Summary of Proceedings

November 16-17, 2015, Inter-governmental Working Meeting on Compounding

On November 16-17, 2015, the U.S. Food and Drug Administration (FDA) convened its fourth inter-governmental working meeting of state government officials (including the District of Columbia and Puerto Rico). Attendees included officials from the state Boards of Pharmacy and Health Departments and organizations that represent state officials, including the National Association of Boards of Pharmacy (NABP) and the Association of State and Territorial Health Officials (ASTHO).

The purpose of this meeting was to discuss oversight of compounding, including implementation of the Compounding Quality Act (CQA) (Title 1 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. A separate session on implementation of the Drug Supply Chain Security Act (Title 2 of the DQSA) was held in the afternoon of November 17. That session is summarized separately.

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

The meeting included discussions of the following topics:

Compounding Regulatory Policy Update

FDA began the November 2015 meeting by providing an update on recent policy developments in the area, as well as other CQA implementation efforts. Since enactment of the CQA, FDA published six final guidance documents, six draft guidance documents, a draft standard memorandum of understanding under section 503A, and a proposed rule that FDA is working to finalize that adds twenty-five new substances to the list of drugs that have been withdrawn or removed from the market for reasons of safety or effectiveness.

FDA described in detail the two draft guidance documents that the agency issued in October 2015:

- "Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act," which sets out the agency's proposed interim policy regarding compounding with bulk drug substances while the agency considers the bulk substances nominated for the 503A bulk drug substances list (see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf); and

- "Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act," which sets out the agency's proposed interim policy regarding compounding with a bulk drug substance while FDA considers the bulk

substances nominated for the 503B bulk drug substances list (see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469122.pdf).

FDA then briefly described the agency's current efforts to finalize several guidances previously published in draft, after considering the public comments. These guidances include: Current Good Manufacturing Practice-Interim Guidance for Human Drug Compounding Outsourcing Facilities Under the Federal Food, Drug, and Cosmetic Act, which is an interim guidance until Current Good Manufacturing Practice rules are adopted; Electronic Product Reporting for Human Drug Compounding Outsourcing Facilities; Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities; and Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application. FDA also provided an update on the Pharmacy Compounding Advisory Committee (PCAC), which held three meetings this year. At those meetings the PCAC reviewed 29 drugs recommended for the withdrawn and removed list and 2 recommended modifications to the current list, 19 substances nominated for inclusion on the section 503A bulks list, and the proposed criteria for the difficult to compound list.

Draft Standard Memorandum of Understanding (MOU) between FDA and the States

FDA provided an overview of the written comments received on the draft standard 503A Memorandum of Understanding (MOU), issued for public comment in February 2015. State officials were given the opportunity to present their views on the draft MOU, including aspects of the draft MOU that they felt needed clarification or presented challenges. Some state officials suggested that while raising the volume percentage that would be deemed "inordinate amounts" may help alleviate access barriers, it may also increase risk to the public health. Others questioned whether exemptions would apply to specialty pharmacies that compound the majority of their products and ship large amounts over state lines, suggesting the need for flexibility in certain situations, which may also include shared services agreements and health systems.
States shared with FDA the difficulties they would face in determining the volume of compounded human drug products distributed out of their state to calculate whether a firm was distributing inordinate amounts where either records do not exist, the relevant information contained in the records is not easily retrievable, or the reported units are vague or ambiguous. States also discussed the need to define "units" and to clarify whether the denominator will include animal drugs and/or OTC products.

States also questioned the feasibility of assessing complaints and reporting to FDA within 72 hours. They also discussed issues associated with applying the MOU to physicians, dentists, and physician assistants who compound, because they are not overseen by the state Boards of Pharmacy. Further, some questioned whether their states could commit to enforcing the terms of the MOU, such as compelling a pharmacy to perform a root cause analysis within their current legal framework. Some state officials expressed concerns that the terms of the MOU are one-sided because it imposes requirements on the states but does not specify FDA's obligations under the MOU.

These are only a sample of the issues raised at the meeting. FDA will consider all of the issues raised as well as the many comments submitted to the docket and will consult with NABP in developing the final MOU.

Information Sharing and Disclosure

FDA officials reviewed the framework under which they are able to share information with the states. For example, although the Freedom of Information Act (FOIA) provides for public disclosure of many FDA records, some information is generally exempt from disclosure (e.g., confidential commercial, trade secret, pre-decisional information, and law enforcement records), and other laws, such as the Privacy Act, may also restrict what FDA can disclose. Certain information that cannot be publicly disclosed can be shared with state officials who are either commissioned by FDA or have signed a "20.88" confidentiality agreement.

FDA then reviewed the response to the disclosure related action items from the March 2015 intergovernmental working meeting. FDA stated that the drug compounding 20.88 agreement can be signed by multiple state agencies such as a state Board of Pharmacy and the state Attorney General's office. If a form FDA-483 or a warning letter is issued, FDA will send a redacted copy to all 50 states, although commissioned state officials and states operating under a 20.88 agreement may request a non-redacted version in accordance with the agreement. Upon request from a commissioned state official or those operating under a 20.88 agreement, typically, FDA may be able to share information related to an inspection within 15 days of when a form FDA-483 is issued. FDA stated that it will work with states that choose not to sign the 20.88 agreement to determine whether state laws are the impediment, and if so, whether the agreement can be modified to allow for some types of information to be disclosed consistent with both federal and state law.

State officials were given the opportunity to describe their experiences with regard to information sharing and the disclosure of information related to compounding. Some states found having commissioned officials to be sufficient. Other states intend to enter into a 20.88 agreement with FDA, but some are concerned that state sunshine laws may prevent them from entering into these agreements. FDA will determine whether a modified Information Sharing Agreement could be developed for use in a state with sunshine laws, and what kinds of information could be shared under such an agreement. FDA and the states committed to continue to work together to improve and streamline information sharing to the extent possible.

A Comparison of U.S. Pharmacopeial Convention General Chapter <797> to the Current Good Manufacturing Practice Regulations Enforced by FDA

FDA delivered a presentation on the differences in sterile drug production practices between *USP* Chapter <797> and FDA's Current Good Manufacturing Practice (CGMP) regulations. In summary, CGMP standards require more frequent monitoring of air quality and pressure, surfaces, equipment, and personnel. Further, under CGMP requirements, certificates of analysis must be confirmed rather than just reviewed, gowning must cover a greater percentage of the compounder's body, and there are stricter sterility measures, laboratory controls, and beyond use dating requirements.

State officials asked if CGMP requirements would be modified for outsourcing facilities. FDA shared that it is working on a final guidance on interim CGMP for outsourcing facilities and will notify the states once it is published. Some states suggested the need for training at outsourcing facilities that operate under CGMP requirements. State officials also indicated the need for state

investigator training on CGMP requirements and requested FDA support.

Inspections of Sterile Compounding Facilities and Enforcement

FDA and state officials discussed inspections of sterile drug compounders, including outsourcing facilities, and the different types of regulatory actions that result from these inspections. Between October 1, 2012, and October 19, 2015, FDA conducted over 250 inspections of compounders. Of the 250 inspections, 60 were of registered outsourcing facilities. The most frequently cited observations were inadequate procedures for sterile drug products and deficiencies in environmental monitoring and sterility testing. Since October 2012, regulatory actions involving compounded drugs included over 100 voluntary recalls, 60 warning letters, 20 state referral letters, and three permanent injunctions.

State officials were given the opportunity to describe their inspection and enforcement efforts. The resources and training available for state inspections vary by state. Some states report difficulty regulating out-of-state pharmacies, and determining the extent of their sterile compounding operations. Some states reported using more comprehensive license applications to better understand the operations of the licensee. Other states require inspections of nonresident pharmacies engaged in sterile compounding before licensure. Some states called for a uniform inspection form. NABP reported that it is in the process of finalizing a standard form.

The standards for inspections of 503A and 503B facilities were discussed. No compounder can make drugs under insanitary conditions, regardless of whether it is a state licensed pharmacy operating under section 503A or registered as an outsourcing facility under section 503B. FDA suggested it would be important for FDA and the states to have a common understanding of what constitutes insanitary conditions. FDA explained that the Agency does not issue warning letters citing CGMP violations to pharmacies unless there is evidence that the pharmacy does not meet the conditions of section 503A (e.g., the pharmacy does not obtain prescriptions for identified individual patients for all of their compounded drug products), but insanitary conditions would be cited, and noted that there is some overlap between insanitary conditions and CGMP violations. For example, failure to conduct smoke studies under dynamic conditions is both an insanitary condition and a CGMP violation. Outsourcing facilities are subject to CGMP requirements for all of the drugs compounded at the facility.

Many states explained that in cases where there is a risk to public safety, typically, an immediate cease and desist order is issued. States asked for clarity on whether state actions would affect FDA registration of outsourcing facilities. FDA reminded the states that outsourcing facility registration does not imply compliance with section 503B, since outsourcing facilities can register and de-register at will.

FDA and state officials committed to continue working together on opportunities for collaboration on inspections of compounders and in regulatory actions resulting from these inspections.

State Handling of Outsourcing Facilities

FDA briefly reviewed some recent outsourcing facility ownership changes, then NABP began the discussion with a report on a state survey it conducted. In the report, NABP explained that some

states license outsourcing facilities as pharmacies, while others license them as wholesale distributors. Some states require a pharmacy license for outsourcing facilities that compound pursuant to patient-specific orders. Although there may be differences in inspection procedures, licensing is generally the same for in-state and out-of-state outsourcing facilities. The report also revealed that most states do not charge a fee for inspections and are moving towards having a separate licensing category for outsourcing facilities.

State officials were given the opportunity to present their legislative initiatives or regulatory framework for outsourcing facilities. Since states have different licensing requirements for outsourcing facilities, concerns were raised that that conflicting state licensing laws may lead to interstate commerce barriers. Regarding CGMP standards, FDA clarified that regardless of whether a state licenses a 503B registered outsourcing facility as a pharmacy, it will be held to section 503B requirements, including CGMP standards. FDA expressed interest in continuing to understand the states' regulatory processes in greater detail and will determine the best approach to continue the dialogue.

November 16-17, 2015, Inter-governmental Working Meeting Action Items:

1. FDA will continue to explore options for sharing information with states that have sunshine laws, including whether a modified information sharing agreement could be developed.

2. FDA will explore whether the 5 year, single signature information sharing agreement could be adapted to cover both compounding and supply chain security so that states would not have to sign multiple agreements.

3. FDA will consider whether and to what extent it could offer training to state inspectors on CGMP standards.

4. FDA will determine how best to communicate with states regarding compounders who restart operations after they were asked to voluntarily cease operations, so that FDA and the states can be sure the firm took adequate steps to correct the deficiencies that led to the request to cease operations.

5. FDA will consider publishing a guidance on insanitary conditions at facilities that engage in compounding.

6. FDA will continue discussions with the states regarding coordinating with the states on the oversight of outsourcing facilities.