



## Notice

This notice is to advise of a change in the U.S. Food and Drug Administration (FDA)'s procedure for inspections of entities that are seeking to compound human drugs in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (i.e., human drug compounders that are not registered with FDA as outsourcing facilities under section 503B).

Effective August 1, 2016, FDA investigators will make a preliminary assessment of whether such entities are compounding their human drugs in accordance with certain conditions of section 503A before closing the inspection. If the investigator issues a "Form FDA-483"<sup>1</sup> list of inspectional observations to the firm, the investigator will *not* include observations that represent deviations solely from FDA's current good manufacturing practice (CGMP) requirements unless it appears, based on the investigator's preliminary assessment, that the firm compounds drugs that do not qualify for the exemptions under section 503A.

Section 503A of the FD&C Act describes the conditions that must be met for a drug product compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to qualify for exemptions from provisions of the FD&C Act requiring pre-market FDA approval of drugs (section 505), labeling with adequate directions for use (section 502(f)(1)), and compliance with CGMP requirements (section 501(a)(2)(B)). If a drug is not compounded in accordance with the conditions in section 503A, it does not qualify for the exemptions in that section and is subject to the approval, labeling with adequate directions for use, and CGMP requirements.

Because a Form FDA-483 does not represent a final Agency determination regarding a firm's compliance, formerly, FDA investigators have been identifying deviations from drug production practices on Forms FDA-483 that could lead to quality problems without regard to whether the observations related to CGMP deficiencies or other deficiencies, such as those relating to the prohibition in section 501(a)(2)(A) of the FD&C Act on preparing, packing, or holding drugs under insanitary conditions whereby they may be contaminated with filth or rendered injurious to health.

After the inspection, when determining whether to pursue regulatory action, such as a warning letter, FDA has considered a number of factors, including evidence concerning compliance with the conditions of section 503A. When FDA has issued a warning letter, FDA has only cited compounders that were not registered as outsourcing facilities for violations of CGMP requirements when the agency had evidence that at least some of their drugs were not compounded in accordance with the conditions of section 503A. Our experience was that in the substantial majority of cases, inspected human drug compounders not registered as outsourcing facilities were compounding at least some of their drugs not in accordance with section 503A,

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<sup>1</sup> A Form FDA-483 is issued to firm management at the conclusion of an inspection when an investigator has observed conditions that in the investigator's judgment may constitute violations of the FD&C Act and related Acts.

subjecting their drugs to CGMP requirements. Nevertheless, FDA has received input from stakeholders that they would like inspectional evidence regarding section 503A to be reviewed earlier, prior to the close of an inspection, and to be taken into consideration in decisions about what to include in any Form FDA-483.

In response to stakeholder input, and as noted above, FDA investigators now will make a preliminary assessment regarding the firm's compliance with certain conditions of section 503A before closing an inspection, and if a Form FDA-483 is issued to the firm it will *not* include observations that represent deviations only from CGMP requirements unless the investigator's preliminary assessment is that the firm compounds drugs that do not qualify for the exemptions under section 503A. After the inspection, FDA will conduct a thorough review of the evidence to evaluate whether the firm compounds all of its drugs in accordance with certain conditions of section 503A and other applicable provisions of Federal law. When FDA's more thorough post-inspection review differs from the FDA investigators' preliminary assessment and reveals that a facility fails to produce drugs in accordance with the conditions of section 503A, FDA intends to consider citing CGMP violations in any regulatory action it decides to pursue.

Importantly, although drug products compounded in accordance with the conditions of section 503A are exempt from certain requirements in the FD&C Act, as described above, they remain subject to all other provisions of the FD&C Act that apply to conventional drug manufacturers, including, but not limited to, the prohibition on preparing, packing, or holding drugs under insanitary conditions. Because section 503A does not provide an exemption from the prohibition on insanitary conditions, FDA investigators will continue to include observations on Forms FDA-483 that appear to constitute insanitary conditions without regard to the investigator's preliminary assessment of a firm's status under section 503A. Investigators may similarly include on Forms FDA-483 observations that appear to violate other legal requirements from which section 503A does not provide an exemption.

Since the 2012 fungal meningitis outbreak in which contaminated injectable drug products compounded by a pharmacy resulted in over 60 deaths and 750 cases of infection, FDA has investigated numerous serious adverse events, including infections and deaths, associated with poor quality (e.g., contaminated or superpotent) sterile and non-sterile compounded drugs. Many compounders have recalled drug products and temporarily or permanently ceased sterile operations as a result of FDA's inspectional findings. FDA intends to continue to inspect compounding facilities and to take action, as appropriate, when the Agency identifies violations of Federal law that could put patients at risk.