

How to Prepare for the FDA's 2019 Enforcement Priorities for the Compounding Industry



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On April 3, FDA Commissioner Scott Gottlieb released a statement outlining the agency's priorities for 2019 (available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm635182.htm>) with respect to compounding pharmacies and the compounding industry. It is clear from Gottlieb's statement that, even nine years later, the 2012 fungal meningitis outbreak is still reverberating within the agency and shaping its activities and policies regarding compounders. The FDA's 2019 priorities suggest a concerted agency effort to increase oversight and scrutiny of compounders, their production practices, and their facilities. This increased oversight likely will result in an increase in the number of inspections and enforcement actions against compounders.

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This article discusses some of the key takeaways from Gottlieb's statement that compounders across the country should be aware of:

1. The FDA's 2019 priorities strongly suggest an increase in scrutiny of insanitary conditions at compounding facilities, and an accompanying uptick in inspections and regulatory actions. Compounders should refamiliarize themselves with the FDA's draft guidance on insanitary conditions in order to ensure compliance and mitigate risk of an enforcement action.
2. In 2019, it is likely that the FDA will expect compounders to take immediate and significant corrective action whenever insanitary conditions are discovered. Compounders should review and implement specific procedures for investigating and remedying suspected or actual insanitary conditions.
3. The FDA plans to finalize its Memorandum of Understanding with the states in 2019, which will lead to increased collaboration and coordination with state regulators in conducting inspections and enforcement actions. Compounders, especially those that distribute large quantities of drugs outside their home state, should ensure their compliance with all applicable laws in their home state and in all states to which they ship drugs.

Given the looming specter of increased scrutiny and enforcement activity, compounders would be wise to evaluate their compliance with applicable standards in light of these priorities, and consider taking appropriate remedial or preventive steps where necessary.

1. The FDA's 2019 priorities suggest a heightened focus on insanitary conditions in compounders' facilities, techniques and supplies, and an increase in enforcement actions for perceived violations.

In his statement, Gottlieb raised the many deficiencies the FDA identified in 2018 across the compounding industry related to insanitary conditions, specifically citing 23 warning letters, 50 product recalls and four consent decrees of permanent injunctions all relating to insanitary conditions or other safety issues. While Gottlieb acknowledged that some compounders "work hard to meet quality standards," his implication was clear: The FDA is not satisfied with the conditions in which drugs are being compounded, and will focus in 2019 on further efforts to identify and punish noncompliant pharmacies.

Gottlieb emphasized the FDA's intent to "strengthen" its regulatory oversight in this area in 2019 and to "advance other new policies." In doing so, Gottlieb specifically referenced (and the online statement linked to) the FDA's September 2018 draft guidance on "Insanitary Conditions at Compounding Facilities" (available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf>). Gottlieb's incorporation of the draft guidance into his remarks strongly suggests that the FDA can and will hold compounders to the standards set forth in the guidance, even as they are being finalized. In fact, he virtually promised as much by describing the FDA's pursuit of compounders that "produce drugs under substandard conditions or use inappropriate practices" as a "key component" of the agency's work in 2019.

Recommendation: Given this warning, compounders should refamiliarize themselves with the FDA's guidance on insanitary conditions, which, generally speaking, focuses on five main areas and provides specific examples for each that inspectors have found in other facilities. The primary areas of focus are:

- *Insanitary conditions in or near the production area.*¹ The FDA specifically cites the presence of insect or animal infestations, viable and nonviable microbial contamination, standing water, and nearby construction as actionable insanitary conditions.
- *Improper aseptic technique.* The FDA identifies the following examples as creating insanitary conditions: deficient gowning, infrequent changing of gloves, personnel with exposed hair or skin, manipulations of purportedly sterile drugs outside an ISO 5 area, and improper sterilization of containers and closures.
- *Improper sterilization technique.* The FDA cites as examples of insanitary conditions instances of compounders using noncertified, compromised or particle-shedding filters for sterilization and applying improper temperature, pressure and time parameters.
- *Deficient compounding facilities.* This area focuses on both design and construction defects — e.g., failure to certify ISO 5 areas (including by performing a smoke test), insufficient pressure differentials between ISO areas, improperly installed HEPA filters and ceiling tiles, and using improper materials during construction — and improper facility maintenance — e.g., lack of routine environmental monitoring (viable and nonviable airborne particulate, surface sampling) and personnel sampling.

- *Insufficient cleaning programs.* The FDA's examples in this area include deficiencies in selecting and using cleaning agents — e.g., infrequent use of sporicidal agents, use of expired cleaning agents, and use of cleaning agents that leave a residue — and failures to employ proper cleaning technique — e.g., infrequent cleaning and allowing for insufficient contact time of disinfecting agents.

Compounders should review their existing policies and practices to ensure strict compliance with the FDA guidance in each of these critical areas.

2. The FDA's 2019 priorities strongly suggest that compounders are expected to take immediate and robust corrective action when insanitary conditions are discovered, and those that do not may face harsher enforcement action.

The other component to the FDA's 2018 draft guidance on insanitary conditions is its heavy focus on corrective actions that should be undertaken by compounders in response to identified deficiencies. The draft guidance would obligate compounders to do the following whenever an insanitary condition is discovered: immediately assess the impact of the condition on drug production; evaluate how widespread the conditions are and over what period of time they occurred; and identify the lots of drugs affected by the conditions. Although the FDA guidance stops short of requiring compounders to cease operations or recall drug products every time an insanitary condition is discovered, it does call on compounders to conduct an evaluation on a case-by-case basis to determine if such action is warranted. The draft guidance also provides a lengthy list of examples of insanitary conditions for which the FDA "strongly recommends" the compounding facility cease operations and issue a recall. These examples include many of the same insanitary conditions discussed above.²

The ultimate consequence of this guidance is to place the burden on compounders to identify, investigate and sufficiently remedy insanitary conditions whenever they are discovered. Gottlieb's reference to, and reliance on, the draft guidance in his remarks suggest that these are standards that federal and state regulators will be looking at and enforcing when they inspect compounding pharmacies going forward. Compounders that have not taken sufficient remedial action, as directed by the guidance, likely will be at increased risk for risk-based inspections and regulatory enforcement action, and may also be perceived as deserving of harsher punishments for violations.

Recommendation: To safeguard against these risks, compounders should draft and implement a procedure providing for an appropriate investigation of suspected or actual insanitary conditions. To the extent compounders already have such a policy, they should review it to ensure it complies with the draft guidance, including the instruction that any investigation should identify the root cause of an insanitary condition, the scope and duration of the condition, the impact the condition had on drug products, and what appropriate remedial actions are required to mitigate the impact of the insanitary condition. Legal counsel can help compounders draft and/or evaluate these policies.

In certain circumstances — such as those involving a particularly serious or widely impactful insanitary condition or when an employee complains about an alleged insanitary condition — compounders should consider engaging legal counsel to actually conduct the investigation. By having legal counsel conduct the investigation, the compounder can fully investigate the circumstances and weigh potential remediation options — including, in particularly serious circumstances, whether a self-report to the FDA or state board is warranted — while under the confidentiality and protections of the attorney-client privilege. Demonstration of good faith efforts to thoroughly investigate and remediate insanitary conditions may enhance a compounder’s position with the government should there ever be a problem. However, compounders often will not know whether the results of such an investigation will be harmful to them until after it is conducted, thereby enhancing the benefits of conducting the investigation in a privileged setting.

3. The FDA’s 2019 priorities discuss enhanced cooperation and coordination with state regulators, which will likely result in more inspections, investigations and enforcement actions against compounders, particularly those that sell products across state lines.

Another primary focus of Commissioner Gottlieb’s remarks concerned the FDA’s plan to finalize its long-awaited Memorandum of Understanding (MOU) with the states in 2019. The most recent version of the MOU — released for public comment in September 2018 — seeks to increase scrutiny and oversight of compounders by obligating states to take certain actions against, and maintain certain information concerning, the compounding pharmacies operating within their borders. Specifically, the MOU obligates signatory states to investigate all complaints related to drug products compounded by in-state pharmacies, take appropriate action in accordance with state law when problems arise to ensure that pharmacies identify root causes and address any public health risks, and, in certain circumstances, provide information to the FDA concerning the conduct

and results of investigations or inspections. Notably, as written, the MOU would require signatory states to investigate complaints of *all* adverse drug experiences and *all* product quality issues, even those characterized as nonserious.

Gottlieb's stated goal of finalizing the MOU in 2019 can be interpreted as a further indication that all compounders can expect increased and more coordinated scrutiny from federal and state regulators going forward. However, the MOU also singles out a subset of compounders over which it purports to exercise even higher scrutiny: compounders that distribute an "inordinate amount" of drugs — which is defined by the MOU as more than 50 percent of the prescriptions they distribute — outside of their home state. States that sign the MOU will be required to track these compounders to a higher degree, including through the mandatory use of surveys and the review of inspection records. Signatory states also will be required to collect and maintain more detailed information on these compounders — *e.g.*, the total number of prescription orders distributed interstate versus intrastate and the number of states in which each is licensed — and report their findings concerning these compounders to the FDA.

Recommendation: The combination of increased reporting and information-sharing from states to the FDA, and the enhanced coordination by those regulators that will result from the FDA finalizing the MOU, threatens to place compounders — especially those that distribute "inordinate" amounts of drugs outside their home state — in a precarious position. The enhanced cooperation between the FDA and states is likely to result not only in more inspections of compounders, but more inspections and inquiries that are focused on specific risks and issues that the government considers critical to public safety and, therefore, more deserving of serious sanctions. This possibility should serve as further motivation for compounders to employ the risk mitigation strategies discussed above. But it should also serve as a special warning to compounders that do distribute large amounts of drugs outside their home state or compounders that are considering expanding their operations in that manner. Given the extra attention likely to be paid to them, compounders that fall into those categories should undertake a rigorous self-assessment to ensure their compliance with all applicable laws and regulations, including compliance with any applicable laws from the states into which drugs are being shipped (in addition to the compounder's home state laws). Compounders should also take measures to ensure they are properly licensed in the states to which they ship drugs. State pharmacy and compounding laws differ by jurisdiction, but legal counsel can help compounders identify and obtain any necessary licenses.

Endnotes

- 1 Unlike the other areas of focus, insanitary conditions in or near the production area apply to both sterile and nonsterile drugs.
- 2 The FDA's full list of exemplar insanitary conditions warranting a cessation of operations and a recall is as follows: vermin or animals in or adjacent to the ISO 5 area; visible microbial growth in or adjacent to the ISO 5 area; sources of nonmicrobial contamination in the ISO 5 area (e.g., rust, glass shavings, hairs, etc.); performance of aseptic manipulations outside the ISO 5 area; exposure of sterile drugs and materials to lower than ISO 5 quality air; presence of unsealed or loose ceiling tiles; ongoing construction adjacent to the production area; frequent pressure reversals; use of noncertified filters or improper use of a pharmaceutical-grade filter for sterilization; and use of improper temperature, pressure and time parameters for sterilization.

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