Summary of Proceedings
September 26-27, 2017, Inter-governmental Working Meeting on Compounding

On September 26-27, 2017, the U.S. Food and Drug Administration convened its sixth inter-governmental 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 inter-governmental working meetings on compounding with state officials and their designated representatives in December 2012, March 2014, March 2015, November 2015, and September 2016. 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 2017 meeting by providing an update on recent policy documents issued since the September 2016 inter-governmental working meeting, including:

- Revised Draft Guidance: Mixing, Diluting, Repackaging Biological Products Outside the Scope of an Approved Biologics License Application
- Final Guidance: Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities
- Final Guidance: Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B
- Final Guidance: Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act
- Proposed Rule: List of Bulk Drug Substances Used to Compound Under Section 503A
- Final and Proposed Rules: List of Drugs That Cannot Be Compounded Under Sections 503A or 503B Because They Have Been Withdrawn or Removed From the Market For Reasons of Safety or Effectiveness

FDA also addressed the agency's continuing work on other policy documents that had been published in draft, including:

- Draft standard memorandum of understanding with states addressing certain distributions of compounded drugs;
- Draft guidance on compounded drugs that are essentially copies of commercially available or approved drugs;
- Draft guidance on insanitary conditions at compounding facilities;
- Draft guidances on compounding and repackaging of radiopharmaceuticals; and

- Draft guidance on the facility definition under section 503B.

FDA also discussed a Federal Register notice to develop the list of bulk drug substances that can be used in compounding under section 503B.

FDA Incidents, Inspections and Enforcement Update

FDA provided an update on regulatory oversight, including enforcement activities. Between October 1, 2016 and September 6, 2017, FDA conducted 138 inspections of compounding facilities, including 100 inspections of facilities seeking to compound drugs under section 503A, and 38 inspections of outsourcing facilities. Seventy-two outsourcing facilities were registered with FDA at the time of the inter-governmental meeting, and 15 of these facilities were new registrants in fiscal year 2017.

There were 30 recall events involving compounded drug products from October 1, 2016, to June 30, 2017. Over the same time period, FDA issued 38 warning letters and 31 letters referring inspectional findings to the state regulatory agency. In addition, FDA worked with the Department of Justice on civil and criminal enforcement actions. One compounder entered into a civil consent decree of permanent injunction. In addition, the owner and director of compliance of a compounding facility were charged criminally in connection with defrauding the United States and distributing adulterated compounded drugs.

FDA also described a new effort to issue compounding risk alerts. Many serious patient illnesses and deaths linked to poor quality compounded drugs have occurred since the 2012 fungal meningitis outbreak. FDA issues compounding risk alerts to communicate information about certain adverse events and risks associated with compounded drugs.

Balancing State and Federal Oversight

State representatives joined FDA for a panel discussion about oversight of compounding facilities and enhanced coordination of FDA and state efforts.

FDA underscored the importance of FDA-state collaboration, including continued collaborations on inspections, investigations, and complaint and incident follow up; and addressing inspection refusals. FDA also described referrals of inspectional findings and complaints to the states when appropriate.

FDA representatives explained that the agency prioritizes oversight of the outsourcing facility sector. In addition, while states have day-to-day oversight responsibility of "traditional" compounding pharmacies, the agency may also conduct some oversight of those entities, focused on larger facilities that ship to multiple states.

State representatives echoed the importance of FDA-state collaboration and welcomed continued dialogue with the agency on improved communication and coordination. One panelist described efforts to collect information on compounding pharmacies regulated by the state, such as out-of-state licenses held by these pharmacies, that may help to better focus state and FDA oversight.

Another panelist expressed that FDA assistance is helpful when a state identifies inappropriate manufacturing activities at a compounding pharmacy.

During subsequent breakout sessions on this issue, FDA and state participants discussed measures to increase collaboration to improve oversight coordination. While some states expressed concerns regarding FDA inspections of state-licensed compounding pharmacies that are not outsourcing facilities, other states agreed that it would be helpful for FDA to prioritize inspections of facilities that operate on a larger scale, such as those that ship compounded drug products to multiple states.

States suggested criteria that FDA could consider using to focus oversight, including the types of sterile products the entity compounds (e.g., intrathecal), volume of production as well as high volume production of a few standardized products, and the number of out-of-state licenses held by a compounder. Some states reported that they already collect some of this data, while others do not.

FDA and state participants suggested ongoing dialogue on what information would be most useful for effective oversight coordination and prioritization, and the best mechanisms to obtain this information.

Outsourcing Facility Oversight

FDA and state panelists shared updates on activities related to regulation and oversight of outsourcing facilities, and discussed both new and persisting challenges.

FDA began the session by describing new initiatives conducted in response to states' requests at the 2016 Inter-governmental Meeting on Drug Compounding. FDA noted that in collaboration with NABP, in November 2017, the agency would provide an educational session to state compliance officers on conducting certain compounding inspections. FDA also announced two resources that were released on the first day of the 2017 Inter-governmental Meeting. First, FDA posted on its website for the first time information from outsourcing facilities' product reports, which describe products compounded by outsourcing facilities over prior six-month periods. Second, FDA published a document titled "Outsourcing Facility Information," a document that consolidates resources for outsourcing facilities. FDA also described ongoing challenges it has observed with regard to regulation and oversight of outsourcing facilities. For example, although FDA may, at an outsourcing facility's request, conduct an abbreviated review of a facility before it begins operations, it is not FDA's practice to inspect an outsourcing facility until the facility is operational. However, some states require a recent FDA inspection as a condition of licensure for outsourcing facilities and do not permit operation in their state without a license.

State panelists described different experiences and challenges regarding oversight of outsourcing facilities. One state panelist explained that although the state promulgated regulations applicable to outsourcing facilities, including resident and nonresident licensure requirements, some difficulties remain. For example, the panelist's state law does not explicitly allow entities registered as drug manufacturers and outsourcing facilities to be co-located in the same building and has never licensed a conventional drug manufacturer and outsourcing facility located in the

same building. However, some entities seek to engage in conventional manufacturing and compounding as an outsourcing facility in the same location, and FDA has proposed in draft guidance that such arrangements may be acceptable under certain conditions.

The state panelists expressed interest in training from FDA on compounding facility inspections. A state panelist noted that state entities responsible for oversight of compounding pharmacies differ from those responsible for outsourcing facilities, and that the state employs one inspector trained in current good manufacturing practice (CGMP) standards.

Animal Drug Compounding

FDA began the panel by providing an overview of certain elements of federal law applicable to animal drug compounding, as well as FDA's policy development to date. FDA explained that sections 503A and 503B of the FD&C Act do not apply to compounded animal drugs, and that animal drugs compounded from bulk drug substances are new animal drugs under the FD&C Act and must meet all requirements for the manufacture of new animal drugs. Recognizing that in some circumstances pharmacies compound animal drugs from bulk substances to meet animal patients' needs, FDA issued draft guidance in May 2015 which described the conditions under which FDA did not intend to take action when animal drugs were compounded from bulk. FDA's work to develop its policies on this matter is ongoing.

A state panelist also shared perspectives on the topic of animal drug compounding. The panelist noted that although the state board was aware of examples of pharmacies compounding large quantities of veterinary drugs for office use, it also observed limited veterinarian knowledge of pharmacy practice laws. The board worked to update its policies to allow a limited amount of compounding for veterinary office use.

Compounding Special Issues

Several FDA and state panelists contributed to a panel session covering a number of special topics related to drug compounding, including compounding for hospitals and long-term care facilities, new and complex compounding activities and technologies, rural issues related to compounding, and compounding and repackaging of radiopharmaceuticals. FDA and the states discussed each topic in further depth in subsequent breakout sessions.

Compounding for hospitals and long-term care facilities

FDA began the session by describing stakeholder feedback on the implications for hospitals and long-term care facilities of policies proposed by FDA regarding patient-specific prescriptions for compounded and repackaged drugs. In an April 2016 draft guidance, FDA proposed a policy applicable to health-system pharmacies pertaining to the distribution within their health system of compounded drugs without first receiving patient-specific prescriptions. FDA shared that some stakeholders felt that FDA's proposed policy was too permissive, while others felt that the proposed flexibilities were not sufficient to address needs for supplies of non-patient-specific compounded products in certain health system locations. FDA is considering how to address these concerns. FDA also noted that, as described in the agency's January 2017 final guidance on

repackaged drugs, the agency is considering the applicability of policies regarding repackaging human drugs to hospitals and health systems and the applicability of a condition in the guidance regarding patient-specific prescriptions to certain non-sterile repackaged drug products distributed to long-term care facilities.

FDA and state panelists noted that long-term care pharmacies often distribute repackaged drugs without first receiving prescriptions for individually identified patients to long-term care facilities for use in emergency boxes or automated dispensing machines. A state panelist further explained that most long-term care facilities require pharmacies to provide medicines in "compliance" packaging to reduce errors, often in unit-of-use packaging such as blister cards. The state panelist also shared that the most commonly compounded products used in long-term care facilities are IV fluids and IV antibiotics, but facilities may also use other compounded products such as total parenteral nutrition (TPN) and chemotherapy drugs.

During breakout sessions, participants discussed compounding for hospital and long-term care facilities in greater depth, including scenarios in which compounded drugs are prepared and provided to clinicians for use before a patient-specific order is generated. Several state participants expressed concern regarding FDA's proposed "one-mile radius" policy for hospitals with respect to the prescription requirement in section 503A, as described in FDA's April 2016 draft guidance. Under this proposed policy, FDA would not intend to take action against a hospital pharmacy for distributing compounded drug products without first receiving a patient-specific prescription provided they are distributed only to healthcare facilities that are owned and controlled by the same entity that owns and controls the hospital pharmacy and that are located within a one-mile radius of the compounding pharmacy, and the products otherwise comply with section 503A and any other applicable requirements of the FD&C Act. State participants noted that many health systems include satellite facilities that would fall outside of a one-mile radius.

New and complex compounding activities and technologies

FDA and state participants also shared information about new technologies as well as potentially complex compounding activities. FDA provided perspectives on certain activities, including compounding of drugs used with complex devices, which can have unique safety considerations and risks, as well as validation of automated technologies such as robotics, blow-fill-seal systems for unit-dose production, and TPN devices. FDA also described its progress to develop a list of drugs that present demonstrable difficulties for compounding. During breakout sessions, state participants expressed concerns about a number of compounding activities, including the use of lyophilizers by compounders, the compounding of implantable hormone pellets including appropriate sterilization practices and finished product quality, and the compounding of peptides. One state reported that they did not allow compounders to produce pellets or lyophilized compounded drug products.

Rural issues related to compounding

FDA and state participants discussed issues related to delivery of compounded drugs in the rural setting. States shared that access to specialized compounding services can be a challenge. They noted that fewer pharmacists are practicing in rural areas, specifically in rural hospitals. States

also described mechanisms, such as remote supervision of compounding, to provide access to compounded drugs in rural locations that may not have regular access to a pharmacist.

States shared that rural health systems often rely on central fill facilities that may supply satellite hospitals and clinics over a broader geographic area, but that rural hospitals are also, in general, interested in sourcing compounded products from outsourcing facilities. States explained that smaller hospitals may experience challenges when looking to purchase from outsourcing facilities; for example, outsourcing facilities may have a defined product list and may not have formulation flexibility, and also may expect orders of a certain size that may exceed the need of the hospital. Some states said they believed that outsourcing facilities will evolve to meet the demands of the market, and that outsourcing facility product reports posted on FDA's website will help purchasers identify what facilities may produce needed products.

Radiopharmaceutical compounding

The final special issues topic discussed by participants was radiopharmaceutical compounding. FDA draft guidance published in December 2016 explains the conditions under which FDA does not intend to take action for violations of new drug approval requirements and certain other requirements of the Act when a state-licensed nuclear pharmacy or Federal facility compounds or repackages radiopharmaceuticals. Another FDA draft guidance published at the same time describes FDA's policies with respect to the application of the conditions of section 503B to an outsourcing facility that compounds radiopharmaceuticals and FDA's policies regarding repackaging of radiopharmaceuticals by 503B outsourcing facilities. During breakout sessions state participants noted that they are still working to develop approaches to inspect and regulate radiopharmaceutical facilities. States also shared that board of pharmacy oversight of radiopharmaceutical facilities is often limited to nuclear pharmacies and does not include other settings such as nuclear medicine departments in hospitals or imaging centers. Entities that inspect these settings, such as the Nuclear Regulatory Commission and Agreement State agencies, typically do not focus on the types of issues that concern boards of pharmacy.

Information Sharing and Technical Assistance

FDA and state panelists provided perspectives on information sharing between FDA and states, and the ways in which it can support respective oversight efforts. FDA noted that information sharing helps both the states and FDA take coordinated and effective oversight actions, and described certain agreements, such as those described in section 20.88 of title 21 of the Code of Federal Regulations (20.88 agreements) that allow FDA to share certain non-public information with states. FDA described scenarios in which FDA proactively shares information with states, such as notifying states of upcoming inspections of compounders in their jurisdictions, and other ways the agency assists states, such as by providing witness testimony to support independent state actions against a compounding facility that FDA has also inspected. FDA also values information from states, such as alerts regarding emergent outbreaks or inspection findings of concern. Such state-provided information can inform FDA's decision to conduct its own inspection of a compounding facility. State participants shared examples of when FDA information and collaboration was helpful to the state, such as in providing witness testimony, inviting states to join FDA inspections, and, under 20.88 agreements or other appropriate

information-sharing agreements, sharing unredacted documents such as FDA Form 483s which describe FDA inspectional observations. Many states expressed that 20.88 agreements were valuable and allowed for better collaboration with FDA.

FDA Educational Session for Compliance Officers

The 2017 Inter-governmental Meeting concluded with a presentation on common observations made during FDA inspections of compounding facilities, and corrective actions compounders have taken to address potential violations. FDA's presentation included topics relevant to CGMP requirements applicable to outsourcing facilities, as described in FDA's 2014 draft guidance, as well as topics relevant to insanitary conditions as described in FDA's 2016 draft guidance. Among other issues, FDA discussed cleaning and disinfecting practices, gowning, aseptic technique, and environmental monitoring.

September 26-27, 2017, Intergovernmental Working Meeting Action Items:

1. FDA will consider, in collaboration with NABP, implementing a quarterly call with state regulators to discuss policy and oversight matters of mutual concern. The agenda for such calls would be collaboratively set by FDA and NABP in advance.

2. FDA will explore ways to continue to improve information sharing with states. For example, data from states can help to inform FDA's risk-based oversight of compounding facilities so that the agency uses its inspection and enforcement resources in a way that has the greatest public health impact. Information from FDA, such as inspectional findings or adverse events related to compounding facilities, can help states address public health concerns affecting their citizens.

3. FDA will work with NABP to identify information that would be useful to states from outsourcing facility product reports. Where identified, FDA will explore ways to make this information more accessible to states.

4. FDA will consider holding, during the 2018 Inter-governmental Working Meeting, a session concerning the use of bulk drug substances in compounding.