

Summary of Proceedings

September 20-21, 2016, Inter-governmental Working Meeting on Compounding

On September 20-21, 2016, the U.S. Food and Drug Administration (FDA) convened its fifth inter-governmental working meeting of state government officials. Attendees included officials from state Boards of Pharmacy and State Health Departments, representatives from the National Association of Boards of Pharmacy (NABP) and the Federation of State Medical Boards (FSMB), and representatives from the Centers for Disease Control and Prevention (CDC).

The purpose of this meeting was to discuss oversight of compounding, including implementation of the Compounding Quality Act (CQA) (Title I of the Drug Quality and Security Act (DQSA)), and to identify opportunities to better protect the public health by strengthening oversight of compounders through improved federal-state collaboration.

FDA previously held inter-governmental working meetings on compounding with state officials and their designated representatives in December 2012, March 2014, March 2015, and November 2015. FDA initiated these meetings after the 2012 fungal meningitis outbreak associated with contaminated compounded drugs, which led to many deaths and serious illnesses across the country.

Compounding Regulatory Policy Update

FDA began the September 2016 meeting by providing an update on recent policy documents issued since the November 2015 inter-governmental working meeting including:

- Draft Guidance: “Insanitary Conditions at Compounding Facilities”
- Draft Guidance: “Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act”
- Draft Guidance: “Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act”
- Draft Guidance: “Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act” (this guidance has since been finalized)
- Draft Guidance: “Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act”
- Draft Guidance: “Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act”
- Final Guidance: “Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act”
- Final Guidance: “Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act”

FDA also briefly addressed the agency’s continuing work on other policy documents that were published in draft, including: “Current Good Manufacturing Practice-Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act,” “Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities

Under Section 503B of the Federal Food, Drug, and Cosmetic Act,” which has since been finalized, “Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities,” which has since been finalized, “Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application,” which has since been reissued as a revised draft, and the 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.” Finally, FDA described efforts to develop regulations regarding the list of drugs that cannot be compounded under the exemptions provided by sections 503A or 503B because they have been withdrawn or removed from the market for reasons of safety or effectiveness, and the list of bulk drug substances that can be used in compounding in accordance with section 503A.

FDA Inspections and Enforcement Update

FDA provided an update on regulatory oversight, including enforcement activities. Between October 1, 2015 and August 23, 2016, FDA conducted 119 inspections of compounding facilities, including 97 inspections of facilities seeking to compound drugs under section 503A, and 22 inspections of outsourcing facilities. There were 48 recall events involving at least 1079 compounded products from October 1, 2015 to August 30, 2016. Over the same time period, FDA issued 55 warning letters and 9 letters referring inspectional findings to the state regulatory agency. Finally, FDA worked with the Department of Justice on civil and criminal enforcement actions. Two compounders entered into civil consent decrees of permanent injunction. In addition, the former president and pharmacist-in-charge of a compounding pharmacy pled guilty and received prison sentences in June of 2016, for their roles in the distribution of adulterated compounded drugs.

FDA also described changes it had implemented in the agency’s inspectional procedures. Beginning in August 2016, FDA investigators make a preliminary assessment of whether a pharmacy (that is not registered as an outsourcing facility) is compounding human drugs in compliance with section 503A before closing the inspection. This assessment informs whether the investigators include observations related to current good manufacturing practice (CGMP) requirements on any Form FDA-483 that is issued. For additional information, see <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM510684.pdf>.

FDA described two of its goals for the upcoming year. First, FDA is working to increase the frequency of outsourcing facility inspections. FDA is also working to obtain additional information to inform its selection of state-licensed pharmacies for risk-based surveillance inspections, to ensure that the agency is using its resources in a way that has the greatest possible public health impact.

State officials indicated that it would be helpful to them to have more information following FDA inspections, particularly of outsourcing facilities. FDA indicated that it is working to more quickly provide public information about the outcome of inspections. FDA also noted that the agency can provide certain non-public information to states when an information-sharing agreement is in place.

FDA/State Collaboration and Communication

State representatives joined FDA for a panel discussion about FDA-state information-sharing. FDA began by reviewing the ways in which FDA may share non-public information with states, including when states enter into agreements with FDA pursuant to 21 CFR 20.88 (20.88 agreements), and when state officials become “commissioned officials” with FDA. FDA established long-term (5-year) 20.88 agreements to cover information-sharing regarding both drug compounding, which ten states have signed, and, in 2016, drug supply chain security. FDA also created a combined agreement to cover both topics. 20.88 agreements require that the state agency certify they are able to protect non-public information received from FDA from public disclosure. Some state officials expressed concern regarding states’ ability to sign 20.88 agreements due to the existence of state “sunshine” laws that govern public access to governmental records. However, FDA noted that, notwithstanding sunshine laws, most states have at least one state agency that has entered into a 20.88 agreement with FDA on various subject matters.

FDA and state officials also discussed priorities with respect to information sharing. FDA indicated that it would like to receive information suggesting that a compounder might be producing drugs in violation of Federal law including, for example, when a compounder is producing contaminated drug products, and information about adverse events. States also noted the importance of receiving information about reports of contamination, product recall information that includes the address of the recalling pharmacy (as pharmacies may operate multiple locations under one name), and information on out of state compounders that may be shipping into their state.

Oversight of Pharmacies: Prescription Requirement

FDA and state panelists shared policy updates and perspectives on prescription requirements for drug compounding, including policies on compounding office stock. FDA described its April 2016, draft guidance on the prescription requirement in section 503A of the FD&C Act, which explains that in order to qualify for the exemptions under section 503A, compounding must be based on the receipt of a valid prescription for an identified individual patient or in limited quantities before the receipt of a valid prescription for an identified individual patient. The draft guidance explains that unlike compounders under section 503A, outsourcing facilities may distribute compounded drugs either with or without first receiving patient-specific prescriptions. FDA received a diverse set of comments on the draft guidance. Some stressed that the prescription requirement is important to address public health concerns and establish clear lines of accountability. Others described FDA’s policy as contrary to Congressional intent, and raised concerns about conflicts with state laws and access to compounded drugs. (FDA issued the final guidance in December 2016).

State officials shared updates from their states regarding their laws and policies related to compounding for office stock. For example, one state official described new rules that clarify that only outsourcing facilities can provide non-patient-specific compounded human drugs. Another state official noted that although the state provides an exemption to their prescription

requirement for compounding certain drugs for ophthalmologist office use, the state's attorney general advised that any such exemption would not affect federal law requiring a valid prescription order for an identified patient.

During subsequent breakout sessions on this issue, many states described current or planned alignment with FDA's policies and perspectives regarding prescription requirements, although it has been difficult and time consuming for some states to implement change. Many states indicated that a final FDA guidance clarifying the agency's position would be helpful. Regarding enforcement, states shared that state inspectors look for valid prescriptions during inspections, and they are seeing less office stock compounding in pharmacies not registered as outsourcing facilities overall. States also noted that, where they are in place, enforcement of office stock volume limitations (e.g., percentage limits) is very challenging.

Although many state officials indicated that they believe that the prescription requirement serves an important public health purpose, some are concerned about access to compounded drugs for office stock. For example, some are concerned about whether outsourcing facilities will compound low volume orders of drugs, or drugs with short beyond-use dates, and outsourcing facilities' ability to fill orders rapidly. However, participants also discussed a potentially problematic cycle. Outsourcing facilities are likely to make a product if there is a market for it. But a market for needed office stock products may be obfuscated if pharmacies not registered as outsourcing facilities continue to compound drug products for office stock, despite the fact that these drugs would not meet the conditions of section 503A. Several states agreed that having a way to publicly share information about the products made by outsourcing facilities would help identify suppliers.

Many other states indicated that they do not believe enforcement of the prescription requirement would lead to access concerns. They noted that their state laws and/or policies require that compounding be based on patient-specific prescriptions, and that it appears that outsourcing facilities have been able to meet the need for non-patient specific compounding.

Oversight of Pharmacies: Quality Standards & Insanitary Conditions

FDA and state panelists discussed quality standards applicable to compounders and FDA's draft guidance concerning insanitary conditions. To help facilities and states understand what FDA considers to be insanitary conditions, the draft guidance describes a non-exhaustive list of examples. The draft guidance also describes actions that facilities should take to address insanitary conditions. FDA reminded participants that neither sections 503A or 503B of the Act provide exemptions from the insanitary conditions provision in federal law—drugs prepared, packed, or held under insanitary conditions whereby they may become contaminated with filth or rendered injurious to health are adulterated under the Act (section 501(a)(2)(A)) regardless of whether the drugs qualify for the exemptions in section 503A or 503B.

FDA described a number of examples of insanitary conditions recently observed during compounding facility inspections: visible microbial contamination; insects; filth under the air flow hood (equipment designed to reduce the risk of airborne contamination during the preparation of sterile products) including multiple pieces of medical supply waste and dust build

up; employees working in cleanrooms with exposed skin; a ceiling above the doorway to the cleanroom with exposed insulation; failure to routinely use an effective sporicidal agent; and non-sterile wipes used to clean surfaces used for “aseptic” (free from contamination) manipulations.

Following FDA’s presentation, state officials described quality standards that they enforce in their states. Discussion included: how state quality standards relate to United States Pharmacopeia (USP) Chapter 797, the interplay between inspections and licensure, and accreditation. State approaches differ. While some include explicit requirements for compliance with USP Chapter 797, others do not. According to one state official, a general provision in its rules for health professionals includes “failing to adhere to applicable practice guidelines, as determined by the commissioner, for the compounding of sterile drugs and products” in a list of activities that are considered unprofessional conduct.

Oversight of Outsourcing Facilities

The FDA-state panel on outsourcing facilities described a range of policy issues related to oversight, which the group subsequently explored in greater depth in a series of breakout sessions. FDA began by describing several issues affecting the outsourcing facility sector that it is aware of through stakeholder listening sessions, comments on draft guidance documents, and other communications. These include the challenge of differing state licensure requirements for outsourcing facilities; ensuring CGMP compliance; and understanding distribution practices in the sector and appropriately enforcing distribution-related statutory provisions.

FDA recognizes that both its own regulation and state regulation have a significant impact on outsourcing facilities and believes there are opportunities to advance a more harmonized regulatory approach that will enhance oversight clarity and support compliance. To that end, FDA shared a set of preliminary recommendations for states regarding oversight approaches and requested feedback. See <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM520830.pdf>.

An NABP official provided perspectives on these oversight issues and also recommended that states create a separate licensure category for outsourcing facilities. NABP said that more frequent inspections of outsourcing facilities by the FDA would help states, many of which require an inspection for state licensure. In addition, states would benefit from more communication from FDA regarding observations, actions, and assessments of outsourcing facilities, such as Forms FDA 483, warning letters, and FDA assessments of firm responses. States described recent and pending legislation regarding outsourcing facilities and CGMP requirements and licensure. State panelists described differing approaches to outsourcing facility oversight. For example, in one state, outsourcing facilities must obtain a state pharmacy permit if they wish to fill patient-specific prescriptions. By contrast, another state described pending legislation that would prevent an outsourcing facility from being concurrently licensed with the board as a compounding pharmacy.

Following the panel, participants divided into several breakout session groups to further discuss issues related to outsourcing facility oversight.

Regarding state licensure, a small number of states reported they had established a specific outsourcing facility licensure or registration category, while other states continue to use existing categories such as manufacturer, wholesale distributor, and pharmacy. While there was agreement that an outsourcing-facility-specific state licensure category has benefits, states shared that establishing new licensure categories through legislation is very difficult. Establishing sub categories under existing statutory categories may be a viable workaround that can be done through regulation. Some participants suggested that FDA could help educate state legislators in support of new licensure category efforts.

States agreed that more frequent FDA inspections of outsourcing facilities and quicker actions taken as a result of the inspections would be helpful. Some states noted they did not have the technical expertise or resources to conduct full CGMP inspections themselves. If and when the states decide they do need to conduct inspections, most states saw benefit to receiving training from FDA on insanitary conditions and key elements of CGMP requirements.

Finally, FDA and state officials also discussed the role of a licensed pharmacist in an outsourcing facility. Most states felt that a pharmacist should be onsite all the time. States thought it would be helpful for FDA to issue guidance on “direct supervision.”

Physician Compounding

The meeting’s final panel focused on compounding by physicians, and included representatives from the FDA, the CDC, the FSMB, and the Ohio and Mississippi Boards of Pharmacy.

FDA noted that section 503A of the FD&C Act applies to physician compounding, and that even if the conditions of 503A are met, drugs compounded by physicians remain subject to other FD&C Act provisions (e.g., the prohibition on insanitary conditions). FDA described potential issues related to physician compounding, including concerns about the ability to ensure physician adherence to and awareness of quality standards through sufficient oversight. Coordinating oversight across multiple federal and state agencies (such as state boards of pharmacy, state boards of medicine, state and local departments of health) presents challenges. Further, FDA generally does not inspect clinics or physicians’ offices and is often not aware of problems unless a complaint is submitted.

CDC explained that outpatient settings are increasingly being identified as sources of outbreaks linked to breaches in infection control and sterile compounding practices. These breaches include failure to follow aseptic practices (including proper hand hygiene), insanitary medication preparation areas, and non-trained/non-qualified personnel performing sterile compounding. CDC also noted that outpatient settings pose unique challenges because there is no clearly established oversight system for monitoring adherence to infection control and sterile compounding standards, and sterile compounding is conducted in the absence of pharmacy controls. There are different state and federal requirements for monitoring and reporting healthcare-associated infections and adverse events. Outpatient settings may warrant increased

attention from state health agencies to ensure that basic standards of infection control and sterile compounding are understood and observed.

An official from FSMB provided perspectives from state regulators of medical practice. She clarified that, unlike state boards of pharmacy, medical boards only have jurisdiction over individual practitioners, not the practice setting. Further, no medical board issues special licenses for physicians that engage in drug compounding. FSMB described a number of challenges to the consistent oversight and regulation of physician compounding, including confusion among its members over whether diluting or reconstituting a drug is considered compounding, limited evidence on the safety of compounding in the office setting, and concerns about access to care if physicians must meet more stringent quality standards, such as those described in proposed revisions to USP chapter 797. FSMB has produced guidance concerning FDA and USP standards, provides educational resources to physicians, and can serve as a communication conduit among stakeholders. FSMB desires a more formalized communication strategy between federal and state agencies to improve collaboration on the topic of physician compounding.

State officials then shared perspectives on physician compounding. Although one state representative explained that his state licenses all locations that hold prescription drugs, including most physician practices, most state boards of pharmacy do not directly oversee compounding that occurs in physician offices.

September 20-21, 2016 Inter-governmental Working Meeting Action Items:

1. FDA will explore developing training for state regulators on insanitary conditions and key elements of current good manufacturing practice requirements.
2. FDA will explore how to provide more information to states that they can use to assess the compliance status of compounders that FDA has inspected, including the significance of particular inspectional observations and violations frequently identified in regulatory actions.
3. FDA will provide information regarding its process for initiating inspections of newly registered outsourcing facilities and evaluate what information it can share with states with respect to such facilities pending an inspection.
4. FDA will explore how states can ascertain, during or after their inspections, whether a drug product compounded by a facility that they inspected was on FDA's drug shortage list at the time of compounding.
5. FDA will consider whether and how it can provide technical assistance when requested by states with respect to potential changes in state laws, regulations or policies related to compounding.
6. FDA will work with NABP, the Federation of State Medical Boards, and the Centers for Disease Control and Prevention to explore educational outreach efforts on compounding drugs regarding, for example, quality standards.