, ANM-116, Transport Airplane Directorate, FAA, 1601 Lind Avenue SW., Renton, WA 98057-3356; telephone 425-227-1137; fax 425-227-1149. Information may be emailed to: 9-ANM-116-AMOC-REQUESTS@faa.gov. Before using any approved AMOC, notify your appropriate principal inspector, or lacking a principal inspector, the manager of the local flight standards district office/certificate holding district office.

(2) *Contacting the Manufacturer*: As of the effective date of this AD, for any requirement in this AD to obtain corrective actions from a manufacturer, the action must be accomplished using a method approved by the Manager, International Branch, ANM-116, Transport Airplane Directorate, FAA; or EASA; or Fokker B.V. Services' EASA DOA. If approved by the DOA, the approval must include the DOA-authorized signature.

**(n) Related Information**

(1) Refer to Mandatory Continuing Airworthiness Information (MCAI) EASA AD 2016-0125, dated June 21, 2016, for related information. You may examine the MCAI on the Internet at <http://www.regulations.gov> by searching for and locating Docket No. FAA-2016-9435.

(2) For service information identified in this AD, contact Fokker Services B.V., Technical Services Dept., P.O. Box 1357, 2130 EL Hoofddorp, the Netherlands; telephone: +31 (0)88-6280-350; fax: +31 (0)88-6280-111; email: [technicalservices@fokker.com](mailto:technicalservices@fokker.com); Internet <http://www.myfokkerfleet.com>. You may view this service information at the FAA, Transport Airplane Directorate, 1601 Lind Avenue SW., Renton, WA. For information on the availability of this material at the FAA, call 425-227-1221.

Issued in Renton, Washington, on November 17, 2016.

**Phil Forde,**

*Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.*

[FR Doc. 2016-28669 Filed 12-15-16; 8:45 am]

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 216**

[Docket No. FDA-2016-N-3464]

RIN 0910-AH29

**List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA or Agency) is proposing a regulation to identify an initial list of bulk drug substances that can be used to compound drug products in accordance with certain compounding provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), although they are neither the subject of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. Specifically, the Agency proposes to place six bulk drug substances on the list. This proposed rule also identifies four bulk drug substances that FDA has considered and proposes not to include on the list. Additional substances nominated by the public for inclusion on this list are currently under consideration and will be the subject of a future rulemaking.

**DATES:** Submit either electronic or written comments on the bulk drug substances list by March 16, 2017. See section VI for the proposed effective

date of a final rule based on this proposed rule.

**ADDRESSES:** You may submit comments as follows:

*Electronic Submissions*

Submit electronic comments in the following way:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

*Written/Paper Submissions*

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

*Instructions:* All submissions received must include the Docket No. FDA-2016-N-3464 for "List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

• **Confidential Submissions**—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

**Docket:** For access to the docket to read background documents or the electronic and written/paper comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** James Flahive, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5108, Silver Spring, MD 20993-0002, 301-796-9293.

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#### I. Executive Summary

##### A. Purpose of the Proposed Rule

FDA is proposing to amend its regulations to add a list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act (21 U.S.C. 353a) (referred to as “the 503A Bulks List”). Bulk drug substances that appear on the 503A Bulks List can be used to compound drug products subject to the conditions of section 503A, although those substances are not the subject of a USP or NF monograph or components of approved drug products.

##### B. Summary of the Major Provisions of the Proposed Rule

FDA is proposing to establish the criteria by which bulk drug substances will be evaluated for inclusion on the 503A Bulks List. Based on the results of its evaluation of nominated bulk drug substances to date, as well as consultation with the Pharmacy Compounding Advisory Committee (PCAC), FDA is also proposing to include six bulk drug substances on the list: Brilliant Blue G, also known as Coomassie Brilliant Blue G-250; cantharidin (for topical use only); diphenylcyclopropenone (for topical use only); N-acetyl-D-glucosamine (for topical use only); squaric acid dibutyl ester (for topical use only); and thymol iodide (for topical use only) and that four other substances not be included on the list: Oxitriptan, piracetam, silver protein mild, and tranilast.

##### C. Legal Authority

Section 503A of the FD&C Act, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)), serves as our principal legal authority for this proposed rule.

##### D. Costs and Benefits

FDA is proposing to place six bulk substances on the 503A Bulks List and not to place four bulk substances on the 503A Bulks List. Because we lack sufficient information to quantify the costs and benefits of this proposed rule, we include a qualitative description of potential benefits and potential costs. We expect that the rule would affect compounding pharmacies and other entities that market the affected substances or drug products made from the affected substances, consumers of drug products containing the affected drug substances, and payers that cover these drug products or alternative drug products.

#### II. Table of Abbreviations and Acronyms Commonly Used in This Document

5-HTP	5-hydroxytryptophan
BLA	Biologics License Application
CFR	Code of Federal Regulations
CSA	Controlled Substances Act
DPCP	Diphenylcyclopropenone
DQSA	Drug Quality and Security Act
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
IND	Investigational New Drug
NAG	N-acetyl-D-glucosamine
NAICS	North American Industry Classification System
NF	National Formulary
NPRM	Notice of Proposed Rulemaking
OTC	Over-The-Counter
PCAC	Pharmacy Compounding Advisory Committee
PHS Act	Public Health Service Act
PRESTO	Prevention of REStenosis with Tranilast and its Outcomes
RFA	Regulatory Flexibility Analysis
SADBE	Squaric acid dibutyl ester
SBA	Small Business Administration
UGT1A1	Uridine diphosphate glucuronosyltransferase 1A1
UK	United Kingdom
USP	United States Pharmacopeia

#### III. Background

##### A. Statutory and Regulatory Background

Section 503A of the FD&C Act (21 U.S.C. 353a) describes the conditions under which a compounded drug product may qualify for an exemption from certain sections of the FD&C Act. Those conditions include that a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician compounds the drug product using bulk drug substances that: (1) Comply with the standards of an applicable USP or NF monograph,<sup>1</sup> if a

<sup>1</sup> FDA has interpreted the statutory language “applicable USP or NF monographs” to refer to official USP or NF drug substance monographs. Therefore, a substance that is the subject of a dietary supplement monograph, but not a USP or NF drug substance monograph, does not satisfy the

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, that appear on the 503A Bulks List. See section 503A(b)(1)(A)(i) of the FD&C Act. This proposed rule proposes criteria for evaluating substances for inclusion on the 503A Bulks List and identifies six substances the Secretary proposes to place on the list. The Agency considered four other substances and is proposing not to include those substances on the 503A Bulks List. Additional substances are under evaluation, and new substances may be added to the list through subsequent rulemaking.

Section 503A adopts the definition of "bulk drug substance" in FDA's drug establishment registration and listing regulations, which was codified at § 207.3(a)(4) (21 CFR 207.3(a)(4)) at the time section 503A was enacted. See section 503A(b)(1)(A) of the FD&C Act. Under the definition, bulk drug substance means 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.

On August 31, 2016, FDA published a final rule in the **Federal Register** to update its registration and listing regulations in part 207 (21 CFR part 207), which included minor changes to the definition of bulk drug substance and moved the definition to § 207.3 (see 81 FR 60170). This definition becomes effective on November 29, 2016. As set forth in § 207.3, "bulk drug substance," as referenced in section 503A(b)(1)(A) of the FD&C Act, means the same as "active pharmaceutical ingredient" as defined in § 207.1(b). An "active pharmaceutical ingredient" is any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient does not include

condition regarding bulk drug substances in section 503A(b)(1)(A)(i)(I) of the Act. Such a substance may only be used as a bulk drug substance under section 503A of the FD&C Act if it is a component of an FDA-approved drug product or is on the 503A Bulks List.

intermediates used in the synthesis of the substance (§ 207.1).

Inactive ingredients used in compounded drug products, such as flavorings, dyes, or diluents, need not appear on the 503A Bulks List to be eligible for use in compounding drug products and will not be included on the list.

#### *B. Regulatory History of the 503A Bulks List*

Section 503A of the FD&C Act was enacted in 1997. 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 503A Bulks List. In 1998, FDA received nominations for 41 different drug substances. Ten of these drug substances were the subject of an applicable USP or NF monograph or were components of FDA-approved drugs and did not need to go on the list to be used in compounding. After evaluating the nominated drug substances and consulting with the PCAC as required by section 503A(c)(2), FDA published a proposed rule listing 20 drug substances for potential inclusion on the initial section 503A Bulks List (64 FR 996, January 7, 1999) (the 1999 Proposed 503A Bulks List). The proposed rule also described 10 nominated drug substances that were still under consideration for the 503A Bulks List. The PCAC reconvened in May 1999 to discuss bulk drug substances included in the proposed rule, in addition to other bulk drug substances (see 64 FR 19791, April 22, 1999).

In February 2001, the U.S. Court of Appeals for the Ninth Circuit held that certain provisions of section 503A of the FD&C Act were unconstitutional restrictions on commercial speech. (See *Western States Med. Ctr. v. Shalala*, 238 F.3d 1090 (9th Cir. 2001).) Furthermore, the Ninth Circuit held that the advertising and solicitation provisions could not be severed from the rest of section 503A and, as a result, found section 503A of the FD&C Act to be invalid in its entirety. In April 2002, the U.S. Supreme Court affirmed the Ninth Circuit's decision that the advertising and solicitation provisions were unconstitutional; it did not, however, rule on the severability of section 503A of the FD&C Act. (See *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002).) In 2008, the U.S. Court of Appeals for the Fifth Circuit held that compounded drugs are subject to regulation by FDA, and that the advertising and solicitation provisions are severable from the rest of section 503A of the FD&C Act. (See *Medical Ctr.*

*Pharm. v. Mukasey*, 536 F.3d 383 (5th Cir. 2008).)

Following a fungal meningitis outbreak in September 2012, FDA sought legislation to, among other things, resolve the split in the Circuits to clarify that section 503A of the FD&C Act was valid nationwide. On November 27, 2013, President Obama signed the Drug Quality and Security Act (Pub. L. 113-54) (DQSA), which contains important provisions relating to the oversight of human drug product compounding. Among other things, the DQSA removed from section 503A of the FD&C Act the provisions that had been held unconstitutional by the U.S. Supreme Court in 2002. By removing these provisions, the DQSA clarified that section 503A of the FD&C Act applies nationwide.

#### *C. Requests for Nominations*

Because of the amount of time that had passed between the publication of the 1999 proposed rule and the enactment of the DQSA, FDA felt it was necessary to begin again to develop the 503A Bulks List. In the **Federal Register** of December 4, 2013 (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 the 503A Bulks List.

Over 2,000 substances were nominated. However, many of those nominations were for a substance that is the subject of an applicable USP or NF monograph or a component of an FDA-approved drug, were not for substances used in compounding as active ingredients, or did not include sufficient information for FDA to evaluate whether the substances should be proposed for inclusion on the 503A Bulks List. To improve the efficiency of the process for developing the 503A Bulks List, FDA reopened the nomination process in July 2014 (79 FR 37747, July 2, 2014) and provided a more detailed description about what information should be included in a nomination to support the Agency's evaluation. FDA stated that bulk drug substances that were previously nominated would not be further considered unless they were renominated and the new nominations were adequately supported. Substances that were already eligible for use in compounding or that were not adequately supported would not be placed on the list.

In response to that solicitation, approximately 740 unique substances were nominated. Of those substances, approximately 315 are components of an FDA-approved drug product or the



subject of an applicable USP or NF monograph. Such substances can be used in compounding under section 503A(b)(1)(A)(i)(I) and (II) of the FD&C Act and, therefore, are not eligible for inclusion on the 503A Bulks List.

At least one of the nominated substances 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 § 207.3(4).

At least one of the nominated substances is a biological product subject to approval in a biologics license application (BLA) under section 351 of the Public Health Service (PHS) Act (42 U.S.C. 262) 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. 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 the drug products or components of the drug products have been found to be unsafe or not effective (section 503A(b)(1)(C) of the FD&C Act) (Withdrawn or Removed List). 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)). The CSA does not allow possession or distribution of Schedule I substances (see 21 U.S.C. 841(a)(1) and 829), except for research purposes (see 21 U.S.C. 823(f)), and Schedule I substances will not be considered for the 503A Bulks List. Those desiring to do research on a Schedule I substance may apply to do so under an investigational new drug (IND) application.

Of the substances that are not components of an approved drug product or the subject of an applicable USP or NF monograph, finished drug products, biological products subject to licensure in a BLA, and do not appear on the Withdrawn or Removed List or Schedule I of the CSA, about 350 substances were nominated with insufficient supporting evidence for FDA to evaluate them.

The remaining substances may be eligible for inclusion on the 503A Bulks List and were nominated with sufficient supporting information for FDA to evaluate them. Ten of those substances have been evaluated and are discussed in section V. The rest will be discussed in future notices of proposed rulemaking (NPRMs) after they have been evaluated. Once the Agency completes its review of the substances that were nominated for the 503A Bulks List with adequate supporting information under the July 2, 2014, request for nominations, FDA will consider additional substances nominated for inclusion on the list if they are eligible and adequate supporting information is submitted to permit FDA to meaningfully evaluate them (see section III).

With regard to the substances nominated with sufficient supporting information for FDA to evaluate them, including the 10 nominated substances discussed in this proposed rule, FDA generally does not intend to take regulatory action against a State-licensed pharmacy, Federal facility, or licensed physician for compounding a drug product using a bulk drug substance that is not the subject of an applicable USP or NF monograph or a component of an FDA-approved drug product, provided that the other conditions in section 503A and the FD&C Act are met, until the substance is addressed in a final rule. FDA is not applying this interim policy to a nominated substance however, if the Agency has identified the substance as posing a significant safety risk,<sup>2</sup> or if the substance was nominated without adequate support. For further information on this subject, see the guidance for industry entitled "Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act" (Ref. 1). As described in the guidance, the following categories of bulk drug substances are identified on FDA's Web site at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf>: (1) The substances nominated with sufficient supporting information that are under evaluation, (2) the substances nominated with sufficient supporting information but with which FDA has identified significant safety risks relating to the

use of these bulk drug substances in compounding, and (3) the substances nominated with insufficient supporting evidence for FDA to evaluate them.

#### IV. Legal Authority

As described in the Background section, section 503A of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist or licensed physician to be exempt from three sections of the FD&C Act (sections 501(a)(2)(B), 502(f)(1), and 505 (21 U.S.C. 351(a)(2)(B), 352(f)(1), and 355)). One of the conditions that must be satisfied for a compounded drug to qualify for the exemptions under section 503A of the FD&C Act is that a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician compounds the drug product using bulk drug substances that: (1) Comply with the standards of an applicable USP or 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, that appear on the 503A Bulks List. See section 503A(b)(1)(A)(i) of the FD&C Act. Section 503A(c)(1) of the FD&C Act also states that the Secretary shall issue regulations to implement section 503A, and that before issuing regulations to implement section 503A(b)(1)(A)(i)(III) pertaining to the 503A bulks list, among other sections, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. Section 503A(c)(2) of the FD&C Act requires the Secretary to issue the regulations in consultation with the USP, and to include in the regulation the criteria for such substances that shall include historical use, reports in peer reviewed journals, and any other criteria the Secretary identifies. Thus, section 503A of the FD&C Act, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act, serves as our principal legal authority for this proposed rule.

#### V. Description of the Proposed Rule

FDA is proposing to add § 216.23 to title 21 of the Code of Federal Regulations (CFR) to set forth criteria to evaluate bulk drug substances for inclusion on the 503A Bulks List. Additionally, after considering 10 bulk drug substances for the 503A Bulks List,

<sup>2</sup> This is not a determination regarding whether the substances will be added to the 503A Bulks list. FDA intends to make that determination after notice and comment rulemaking, as set forth in this proposal.

FDA proposes to codify the initial 503A Bulks List to include 6 of the bulk drug substances that were considered and to identify 4 substances that were considered and would not be placed on the list. The criteria and the bulk drug substances considered for inclusion on the list are described in the paragraphs that follow.

#### *A. Criteria for Evaluating Bulk Drug Substances for the 503A Bulks List*

Section 503A(c)(2) of the FD&C Act provides that the criteria for determining which substances should appear on the 503A Bulks List shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary of Health and Human Services may identify. Consistent with the July 2, 2014, **Federal Register** notice (79 FR 37747) soliciting nominations for this list, and as presented to and discussed with the PCAC in February 2015 (Ref. 2), FDA proposes that the following criteria be used to evaluate the nominated substances:

- The physical and chemical characterization of the substance;
- Any safety issues raised by the use of the substance in compounded drug products;
- The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and
- 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.

In evaluating candidates for the 503A Bulks List under these criteria, the Agency proposes to use a balancing test. Specifically, the Agency proposes to consider each criterion in the context of the others and balance them, on a substance-by-substance basis, to decide whether a particular substance is appropriate for inclusion on the 503A Bulks List.

Under the first criterion, the physical and chemical characterization of the substance, FDA would consider each substance's purity, identity, and quality. Based on attributes such as the substance's molecular structure, stability, melting point, appearance, likely impurities, and solubilities, FDA would determine whether the substance can be identified consistently based on its physical and chemical characteristics. If a substance cannot be well characterized chemically and physically, the Agency proposes that this criterion weigh against its inclusion

on the 503A Bulks List because there can be no assurance that its properties and toxicities, when used in compounding, would be the same as the properties and toxicities reported in the literature and considered by the Agency.

Under the second criterion, FDA would consider the safety issues raised by the use of each substance in pharmacy compounding. Based on FDA's review of the substances nominated to date, it is unlikely that candidates for the 503A Bulks List will have been thoroughly investigated in *in vitro* or in animal toxicology studies, or that there will be well-controlled clinical trials to substantiate their safe use in humans. Thus, in evaluating list candidates, the Agency is likely to have at its disposal very limited information, or in some cases no information, of the type and quality that is ordinarily required and evaluated as part of the drug approval process.

To evaluate the safety of the substances then, the Agency proposes to rely on available information, including reports in peer-reviewed medical literature, about each substance's pharmacology, acute toxicity, repeat dose toxicity, mutagenicity, developmental and reproductive toxicity, and carcinogenicity. The Agency would also rely on reports and abstracts in the literature about adverse reactions the substances have caused in humans. In applying the safety criterion, FDA also proposes to consider the availability of approved drug products or drug products that follow an OTC monograph (OTC monograph products). The existence of approved drug products or OTC monograph products would likely weigh against inclusion on the proposed list when the toxicity of a particular substance appears to be significant or where there are other safety concerns associated with the use of the substance in compounded drug products.

Under the third criterion, FDA proposes to consider the available evidence of the substance's effectiveness or lack of effectiveness for a particular use, including reports in peer-reviewed medical literature, if any such evidence exists. In the new drug approval process, applicants are required to demonstrate effectiveness under the substantial evidence standard described in section 505(d) of the FD&C Act. FDA recognizes that few, if any, of the candidates for the 503A Bulks List will have been studied in adequate and well-controlled investigations sufficient to satisfy this standard. Thus, in its balancing of the relevant criteria, the Agency would take into account

whatever relevant evidence concerning effectiveness is available.

For example, for substances that have been widely used for a long period of time, the literature may include anecdotal reports of effectiveness for a particular use or reports of one or more trials suggesting possible effectiveness. Conversely, the literature may contain anecdotal or clinical evidence that a particular bulk drug substance was not effective for a particular use (negative effectiveness data). When evaluating a bulk drug substance that is proposed for the treatment of a less serious illness, FDA would generally be more concerned about the safety of the substance than about its effectiveness. Thus, the availability of minimal effectiveness data, or the existence of mere anecdotal reports, would be less likely to preclude inclusion of the substance on the list. However, for a bulk drug substance that is proposed to treat a more serious or life-threatening disease, there may be more serious consequences associated with ineffective therapy, particularly when there are approved drug products or OTC monograph products. In those cases, the existence of approved drug products or OTC monograph products would likely weigh against inclusion on the proposed list, and the availability of minimal effectiveness data, or the presence of negative effectiveness data, would weigh more heavily against placement on the list in FDA's balancing of the relevant criteria.

Under the fourth criterion, the historical use of the substance in pharmacy compounding, FDA proposes to consider the length of time the substance has been used in pharmacy compounding, the medical conditions it has been used to treat, how widespread its use has been, including use in other countries, and any references in peer-reviewed medical literature. The Agency proposes that the longer a substance has been used in pharmacy compounding and the broader its use, the more this criterion will weigh in favor of inclusion of the substance on the list.

#### *B. Methodology for Developing the 503A Bulks List*

FDA reviewed the substances addressed in this proposed rule in the context of adequately supported nominated uses. In certain circumstances, FDA also reviewed substances in the context of unnominated or inadequately supported uses because, for example, such uses appear to be widespread, are intended to treat serious conditions, or pose serious risks to patients. The

information that FDA assessed to evaluate the substances addressed in this proposed rule under each of the proposed evaluation criteria was obtained from publicly available sources, including peer-reviewed medical literature. Some of this information was referenced in the nominations, and the remainder FDA gathered through independent searches of medical and pharmaceutical databases. FDA did not review raw data. The nature, quantity, and quality of the information FDA assessed varied considerably from substance to substance. In some cases, there were very little data. For other substances, reports in the literature were more plentiful and sometimes comprised hundreds or thousands of articles. In those cases, generally the Agency limited its review to a sample of the best literature sources available (e.g., review articles in widely known, peer-reviewed journals; meta-analyses; reports of randomized controlled trials).

FDA's evaluation of the nominated substances was, necessarily, far less rigorous and less comprehensive than the Agency's review of drugs as part of the new drug approval process. The new drug approval process is conducted based on extensive data compiled and submitted with new drug and abbreviated new drug applications, which are not available for the nominated substances. Additionally, the Agency's review during the drug approval process includes premarketing evaluation of a specific drug formulation, the sponsor's chemistry and manufacturing controls, and the establishments where approved drugs will be manufactured. In contrast, these bulk drug substances will be evaluated only for possible use in compounded drugs.

Therefore, the proposed inclusion of a drug substance on the 503A Bulks List should not, in any way, be equated with or considered an FDA approval, endorsement, or recommendation of any drug compounded using the substance. Nor should it be assumed that a drug compounded using the substances on the proposed list has been proven to be safe and effective under the standards required for Agency approval. Any person who represents that a compounded drug made with a bulk drug substance that appears on this list is FDA approved, or otherwise endorsed by FDA generally, or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act.

On February 23 and 24, 2015, and on June 17, 2015, FDA consulted with the PCAC created under section 503A(c)(1)

of the FD&C Act, about the criteria proposed to evaluate substances nominated for the list and about the 10 substances that are addressed in this proposed rule (Refs. 2–4). The Agency has considered all of the PCAC's recommendations in developing this proposed rule, and the Agency intends to continue to consult with the PCAC in evaluating future candidates for the 503A Bulks List. The first 10 substances evaluated are addressed in this proposed rule. Going forward, FDA intends to publish NPRMs proposing additional substances be placed on the list or not placed on the list on a rolling basis as evaluations are completed. Depending on the length of time it takes to complete a rulemaking, multiple rulemakings may be ongoing simultaneously.

Section 503A of the FD&C Act requires that FDA create the 503A Bulks List by regulation, in consultation with the USP. See section 503A(c)(2) of the FD&C Act. To this end, FDA has been periodically meeting with USP and discussing the 503A Bulks List (Refs. 5 and 6). After publication of this NPRM, the public will have an opportunity to comment on the proposed rule. After considering the comments on this proposed rule submitted to the docket, FDA will issue the 503A Bulks List as a final rule, which will be codified in the CFR. The final version of the rule may include all, none, or only some of the substances proposed here for inclusion on the 503A Bulks List, depending on the comments received, and will also identify those substances the Agency has determined should not be placed on the list. The Agency may amend the 503A Bulks List to add or delete substances after further notice and comment rulemaking.

Individuals and organizations may petition FDA to amend the list (to add or delete bulk drug substances) at any time after the final rule is published (see 21 CFR 10.30). Individuals and organizations may also nominate new substances for the 503A Bulks List or comment on nominated substances that have not yet been addressed in an NPRM via Docket No. FDA-2015-N-3534 while that docket is open.

#### *C. Substances Proposed for Inclusion on the 503A Bulks List*

Under section 503A(c)(2) of the FD&C Act, FDA is proposing that the following six bulk drug substances, which are neither the subject of a current applicable USP or NF monograph nor components of FDA-approved drugs, be included on the 503A Bulks List, and the drug products compounded with those substances may qualify for the

exemptions provided for in section 503A of the FD&C Act (i.e., from sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act). When a salt or ester of an active moiety is listed, only that particular salt or ester may be used. The base compound and other salts or esters of the same active moiety must be evaluated separately for eligibility for the 503A Bulks List. Additionally, when a bulk drug substance is included on the 503A Bulks List subject to certain restrictions (for example, for a particular route of administration (e.g., topical)), only dosage forms for that route of administration may be compounded with that bulk drug substance.

The following bulk drug substances are being proposed for the 503A Bulks List, to appear in § 216.23(a) of Title 21 of the CFR:

#### 1. Brilliant Blue G

Brilliant Blue G, also known as Coomassie Brilliant Blue G-250,<sup>3</sup> was evaluated for use as a dye used in staining for visualization during ophthalmic procedures. It is well characterized physically and chemically. There are potential mutagenic and carcinogenic concerns associated with Brilliant Blue G; however, those concerns are mitigated in clinical use because the dye is immediately washed out of the eye after administration, and tissue that is stained with the dye is removed as part of the surgical procedure. Published clinical trials provide some evidence for efficacy of Brilliant Blue G in staining the internal limiting membrane. Brilliant Blue has had relatively widespread use for staining the internal limiting membrane during retinal surgery for approximately 10 years. There is one product that is FDA-approved for staining the internal limiting membrane and the anterior capsule.

FDA proposed to the PCAC that Brilliant Blue G be included on the 503A Bulks List (Ref. 7), and at its meeting on June 17, 2015, the PCAC voted to include Brilliant Blue G on the list (Ref. 4). The proposed rule would place Brilliant Blue G on the 503A Bulks List.

#### 2. Cantharidin

Cantharidin, which is obtained from various species of blister beetle, was

<sup>3</sup> While there are other substances referred to by the name "Brilliant Blue," only Coomassie Brilliant Blue G-250 (CAS RN 6104-58-1, UNII M1ZR790SI) was evaluated, and the Agency is proposing only that substance for inclusion on the 503A Bulks List. The other substances referred to as "Brilliant Blue" would have to be nominated and separately evaluated for consideration for inclusion on the 503A Bulks List.

evaluated for topical use<sup>4</sup> in the treatment of warts and molluscum contagiosum. It is well characterized physically and chemically. Cantharidin is extremely toxic, due to its potential for severe irritation. However, clinical data accumulated since 1958 indicate that, with careful use under physician direction, toxicities observed with cantharidin, are no worse than and sometimes less severe than those seen with other destructive modalities in the treatment of molluscum contagiosum and warts. Evidence of some efficacy of cantharidin in the treatment of warts and molluscum contagiosum has been reported in the literature. It appears to have been widely used to treat molluscum contagiosum and warts since the 1950s. There are no approved prescription or OTC monograph products for molluscum contagiosum. For warts, there are no prescription drug products approved for use outside of the genital area. A variety of OTC monograph products containing salicylic acid are available.

FDA proposed to the PCAC that cantharidin be included on the 503A Bulks List for topical use only (Ref. 8). At the PCAC meeting on February 24, 2015, the PCAC voted to include cantharidin on the list (Ref. 3). Because the supported nominations and the Agency's review were limited to the topical use of this substance, the proposed rule would place cantharidin on the 503A Bulks List for topical use only.

### 3. Diphenylcyclopropenone (DPCP)

DPCP was evaluated for topical use in the treatment of alopecia areata and nongenital warts. It is well characterized physically and chemically but degrades readily by hydrolysis in an alcoholic base or exposure to light. Known safety concerns about the use of DPCP are limited to reported adverse effects primarily due to its action as a contact sensitizer to elicit contact dermatitis. Evidence of some efficacy of DPCP in the treatment of alopecia areata and recalcitrant nongenital warts has been reported in the literature. DPCP has been used to treat resistant non-genital warts and alopecia areata for over 30 years. The only FDA-approved drug product indicated for the treatment of alopecia areata is intralesional injection of corticosteroid suspensions. For warts, there are no approved prescription drug products outside of the genital area. A variety of OTC monograph products are available containing salicylic acid at

percentages varying from 17 to 40 percent.

FDA proposed to the PCAC that DPCP be included on the 503A Bulks List (Ref. 8). At its meeting on February 24, 2015, the PCAC voted to include DPCP on the list (Ref. 3). Because the supported nominations and the Agency's review were limited to the topical use of this substance, the proposed rule would place DPCP on the 503A Bulks List for topical use only.

### 4. N-acetyl-D-glucosamine (NAG)

NAG, also known as acetyl-D-glucosamine or N-acetyl glucosamine, was evaluated for topical use in the treatment of hyperpigmentation and other skin conditions. It is well characterized physically and chemically. Topical use of NAG has been associated with relatively minor and infrequent side effects. Studies have indicated that NAG may be effective for reducing diffuse and local facial hyperpigmentation. NAG has been used topically for the treatment of hyperpigmentation since the mid-2000s. There are FDA-approved drug products indicated for the treatment of hyperpigmentation and other skin conditions, which are not serious or life-threatening conditions.

FDA proposed to the PCAC that NAG be included on the 503A Bulks List for topical use only (Ref. 7). At the PCAC meeting on June 17, 2015, the PCAC voted to include NAG on the list (Ref. 4). Because the supported nominations and the Agency's review were limited to the topical use of this substance, the proposed rule would place NAG on the 503A Bulks List for topical use only.

### 5. Squaric Acid Dibutyl Ester (SADBE)

SADBE was evaluated for topical use in the treatment of alopecia areata and recalcitrant nongenital warts. It is well characterized physically and chemically but hydrolyzes readily in the presence of water. The adverse effects from use of SADBE are primarily related to its action as contact sensitizer. Evidence of some efficacy of SADBE in the treatment of recalcitrant nongenital warts and alopecia areata has been reported in the literature. SADBE has been used in the treatment of resistant nongenital warts and alopecia areata for 30 to 40 years. The only FDA-approved drug product indicated for the treatment of alopecia areata is intralesional injection of corticosteroid suspensions. For warts, there are no prescription drug products approved for use outside of the genital area. A variety of OTC monograph products are available containing salicylic acid at percentages varying from 17 to 40 percent.

FDA proposed to the PCAC that SADBE be included on the 503A Bulks List (Ref. 8). At its meeting on February 24, 2015, the PCAC voted to include SADBE on the list (Ref. 3). Because the supported nominations and the Agency's review were limited to the topical use of this substance, the proposed rule would place SADBE on the 503A Bulks List for topical use only.

### 6. Thymol Iodide

Thymol iodide was evaluated for use as a topical treatment for ulcerations and skin infections, as well as an intrapleural treatment for pleural effusions. It is well characterized physically and chemically. Reports indicate that it has been used without major complications. Literature reports some efficacy of thymol iodide for pleural effusions, which are serious and can be life-threatening conditions. Data regarding the effectiveness of thymol iodide in compounding for topical use on wounds or ulcers in various skin conditions is limited; however, these skin conditions generally are not serious or life-threatening. Thymol iodide has been in use for over 100 years. Regarding use as an antiseptic in surgery and use as an external application to wounds or ulcers in various skin conditions, approved and OTC monograph products are available. There are also FDA-approved products available to treat malignant pleural effusions.

FDA proposed to the PCAC that thymol iodide be included on the 503A Bulks List (Ref. 8). At its meeting on February 23, 2015, the PCAC voted to include thymol iodide on the list (Ref. 2). Because the supported nominations were limited to the topical use of this substance, and because pleural effusions are serious and potentially life-threatening conditions for which there are approved products available, the proposed rule would place thymol iodide on the 503A Bulks List for topical use only.

### D. Substances Considered and Not Proposed for Inclusion on the 503A Bulks List

FDA is proposing that four of the bulk drug substances that it has evaluated not be included on the 503A Bulks List. Bulk drug substances that are considered for the 503A Bulks list but not placed on the list cannot be used to compound drug products that would qualify for the exemptions in section 503A. If a prescribing practitioner nevertheless believes that a patient should be treated with a drug product compounded from such a bulk drug substance, it may be possible to obtain

<sup>4</sup> Except where specified otherwise, "topical use" means for application on the skin only and does not include oral, intravaginal, or ophthalmic use.

the drug under an IND. For information about the requirements for proceeding under an IND, visit FDA's Web site at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm>.

The four bulk drug substances that have been evaluated and that FDA is not proposing to place on the list, and the reasons for that proposal, are as follows:

### 1. Oxatriptan

Oxatriptan, also known as 5-hydroxytryptophan (5-HTP), was evaluated as a treatment for depression and insomnia. It is a hydroxylated form of a naturally occurring amino acid, tryptophan. Oxatriptan is well characterized physically and chemically. However, there are significant safety concerns related to its use. Based upon its mechanism of action, concomitant use of oxatriptan with antidepressant drugs could result in serotonin syndrome, a serious and life-threatening drug interaction. Additionally, medications used to treat depression have been linked to an increase in suicidal thinking and behavior. There are no data to suggest that oxatriptan would be free of similar risks, and compounded drugs do not include labeling that would adequately warn physicians and patients of such risks. Other potential adverse reactions include moderate gastrointestinal effects, which are common upon administration of oxatriptan.

Data supporting the efficacy of oxatriptan for depression are limited, and there is no evidence to support long-term efficacy of oxatriptan for the treatment of this chronic disease. Depression is a serious and potentially life-threatening condition, and there are multiple FDA-approved antidepressants that have been shown to be safe and effective in their approved forms that are appropriately labeled. Regarding the use of oxatriptan to treat insomnia, the clinical trials examining insomnia were too poorly designed and/or executed to assess efficacy. There are multiple FDA-approved drug products available for the treatment of insomnia. The length of time oxatriptan has been used in compounding is uncertain, although it has been discussed in scientific journals dating back approximately 40 years.

On balance, the physiochemical characteristics, the safety concerns, lack of evidence of effectiveness, and historical use of oxatriptan weigh against inclusion of this substance on the 503A Bulks List. In particular, the Agency's proposal regarding this substance is based on the seriousness of

the safety concerns related to the use of oxatriptan for depression in lieu of, or causing a delay in the use of an approved product, the lack of adequate warnings that would inform patients and prescribers of the risks associated with taking an oxatriptan product, and the availability of approved drug products for the treatment of depression, a potentially life-threatening condition. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 7). At its meeting on June 17, 2015, the PCAC voted not to include oxatriptan on the list (Ref. 4). The proposed rule would not place oxatriptan on the 503A Bulks List.

### 2. Piracetam

Piracetam was evaluated as a treatment for enhancing cognitive skills in treating a variety of cognitive disorders, including Alzheimer's disease. It has also been studied for treatment of coagulation disorders and vertigo. It is well characterized physically and chemically. Piracetam is approved in the United Kingdom (UK) as a prescription drug for the adjunctive treatment of cortical myoclonus. The labeling of the UK product identifies that the drug is renally excreted, that the dosage should be adjusted in the presence of renal disease, and that it is contraindicated in end-stage renal disease. Piracetam acts by multiple mechanisms to prolong bleeding time and is therefore not recommended for use by individuals with medical conditions that prolong bleeding time or that are taking concomitant anticoagulants or other medications that prolong bleeding (Ref. 9). Piracetam is not recommended for women who are pregnant, planning to become pregnant, or breastfeeding, because, according to the UK product's labeling, the drug has been shown to cross the placenta and be excreted in human milk. It is also recommended that individuals required to restrict their salt intake avoid piracetam (id.).

Piracetam was assessed for the treatment of mild cognitive impairment, a potential component of Alzheimer's disease, in a large, well-conducted, controlled clinical trial that failed to demonstrate efficacy. Studies of the efficacy of piracetam for other indications have been inconclusive, many of which were poorly designed or executed, or used flawed statistical methods to analyze the results. Piracetam's regulatory approval in the UK for the treatment of cortical myoclonus, which is not among the uses for which piracetam was nominated, was based on a single center,

retrospective review of 40 patients treated with piracetam (id.). FDA-approved products are available for treatment of the conditions, and conditions related to, those for which piracetam was nominated, for example, for Alzheimer's disease, which is frequently preceded by mild cognitive impairment. Regarding historical use, piracetam has been available for approximately 40 years.

On balance, the physiochemical characteristics, safety concerns, inconclusive evidence of effectiveness, and historical use of piracetam weigh against inclusion of this substance on the list. In particular, the Agency's proposal regarding this substance is based on the limited evidence of benefit associated with piracetam, the seriousness of the conditions for which piracetam was nominated to be used, and the availability of safe and effective FDA-approved medications for many of these uses. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 8). At its meeting on February 24, 2015, the PCAC voted not to include piracetam on the list (Ref. 3). The proposed rule would not place piracetam on the 503A Bulks List.

### 3. Silver Protein Mild

Silver protein mild, also known as mild silver protein, was evaluated for use as an anti-infective agent for ophthalmic use. Silver protein mild is not well characterized because the term "silver protein mild" is used to refer to a variety of different drug products. There are also safety concerns associated with the use of silver protein mild. It can cause argyria, which is a permanent ashen-gray discoloration of the skin, conjunctiva, and internal organs. Regarding effectiveness, silver protein mild has been found to be inferior to another treatment in clinical trials. A number of FDA-approved anti-infective agents for ophthalmic use are available and have been shown to be both safe and effective. While it has a long history of use, dating back to the early 1900s, the use of silver protein mild declined dramatically after the introduction of FDA-approved ocular anti-infectives.

On balance, the physiochemical characteristics, safety issues, questionable effectiveness, and historical use of silver protein mild weigh against inclusion of this substance on the 503A Bulks List. In particular, the Agency's proposal is based on the facts that silver protein mild is not well characterized, that in clinical trials it has been found to be inferior to another treatment and

numerically inferior to no treatment at all, and that chronic use may result in permanent discoloration of the conjunctiva, cornea, and/or lens. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 8). At its meeting on February 23, 2015, the PCAC voted not to include silver protein mild on the list (Ref. 2). The proposed rule would not place silver protein mild on the 503A Bulks List.

#### 4. Tranilast

Tranilast, an antiallergic agent, was evaluated for the treatment of allergic disorders, arthritis, dry eye syndrome, keloids, and hypertrophic scars. It is approved in South Korea and Japan for the treatment of asthma, keloids, and hypertrophic scarring, and as an ophthalmic solution for allergic conjunctivitis. It is well characterized physically and chemically. However, there are significant safety concerns associated with its systemic administration. In a well-controlled clinical trial with nearly 12,000 participants (the Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) Trial) (Ref. 10), tranilast was associated with significantly elevated liver enzymes (three times the upper limit of normal) in 11 percent of patients within 1 to 3 months of drug initiation, as well as anemia, renal failure, rash, and dysuria.<sup>5</sup> Liver toxicity is of particular concern because many of the conditions for which tranilast was nominated are chronic conditions. While there is some evidence that tranilast may be effective for allergic disorders, evidence of effectiveness for other uses is either not available or inconclusive. For allergy, arthritis, and ophthalmic indications, there are numerous FDA-approved and OTC monograph products. The length of time tranilast has been used in compounding is uncertain, although it has been discussed in scientific journals dating back approximately 40 years.

On balance, the physicochemical characteristics, safety concerns, lack of evidence of effectiveness, and historical use of tranilast weigh against inclusion of this substance on the 503A Bulks List, particularly given the seriousness of the safety concerns related to hepatotoxicity of tranilast and

contraindications in pregnant and breastfeeding women, the availability of approved products for most of the proposed uses, and the lack of evidence that tranilast is effective. FDA proposed to the PCAC that this substance not be included on the 503A Bulks List (Ref. 7). However, at its meeting on June 17, 2015, the PCAC voted to include tranilast on the list for topical use only (Ref. 4).

Subsequent to that meeting, FDA reviewed the topical use of tranilast further. It obtained the label of the Japanese tranilast product, RIZABEN, but found no information on the transdermal absorption or other pharmacokinetics of tranilast when applied topically to healthy or diseased human skin (Ref. 11). The labeling of the Japanese product identifies a number of safety concerns, including a contraindication in pregnant women, especially during the first trimester of pregnancy, and in those who might be pregnant, due to evidence of teratogenicity in animal studies (*id.*). The labeling also states that tranilast is detected in breast milk and should be avoided by breastfeeding women. In addition, the RIZABEN label lists a drug interaction with warfarin and identifies a number of serious adverse events, particularly those that are hematologic in nature (leukopenia, thrombocytopenia, anemia, hemolytic anemia), associated with the oral use of tranilast. Safety information regarding other routes of administration is limited.

FDA also noted evidence that some increases in some liver function tests (bilirubin) are explained by tranilast inhibition of uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) especially in patients with a genotype for Gilbert's Disease. Increases in liver transaminases observed with tranilast are not typically seen with inhibition of UGT1A1. It is speculated that tranilast impairs the metabolism of drugs that are metabolized by UGT1A1. If these drugs are associated with transaminase elevations, inhibiting the drug's metabolism may lead to liver transaminitis.

As was found in the Agency's initial review and presented to the PCAC, there is no persuasive information available regarding the safety or effectiveness of topical tranilast. FDA has identified only two reports in the literature describing the efficacy and safety of tranilast administered topically for the treatment of keloids and hypertrophic scars (Refs. 12 and 13). One of those studies was an open-label trial, and the other was a case series. Between the two studies, only five patients were exposed to topical tranilast.

As stated previously, FDA has serious concerns about the safety of tranilast when administered orally. The Agency has insufficient information about the systemic absorption of topical tranilast formulations to determine whether topical administration of the drug product would present the same safety concerns. Given the lack of information available about the safety and efficacy of topical tranilast, and safety concerns related to the oral use of this product, the proposed rule would not place tranilast on the 503A Bulks List.

#### VI. Proposed Effective Date

The Agency proposes that any final rule based on this proposal will become effective 30 days after the date of publication of the final rule in the **Federal Register**.

#### VII. Analysis of Environmental Impact

FDA has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### VIII. Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the proposed rule. We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we find little evidence that a substantial number of small entities would be affected by the proposed rule or that the economic impact on each affected small entity would be significant, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to

<sup>5</sup> During the PCAC meeting on June 17, 2015, the PRESTO trial was criticized by one of the tranilast nominators as having insufficiently accounted for the medical history of the subjects, among other things (see Ref. 4). To the contrary, the five-arm trial design appears to have been properly controlled for the patients' various medical conditions, and signals of liver toxicity were consistent across arms (see Ref. 10).

prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal

governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$146 million, using the most current (2015) Implicit

Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

TABLE 1—ECONOMIC DATA: COSTS AND BENEFITS STATEMENT

Category	Primary estimate	Low estimate	High estimate	Units year dollars	Discount rate (%)	Period covered (years)	Notes
<b>Benefits</b>							
Annualized Monetized \$ mil/year.	Not Estimated (N.E.)	.....	.....	.....	7	10	.....
Annualized Monetized \$ mil/year.	N.E	.....	.....	.....	3	10	.....
Annualized Quantified.	N.E	.....	.....	.....	7	.....	.....
Annualized Quantified.	N.E	.....	.....	.....	3	.....	.....
Qualitative	Not including four bulk drug substances from the 503A Bulks List would limit the use of potentially ineffective or unsafe unapproved drugs.	.....	.....	.....	.....	.....	.....
<b>Costs</b>							
Annualized Monetized \$ mil/year.	N.E	.....	.....	.....	7	10	.....
Annualized Monetized \$ mil/year.	N.E	.....	.....	.....	3	10	.....
Annualized Quantified.	\$118 to \$235 one-time per firm costs.	.....	.....	2014	7	.....	.....
Annualized Quantified.	\$118 to \$235 one-time per firm costs.	.....	.....	2014	3	.....	.....
Qualitative	.....	.....	.....	.....	.....	.....	.....
<b>Transfers</b>							
Federal Annualized Monetized \$ mil/year.	.....	.....	.....	.....	7	.....	.....
Federal Annualized Monetized \$ mil/year.	.....	.....	.....	.....	3	.....	.....
From/To	From: .....	.....	.....	To: .....	.....	.....	.....
Other Annualized \$ mil/year.	N.E	.....	.....	.....	7	.....	.....
Other Annualized Monetized \$ mil/year.	N.E	.....	.....	.....	3	.....	.....

TABLE 1—ECONOMIC DATA: COSTS AND BENEFITS STATEMENT—Continued

Category	Primary estimate	Low estimate	High estimate	Units year dollars	Discount rate (%)	Period covered (years)	Notes
From/To .....	From: Producers of bulk drug substances not proposed for inclusion and compounding pharmacies using these substances.	.....	.....	To: Producers of alternative treatments, consumers, using these treatments and payers for these treatments.	.....	.....	.....
<b>Effects</b>							
State, Local, and/or Tribal Government: No effect. Small Business: Unknown effect. Wages: No effect. Growth: No effect.							

The Economic Analysis of Impacts of the proposed rule performed in accordance with Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act is available at <http://www.regulations.gov> under the docket number for this proposed rule (Ref. 14) and at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>. We invite comments on this analysis.

**A. Summary of the Costs of the Rule**

We lack data on the scope of the current use of the affected bulk drug substances and the number of firms that would be affected by the rule. Without this information, we cannot quantify the total potential costs of the proposed rule. Potential costs include administrative costs, additional costs for consumers and payers if alternative therapies are more costly than the affected compounded drug products, and a potential loss of producer surplus if producers use additional resources in response to the rule. We estimate that each affected firm would spend 1 to 2 hours on administrative costs to read and understand the rule. The average hourly wage for a pharmacist in 2014 equals about \$57, or \$114 including 100 percent overhead. Thus, each affected firm would incur administrative costs that range from \$118 to \$235. We request comment on the potential costs and number of firms affected by the proposed rule.

**B. Summary of the Benefits of the Rule**

The benefits of the rule are unquantified. We include a qualitative discussion of potential benefits. For consumers who switch to more effective treatments, there would be benefits as consumers experience better health outcomes than they do currently.

**C. Summary of the Impact on Small Entities**

The Regulatory Flexibility Act requires a Regulatory Flexibility Analysis (RFA) unless the Agency can certify that the proposed rule would have no significant impact on a substantial number of small entities. The Small Business Administration (SBA) establishes thresholds for small entities by North American Industry Classification System (NAICS); the SBA considers small any entity below these thresholds. Firms affected by the proposed rule would fall into three major industries, NAICS 325412 Pharmaceutical Preparation Manufacturing, NAICS 424210 Drugs and Druggists' Sundries Merchant Wholesalers, and NAICS 446110 Pharmacies and Drug Stores. The thresholds for these industries are 750 employees for NAICS 325412, 100 employees for NAICS 424210, and annual sales of \$27.5 million for NAICS 446110.

We lack data on the number or size of manufacturers, wholesalers, and compounding pharmacies that would be affected by the proposed rule. Moreover, we find little evidence of widespread

use of four bulk drug substances not proposed for inclusion on the 503A Bulks List. This suggests that the impact of the rule would likely not be significant on small entities. Because we find little evidence that a substantial number of small entities would be affected by the proposed rule or that the economic impact on each affected small entity would be significant, we believe that the proposed rule would not have a significant economic impact on a substantial number of small entities, but the impacts are uncertain. We request detailed comments and data on the number of small entities that would be affected by the proposed rule, as well as data on the economic impact of the proposed rule on these small entities.

**IX. Paperwork Reduction Act of 1995**

The submission of comments on this proposed rule would be submissions in response to a Federal Register notice, in the form of comments, which are excluded from the definition of "information" under 5 CFR 1320.3(h)(4) of Office of Management and Budget regulations on the Paperwork Reduction Act (i.e., facts or opinions submitted in response to general solicitations of comments from the public, published in the Federal Register or other publications, regardless of the form or format thereof, provided that no person is required to supply specific information pertaining to the commenter, other than that necessary for self-identification, as a condition of the Agency's full consideration of the



comment). The proposed rule contains no other collection of information.

## X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the proposed rule, if finalized, would not contain policies that would have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

## XI. References

The following references are on display in the Division of Dockets Management (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <http://www.regulations.gov>. FDA has verified the Web site addresses, as of the date this document publishes in the **Federal Register**, but Web sites are subject to change over time.

1. FDA, "Guidance for Industry: Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act," (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf>), 2016.
2. FDA, Transcript of the February 23, 2015, Meeting of the Pharmacy Compounding Advisory Committee (Afternoon Session), 2015, (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM444500.pdf>).
3. FDA, Transcript of the February 24, 2015, Meeting of the Pharmacy Compounding Advisory Committee, 2015, (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM444501.pdf>).
4. Transcript of the June 17, 2015, Meeting of the Pharmacy Compounding Advisory Committee (Afternoon Session), 2015, (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM458513.pdf>).
5. Memorandum to File on FDA Consultations with USP, September 26, 2016.
6. Letter from USP to FDA, October 7, 2016.
7. FDA Briefing Document for the June 17–18, 2015, Meeting of the Pharmacy

Compounding Advisory Committee, 2015, (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf>).

8. FDA Briefing Document for the February 23–24, 2015, Meeting of the Pharmacy Compounding Advisory Committee, 2015, (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM433804.pdf>).

9. Obeso, J. A., et al., "Piracetam in the Treatment of Different Types of Myoclonus," *Clinical Neuropharmacology*, 11(6): 529–536, 1988.

10. Holmes, D.R., Jr., M. Savage, J.M. LaBlanche, et al., "Results of Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) Trial," *Circulation*, 106(10): 1243–1250, 2002.

11. FDA Supplemental Review of Topical Tranilast, April 25, 2016.

12. Shigeki, S., T. Murakami, N. Yata, and Y. Ikuta, "Treatment of Keloid and Hypertrophic Scars by Iontophoretic Transdermal Delivery of Tranilast," *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery*, 31(2): 151–159, 1997.

13. Banov, D., F. Banov, and A.S. Bassani, "Case Series: The Effectiveness of Fatty Acids From Pracaxi Oil in a Topical Silicone Base for Scar and Wound Therapy," *Dermatology and Therapy*, 4(2): 259–269, 2014.

14. Economic Analysis of Impacts.

### List of Subjects in 21 CFR Part 216

Drugs, Prescription drugs.  
Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, the Food and Drug Administration proposes to amend 21 CFR part 216 as follows:

### PART 216—HUMAN DRUG COMPOUNDING

■ 1. The authority citation for part 216 is revised to read as follows:

**Authority:** 21 U.S.C. 351, 352, 353a, 353b, 355, and 371.

■ 2. The heading for part 216 is revised to read as set forth above.

■ 3. Section 216.23 is added to read as follows:

**§ 216.23 Bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act.**

(a) The following bulk drug substances can be used in compounding under section 503A(b)(1)(A)(i)(III) of the Federal Food, Drug, and Cosmetic Act.  
Brilliant Blue G, also known as Coomassie Brilliant Blue G–250.  
Cantharidin (for topical use only).  
Diphenylcyclopropenone (for topical use only).

N-acetyl-D-glucosamine (for topical use only).

Squaric acid dibutyl ester (for topical use only).

Thymol iodide (for topical use only).

(b) After balancing the criteria set forth in paragraph (c) of this section, FDA has determined that the following bulk drug substances will not be included on the list of substances that can be used in compounding set forth in paragraph (a) of this section:

Oxtripitan.

Piracetam.

Silver Protein Mild.

Tranilast.

(c) FDA will use the following criteria in evaluating substances considered for inclusion on the list set forth in paragraph (a) of this section:

(1) The physical and chemical characterization of the substance;

(2) Any safety issues raised by the use of the substance in compounded drug products;

(3) The available evidence of the effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and

(4) 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.

(d) Based on evidence currently available, there are inadequate data to demonstrate the safety or efficacy of any drug product compounded using any of the drug substances listed in paragraph (a) of this section, or to establish general recognition of the safety or effectiveness of any such drug product. Any person who represents that a compounded drug made with a bulk drug substance that appears on this list is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the Federal Food, Drug, and Cosmetic Act.

Dated: December 9, 2016.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2016–30109 Filed 12–15–16; 8:45 am]

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