Summary of Proceedings
September 25-26, 2018, Intergovernmental Working Meeting on Compounding

On September 25-26, 2018, the U.S. Food and Drug Administration (FDA) convened its seventh intergovernmental working meeting of state government officials. Attendees included officials from state boards of pharmacy and State health departments, and representatives from the National Association of Boards of Pharmacy (NABP).

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 intergovernmental working meetings on compounding with state officials and their designated representatives in December 2012, March 2014, March 2015, November 2015, September 2016, September 2017, and September 2018. 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.

State Legislative and Regulatory Updates

The September 2018 meeting began with a panel session describing recent state legislative and regulatory updates related to drug compounding. States described efforts in different stages of advancement. One state adopted new regulations in 2018 following 2017 passage of legislation that gave the Board of Pharmacy statutory authority to regulate compounding by pharmacists and pharmacies. In another state, compounding regulations establishing new licensure categories and reporting requirements, among other items, were near finalization. A third state described work to prepare for future rule revisions, including work to obtain additional information about both resident and nonresident compounding facilities.

Representatives from NABP described updates to the NABP Model Act regarding compounded drug preparations for veterinary use and shared an update on State participation in NABP's Multistate Pharmacy Inspection Blueprint Program.

FDA-State Memorandum of Understanding

Following state updates, FDA and state representatives participated in a panel session on the revised draft standard FDA-State Memorandum of Understanding (MOU) released by FDA on September 7. The MOU, described in section 503A of the Federal Food, Drug and Cosmetic Act (FD&C Act), is intended to address distribution of inordinate amounts of compounded drug products interstate and provide for appropriate investigation by a state agency of complaints relating to compounded drug products distributed outside such state.

FDA provided an overview of the revised draft MOU and explained several revisions made in response to stakeholder feedback. These included raising the threshold for "inordinate amounts" to mean that the number of prescription orders for compounded drug products distributed

interstate by a compounder during any calendar month is greater than 50% of the number of prescription orders for compounded drug products distributed or dispensed both intrastate and interstate by the compounder during that month. Revisions also describe the provision of certain information by states to FDA when the threshold is met rather than a state taking action against a compounder; additional mechanisms for states to obtain information about the distribution of inordinate amounts; state investigation of complaints in a manner they deem appropriate and in accordance with state law rather than describing specific required steps; and revisions to state responsibilities related to compounding done by physicians.

During panel discussion and subsequent breakout sessions, states shared support for the changes made by FDA, many expressing that these changes were steps in the right direction. However, states shared remaining concerns with FDA, including concerns about the ability of the state board of pharmacy to sign an MOU that contains any obligations with regard to compounding done by physicians. Some states also expressed concerns about having sufficient resources to collect and vet information from compounders regarding the distribution of inordinate amounts of compounded drugs across state lines.

FDA emphasized to participants that the MOU was issued as a revised draft to obtain additional feedback and encouraged states to submit detailed comments for agency consideration. FDA shared that the agency would be carefully considering the perspectives shared at this meeting as well as all comments submitted to the docket.

Use of Compounded Drugs when an Approved Drug Is Medically Appropriate

FDA and state representatives participated in a panel session on approaches to ensure compounded drugs are not used when an approved drug is appropriate for patient care. FDA began the session by describing associated risks with compounding, including unnecessary patient exposure to drugs that have not been evaluated for safety, effectiveness, and quality prior to marketing, and the potential to undermine the drug approval process. FDA then described provisions of federal law that limit the compounding of drugs that are "essentially copies" of approved or commercially available drug products, and FDA final guidance on these provisions published in January 2018.

Two state panelists then described approaches taken in their states to address compounded "copies" of commercially available drugs. Both states place restrictions on this practice, and take steps to enforce those restrictions, primarily during inspections of compounding facilities. One state reported asking questions about copies during inspections, and another described requesting and reviewing production records over the prior six months to search for potential copies. Both states described examples where compounders were producing drugs the state determined to be copies of approved products primarily to offer a lower-cost option than the approved drug.

Compounding and Repackaging of Radiopharmaceuticals

FDA next provided a presentation on how federal law and FDA policy address the compounding and repackaging of radiopharmaceuticals. FDA provided an overview of final guidance

documents published in September 2018 on the compounding and repackaging of radiopharmaceuticals; one applicable to outsourcing facilities, and another applicable to state-licensed nuclear pharmacies and other entities. FDA reviewed enforcement policies described in the guidances regarding compounded or repackaged radiopharmaceuticals that have only a "minor deviation" from an approved radiopharmaceutical, such as a change in radioactivity, volume, or step-by-step procedures. FDA also described enforcement policies related to compounding and repackaging of radiopharmaceuticals from a bulk drug substance when an approved product is in shortage, or a patient needs a variation of a product that cannot be achieved by manipulating the approved product.

Insanitary Conditions in Compounding Facilities and CGMP Requirements for Outsourcing Facilities

FDA began the second day of the meeting with a presentation on the conditions FDA observes when inspecting compounding facilities, as well as corrective actions taken by compounders to address deficiencies. FDA described examples of substandard conditions related to facility design and equipment, aseptic production, and environmental and personnel monitoring.

Examples ranged from visible filth on equipment and ongoing construction near places where sterile drugs are prepared, to the use of non-sterile wipes to clean surfaces used for aseptic production, and improper personnel movements in controlled air space that could disrupt unidirectional air flow and increase contamination risk. For deficiencies related to topics such as cleaning procedures and technique of personnel technique, FDA explained that appropriate corrective actions may include revised SOPs to addresses the deficient practices, invoices to show the purchase of appropriate supplies, retraining of personnel, and potentially reinspection to observe operations and ensure problems have been corrected.

FDA also described examples of observations related to CGMP compliance by outsourcing facilities, such as failure to use full sterile gowning, lack of adequate investigations into complaints and out-of-specification results, and deficient systems for monitoring environmental conditions, including air, surfaces and personnel, which under CGMP is recommended to occur daily.

Insanitary Conditions – Policy Update

FDA next provided an overview of a revised draft guidance on insanitary conditions at compounding facilities released in September 2018. FDA began by explaining that a drug is considered to be adulterated under federal law if it has been prepared, packed, or held under insanitary conditions whereby it may become contaminated with filth or rendered injurious to health, and that this provision applies to all drugs, regardless of where or how they are made. FDA explained that in issuing the draft guidance, the agency is seeking to provide real-world examples of insanitary conditions, including those that are particularly serious, both as a resource for compounders as well as for states to use during inspections and for regulatory actions they may pursue.

FDA described certain changes made to the revised draft guidance, including policies on compounding by physicians in their offices for use in-office with their patients. FDA also reviewed examples of particularly serious insanitary conditions described in the guidance, such as visible microbial growth in the ISO-5 area, use of a filter for product sterilization that is not certified as pharmaceutical-grade and sterilizing-grade, and use of parameters for sterilization (e.g., temperature, pressure, time) that are not lethal to resistant microorganisms.

State participants shared concerns regarding FDA's proposed policy in the revised draft guidance on compounding by physicians, expressing that it could create an inappropriately lower standard for compounding that occurs in physician offices.

Notes from the Field: FDA Investigator Perspectives

Participants then heard perspectives on FDA's inspectional process, including an account of first-hand experiences from an FDA field investigator. FDA speakers described the agency's procedures during an inspection, which includes an initial visual inspection, as well as separate reviews of sterile and non-sterile production, as necessary. FDA explained that for compounders that are not outsourcing facilities, FDA investigators make an initial evaluation of the facility's compliance with the conditions of Section 503A, which includes receipt of patient-specific prescriptions for all compounded products. If the firm appears to be compliant, FDA will not include observations related to conditions that only relate to CGMP requirements in a Form FDA 483.

FDA speakers emphasized the importance and value of FDA-state collaboration during oversight activities, noting that, in a number of cases, states have provided information to the FDA regarding insanitary conditions that prompted FDA inspections, and eventually to agreements by a compounding facility to cease sterile production operations and/or recall products. FDA also expressed appreciation of state support when FDA encounters challenges such as when facilities refuse to allow FDA investigators to observe compounding operations or to provide them with production records.

Oversight of Drug Compounding

FDA and state representatives then participated in a panel session on oversight programs for drug compounding. FDA opened the panel by providing an update on the agency's oversight activities. During fiscal year 2017, FDA conducted 141 inspections of compounding facilities, including 102 inspections of facilities seeking to compound drugs under section 503A, and 39 inspections of outsourcing facilities. FDA also issued 63 warning letters and 45 letters referring inspectional findings to the state regulatory agency, and there were 41 recall events related to compounded drugs.

FDA reported ongoing work with the Department of Justice on civil and criminal enforcement actions, including two compounders that entered into civil consent decrees of permanent injunction in April and June of 2018. Finally, FDA emphasized the importance of FDA-state collaboration, and described ways in which FDA and state regulators can support each other, such as through information-sharing and joint inspections. FDA encouraged participants that

had not already done so to consider entering into formal arrangements to allow greater information-sharing, such as through agreements described under 21 CFR 20.88, or by becoming commissioned officials with the FDA.

Following FDA's remarks, state panelists shared updates on their oversight activities for compounding, and their perspectives on FDA-state collaboration. Two state participants shared that inspection frequency for compounding facilities differs depending on the facilities' activities. In one state, compounders that hold a special sterile compounding permit are inspected annually. In another state, inspections occur every one-to-four years, with compounders seen as "high-risk" inspected most frequently. States shared that inspection duration ranges from a few hours to a few days, again depending on the type of facility and its activities. One state also licenses and inspects physicians that engage in compounding.

State panelists reported positive collaborative interactions with FDA in support of compounding oversight activities. States described examples of shared information leading to joint compounding facility inspections, as well as help and informational support provided by FDA regarding nonresident compounding pharmacies found to be shipping potentially substandard products into the state. One state explained that while they are not always able to attend a full FDA inspection, which may last over a week, they ensure they are present on the last day so that they may obtain a copy of a Form FDA 483, if issued, directly from the firm. This ensures the state has immediate access to the information in the 483 to support an independent investigation regarding the facility, if needed.

Use of Bulk Drug Substances in Compounding

FDA next presented on the agency's policies and activities related to bulk drug substances that may be used in compounding. After describing the statutory provisions in sections 503A and 503B related to bulk drug substances, FDA provided information on processes and work to date to establish lists of bulk drug substances that may be used in compounding under sections 503A and 503B (the 503A and 503B bulks lists). FDA most recently convened the Pharmacy Compounding Advisory Committee on September 12 to discuss FDA-evaluation of five bulk drug substances nominated for the 503A bulks list. FDA recommended that four of these substances be included on the 503A bulks list, and that one (quercetin dihydrate) not be included on the list.

Regarding the 503B bulks list, FDA described the draft guidance published in March 2018 titled, "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B." As described in the draft guidance, the 503B Bulks List may include a bulk drug substance if there is a clinical need for an outsourcing facility to compound the drug product, and the drug product must be compounded using the bulk drug substance. FDA also described a proposal published in the Federal Register in August 2018 proposing to not include three bulk drug substances – bumetanide, nicardipine hydrochloride, and vasopressin – on the 503B Bulks List.

Outsourcing Facility Oversight & Breakouts

The final session of the 2018 meeting addressed topics related to oversight of outsourcing facilities. Participants discussed these topics first in breakout sessions, and then reconvened for a final panel and audience discussion to review common issues identified. States described a range of approaches with regard to outsourcing facility oversight. While many states license outsourcing facilities, only some states inspect these firms. Of states that inspect, few look at compliance with CGMP requirements, and some may inspect simply because a state inspection is required for licensure. Some states felt that FDA, not states, should regulate outsourcing facilities, while others saw an ongoing role for state oversight and responsibility.

States shared that they may seek to use FDA documents and actions, such as Forms FDA 483 and warning letters, to pursue certain actions such as developing complaints or pursuing fines, licensure suspensions, or other actions. In some cases, some states may rely on FDA documentation alone, but many also conduct independent investigations or other due diligence to inform their actions. FDA reminded participants that Forms FDA 483 and warning letters do not represent final agency action. State panelists were open to sharing information with FDA about the actions they take based on FDA documents, and states were broadly interested in more information from FDA about outsourcing facility compliance to help inform appropriate state actions.

Overall, states saw the optimal role of outsourcing facilities in healthcare as entities that can help supply drugs in shortage and supply hospitals with needed ready-made formulations. Most did not see a role for outsourcing facilities in doing patient-specific compounding. Some states actively prohibit it. States shared concerns about outsourcing facilities becoming unregulated manufacturers, about facilities that compound one sterile product just to be able to make many pain creams and pellets, and about pharmacies with a history of violations becoming outsourcing facilities.

September 25-26, 2018 Intergovernmental Working Meeting Action Items:

- FDA will work to consider and develop systems states may use to obtain information to address the distribution of “inordinate amounts of compounded drug products interstate” under the standard Memorandum of Understanding, once final.
- FDA will continue to engage with state regulators to understand any insanitary conditions they are observing in non-pharmacy settings in their states.
- FDA will continue to engage with state regulators to better understand state actions that are informed by FDA Forms 483 and other FDA documents.
- In consultation with NABP, FDA will consider providing states additional resources and in-person training opportunities regarding insanitary conditions and key current good manufacturing practice requirements.