

Food and Drug Law Alert

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FDA Issues Additional Guidance Documents for Compounding Pharmacies and Outsourcing Facilities; Addresses Repackaging

The U.S. Food and Drug Administration (FDA) announced the availability of four new Draft Guidance documents and a draft Memorandum of Understanding (MOU) between the FDA and individual states. The Draft Guidance documents continue FDA's implementation of the pharmaceutical compounding provisions of the Drug Quality and Security Act (DQSA), addressing which entities should register as "Outsourcing Facilities," adverse event reporting for Outsourcing Facilities and the repackaging of drugs and biologics by both FDA-registered Outsourcing Facilities and state-licensed compounding pharmacies.

Comments on the draft MOU are due to the FDA by Thursday, June 18, 2015. Comments on the other draft guidance documents are due to FDA by Tuesday, May 19, 2015.

The first Draft Guidance, "For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA)," describes the types of entities that should and should not register as Outsourcing Facilities under the newly established section 503B of the FDCA. In order to register as an Outsourcing Facility, an entity must be engaged in the compounding of sterile human drugs, which means entities should not register if they only engage in one or more of the following activities: compounding nonsterile drugs; compounding sterile or nonsterile veterinary drugs; or repackaging sterile or nonsterile drugs. If an entity elects to register as an Outsourcing Facility, FDA intends to subject all products to the requirements of section 503B—including Current Good Manufacturing Practices (CGMPs), adverse event reporting and product labeling requirements—regardless of whether a specific product is nonsterile, for veterinary use or prepared in response to receipt of an individual patient prescription (which is not required under section 503B). FDA also reiterates that registered Outsourcing Facilities are not required to be licensed pharmacies or to obtain prescriptions, but they must nevertheless obtain a prescription to dispense directly to a patient.

Two Draft Guidances relate to repackaging. The first, "Repackaging of Certain Human Drugs by Pharmacies and Outsourcing Facilities," governs the repackaging of sterile and nonsterile drugs, which FDA has distinguished from drug compounding. Early congressional deliberations concerning the DQSA contemplated addressing drug repackaging, but Congress ultimately chose not to do so. The Draft Guidance defines repackaging as "taking a finished drug product from the [original] container . . . and placing it into a different container without further manipulation of the drug," as well as "placing the contents of multiple containers (e.g., vials) of the same finished drug product into one container, as long as the container does not include other ingredients." In the guidance, FDA asserts that repackaging does not fit within the definition of "compounding" and thus is not eligible for the exemptions for drugs compounded in accordance with sections 503A or 503B of the FDCA. Nevertheless, FDA proposes to exercise enforcement discretion and refrain from enforcing the full FDCA—including the requirement to

obtain premarket approval of any new drug—against state-licensed pharmacies, federal facilities and Outsourcing Facilities that repackage in compliance with the conditions set forth in the Draft Guidance. For Outsourcing Facilities, these conditions generally mirror the requirements in section 503B for compounding drugs, except that the beyond use date (BUD) for a repackaged drug would be prescribed in the guidance rather than result from CGMP standards, and distribution is subject to applicable state requirements. The conditions are slightly modified for state-licensed pharmacies and federal facilities, which would be required to obtain a prescription to repackage drugs to fall within the Draft Guidance.

The second, “Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application (BLA),” governs the admixing or repackaging of products subject to a BLA under section 351 of the Public Health Service Act (PHSA). Although congressional deliberations on the DQSA contemplated addressing compounding of biologics, again Congress ultimately chose not to include biologics in section 503B. Likewise, section 503A does not apply to the compounding of biologics. Conditions for state-licensed pharmacies, federal facilities and Outsourcing Facilities are parallel to their respective conditions under the Draft Guidance on repackaging of drugs, except that the BUDs are shorter. In addition, these conditions also apply to “prescription sets,” which FDA defines as vials of premixed, standardized and non-standardized allergenic extracts for subcutaneous immunotherapy.

Once finalized, these guidance documents on repackaging will supersede section 506F of the FDCA as applied to repackaging of single-dose vials in hospital-based pharmacies. In the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), Congress established interim criteria for repackaging drugs in shortage, which by law would sunset once FDA issued guidance.

The final Draft Guidance, “Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act,” covers obligations to report serious adverse events to FDA under section 503B. By cross-reference to the regulation governing adverse event reporting for prescription drugs at 21 C.F.R. § 310.305, the Draft Guidance defines “serious adverse drug experience” and “unexpected adverse drug experience.” Registered Outsourcing Facilities must report all serious, unexpected adverse events associated with their compounded drugs, and FDA further encourages facilities to report all serious adverse events, unexpected or otherwise. Facilities must actively investigate and report to FDA within 15 calendar days on four data elements: (1) an identifiable patient, (2) an identifiable reporter, (2) a suspect drug and (4) a serious adverse event, as set out in the guidance. Until FDA makes system updates and issues additional guidance to facilitate electronic reporting, adverse events are to be reported to FDA in hard copy on a Form FDA 3500A. Outsourcing Facilities must maintain all investigational findings for 10 years, which are subject to FDA inspection.

Lastly, the “Draft Memorandum of Understanding (MOU) Between a State and the U.S. Food and Drug Administration Addressing Certain Distributions of Compounded Human Drug Products” provides a draft template, for comment, of the agreement between FDA and state governments to facilitate the interstate shipment of compounded drugs. Following the establishment of section 503A by the Food and Drug Administration Modernization Act of 1997 (FDAMA), FDA published a draft MOU to impose certain enforcement obligations on states that entered into the agreement and to permit pharmacies in those

states to ship up to 20 percent of their compounded drug products across state lines. If a state did not enter into the MOU, pharmacies in the state would be limited to a threshold of five percent of their compounded drug products for interstate shipment, as required by section 503A(b)(3)(B)(ii) of the FDCA. However, FDA never finalized the prior draft MOU and, due to legal uncertainties, the agency did not consistently enforce the limitations on interstate shipment or other provisions of section 503A.

Once in place, the new MOU will serve as an agreement between FDA and individual states that dictates each signatory state's agreement to investigate complaints about drugs compounded by state-licensed pharmacies and to notify FDA of violations of the FDCA, in particular whether a pharmacy is distributing inordinate amounts of compounded products interstate in violation of section 503A. FDA will consider interstate shipments to be "inordinate" if the total units of compounded human drug products shipped out of state is equal to or exceeds 30 percent of all drug products (including non-compounded) distributed both interstate and intrastate during any calendar month. Importantly, no distinction is made between distributing and dispensing, but the calculation excludes products that are dispensed in-state and then carried across state lines by the patient or an agent.

Following the 120-day public comment period and subsequent publication of the final MOU, states will have 180 days to decide whether to enter into the agreement. The MOU can be terminated by either FDA or the state upon 30-days' written notice. The MOU does not apply to Outsourcing Facilities registered in accordance with section 503B.

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