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Manufacturing Guidelines Play Vital Role in Safety of Compounded Drugs

Compliance by outsourcing facilities decreases patient risks

Overview

Compounded drugs can serve an important role for patients whose clinical needs cannot be met by medications approved by the U.S. Food and Drug Administration (FDA). While these drugs are generally prepared for individuals based on a patient-specific prescription, medical providers may also seek non-patient-specific supplies of compounded drugs—known as office stock—to administer in an outpatient or hospital setting. For example, many hospitals maintain stocks of compounded injections to relieve pain that can be administered to patients with an immediate need. Under federal law, only certain compounders known as outsourcing facilities can compound and distribute non-patient-specific drug products for use as office stock.

Office stock products present risks. They are often stored before use, which increases the opportunity for contaminants such as bacteria and fungus to grow to dangerous levels, or for ingredients to deteriorate, which can cause drugs to become less potent or degrade in ways that pose safety concerns. Also, because such drugs are sometimes produced at significant scale, more patients are potentially exposed if products are contaminated or otherwise substandard.

To reduce these risks, outsourcing facilities must comply with Current Good Manufacturing Practice (CGMP) requirements, issued by FDA, that also apply to conventional pharmaceutical companies. The table below highlights key CGMP topics from draft guidance FDA issued in December 2018, and provides examples of how these guidelines decrease risks to patient safety.

Current Good Manufacturing Practice (CGMP) Requirements for Outsourcing Facilities and Patient Safety

Focus is on drugs' sterility, strength, and labeling, and avoiding mix-ups

Topics discussed in draft guidance[1]	Summary	How does this section help decrease patient safety risks?[2]
Facility design	The areas in which drug components, final products, or in-process materials or equipment are prepared, held, or transferred are designed to minimize contamination of the final product. For example, the facility design and operation ensures "cascading air quality," whereby the most stringent air quality requirements are applied to the areas where sterile drugs are aseptically processed and/or sterilized. The CGMP provisions are slightly less strict in the parts of the facility outside those critical areas. This type of layout decreases the risk of contamination and helps protect the area where sterile compounding occurs.	Proper facility design can help prevent contaminants in the air or on room surfaces—including pathogenic microbes as well as other things that could injure a patient, such as metal shards—from ending up in the drugs made or stored there. In 2014, a compounder recalled all sterile drugs and ceased compounding operations after a Food and Drug Administration inspection revealed several problematic conditions at the facility. Issues included a lack of positive air pressure in the critical "clean room," which compromised the cleanliness of the room's air, and equipment that was placed directly under air filters, potentially obstructing airflow. The government later entered into an agreement with the owner of the facility, under which he was prohibited from compounding drugs unless he complied with federal law.[3]
Control systems and procedures for maintaining suitable facilities	Facilities implement measures to prevent contamination or mix-ups during the compounding process. This section includes guidance on the appropriate schedules, methods, equipment, and materials that are used during cleaning in compounding facilities. It also outlines essential handling procedures. For example, if powdered drugs are being used, procedures are in place to prevent cross-contamination; otherwise they can, for example, drift through the air and contaminate other drugs. Additionally, it describes control systems that ensure appropriate airflow, air pressure, humidity, and temperature; ways in which these measurements are monitored; and steps that are taken if inappropriate conditions are detected (such as immediately correcting the problem or stopping production until corrected).	Cross-contamination or mix-ups during the compounding process can threaten patient safety. In 2011, five patients were blinded after receiving eye injections that contained trace amounts of an unintended medication.[4]
Environmental and personnel monitoring	Procedures are used to monitor the air and surfaces in compounding environments, as well as the gloves and gowns of people working within them, for contaminants and to address any problematic findings by investigating the results and taking appropriate corrective actions.	The personnel who produce sterile drugs are the greatest potential source of contamination.[5] In 2017, 41 patients who had received shots in their joints developed joint infections caused by microorganisms found in human mouths.[6] Proper monitoring of the environment and personnel can help to reduce this risk.

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Equipment, containers, and closures	Controls are in place, including evaluating equipment, containers, and closures that will come into contact with drug products to ensure they are adequate for their intended use. Equipment surfaces do not chemically interact with or absorb the drug or drug components in a way that compromises the quality of the product. Containers and closures are themselves sterile and able to maintain sterility of the compounded product during use and storage.	Particles on unsterilized equipment can contaminate the drugs the equipment is being used to make. Improperly stored drug products may degrade or be contaminated. In 2015, FDA warned health care professionals not to use compounded or repackaged medications stored in syringes produced by a certain manufacturer, because the drugs could lose potency over time due to a possible interaction with the syringes' rubber stoppers. The company later informed the agency that it had ceased using the stoppers in question.[7]
Components	Facilities establish appropriate specifications for the components used in each drug product. Each lot of components is tested to verify identity and evaluated for conformity with those specifications before use. Components are retested after long periods of storage or exposure to conditions that might undermine their quality, such as heat or light.	Facilities sometimes use nonsterile bulk ingredients that are not subject to review before being sold and thus may not have been tested previously for impurities and other important characteristics, so it is important for facilities to do such testing themselves before using the ingredients. If components include contamination or have degraded over time, then final products can be negatively affected. Testing allows producers to reject components that do not meet specifications and ensures the final product made with those components is safe. In 2018, FDA issued an alert about the recall of an ingredient used in compounded drugs prescribed for underactive thyroid. The agency's tests had found that the ingredient, made by a manufacturer with serious quality deficiencies, had inconsistent potency. Risks associated with over- or undertreatment of underactive thyroid could result in permanent or life-threatening adverse health consequences.[8]
Production and process controls	Facilities develop written procedures to ensure that their manufacturing process consistently results in drug products that meet standards for identity, strength, quality, and purity. For example, if the actual yield of a batch of drugs is significantly different from what was projected, this indicates a possible production problem. The cause is investigated, and the entire batch might be rejected. This section also details the special processes that are implemented for sterile drug manufacturing, including training and oversight for personnel manipulating sterile products, as well as techniques intended to maintain the sterility of items and surfaces, such as procedures for putting on sterile gowns, and other essential considerations.	Contamination or other serious quality problems may occur at multiple steps along the manufacturing chain. These procedures help to ensure the quality and safety of the final compounded drug product by stating step by step how products are to be compounded, which tests and inspections are performed during production, and how to ensure that all key processes are well-controlled.

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Release testing	Appropriate specifications are established for each finished drug product, and finished products are tested to verify they meet these specifications before being distributed. Specifically, each batch is tested to confirm it meets specifications for sterility, pyrogenicity (whether it contains substances that cause fever), identity, and potency. Representative samples (e.g., of each lot or batch) must be retained to facilitate testing.	While release testing cannot compensate for other inadequate quality controls, it is performed to confirm the quality and safety of the compounded product and can serve as a control measure to ensure that products containing contaminants and other quality deficiencies are not distributed. If appropriate release testing processes are not in place, the consequences can be grave. In 2007, three patients died of fatal overdoses after receiving infusions of colchicine from vials in which the drug was eight times more concentrated than the label indicated. The deaths were attributed to a measurement error at the compounding pharmacy that distributed the overly potent vials.[9]
Laboratory controls	Any laboratory involved in testing components, in-process materials, or finished drug products has controls to ensure the reliability of its own tests. Laboratories can be part of an outsourcing facility or external to it, but the facility retains ultimate responsibility for laboratories following all necessary controls.	If a laboratory's test results are not valid, it could miss indications of a problem that leads to unsafe drugs. In 2013, while inspecting a laboratory that conducted sterility and other quality testing for compounders, FDA observed testing methods that could result in pharmacies receiving inaccurate test results. Three compounding pharmacies then recalled products that had been tested by that laboratory.[10]
Stability and expiration dating	Facilities assess the stability of finished drug products to determine how long each can be safely used. Compounded drugs are then assigned appropriate expiration dates based on how long the product is shown to be stable in its specific container and dosage form.	Like any drug, compounded drugs can lose potency or otherwise degrade over time, even when properly stored. Stability testing establishes the period of time during which a finished product is expected to maintain its quality under specific storage conditions.
Packaging and labels	Packaging is appropriate to ensure the sterility (if applicable) and integrity of the product until it is administered to the patient. Labels contain required information, and labeling controls are in place to prevent mix-ups or mislabeling.	Incorrect product labels can lead to the wrong active ingredients, combination of ingredients, or concentration of ingredients being administered to patients for whom they are not clinically appropriate, leading to serious adverse events or even death. In 2015, FDA received reports of adverse events in neonatal infants who had been administered a compounded sedative. Testing showed the product to be more potent than the label indicated, and the firm recalled the product.[11]

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Quality assurance activities/ complaint handling	Facilities have an independent quality-control unit whose responsibilities include ensuring each batch of finished drug product is sampled and tested to see that it meets appropriate specifications for release. This unit also investigates possible problems in the facility, such as unexpected test results; drugs that are substandard, mislabeled, or otherwise do not meet user expectations; or environmental and personnel monitoring results that exceed alert or action limits. These control units have authority to conduct full investigations of suspicious products and halt distribution pending results.	Quality assurance allows outsourcing facilities to examine and alter processes and systems as a whole. It also ensures that the specific procedures are carried out and that quality issues are investigated when they arise. If gaps are identified, the facility can investigate and take corrective and preventive actions. If investigations are not completed (and/or corrective actions are not taken) after concerns with a drug are identified, other products made under the same quality procedures could be affected, leading to problems with those drugs, too. In 2016, after an outsourcing facility recalled morphine injections that were 25 times stronger than indicated on the label and were linked to serious adverse events in three infants, FDA inspected the facility, which was still compounding other products. Inspectors observed a number of problems, and the agency advised health care professionals not to use any of the facility's products that were intended to be sterile. Eventually the facility recalled all of those products.[12]

Endnotes

1 FDA's regulations regarding CGMP requirements for finished pharmaceuticals in Chapter 21 of the Code of Federal Regulations (21 CFR), Parts 210 and 211, provide for systems that ensure proper design, monitoring, and control of manufacturing processes and facilities to ensure the identity, strength, quality, and purity of drug products.

2 On Dec. 10, 2018, FDA issued draft guidance that described its specific expectations for outsourcing facilities regarding compliance with CGMP. U.S. Food and Drug Administration, "Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug and Cosmetic Act" (2018), https://www.fda.gov/downloads/drugs/guidances/ucm403496.pdf. Although it is a draft version, it is applicable until FDA issues final regulations (or an updated draft).

3 U.S. Food and Drug Administration, "Federal Judge Enters Order of Permanent Injunction Against Paul W. Franck," news release, April 29, 2016, https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm498447.htm.

4 U.S. Department of Veterans Affairs, Office of Inspector General, "Healthcare Inspection: Oversight Review of Ophthalmology Adverse Drug Events, VA Greater Los Angeles Healthcare System, Los Angeles, California," Report No. 12-01515-151 (2012), https://www.va.gov/oig/pubs/VAOIG-12-01515-151.pdf.

5 Eric S. Kastango and Katherine H. Douglass, "Quality Standards for Large Scale Sterile Compounding Facilities" (2014), Clinical IQ LLC, http://www.clinicaliq.com/images/stories/clinicaliq_compounding%20quality%20standards.pdf.

6 Kathleen Ross et al., "Outbreak of Septic Arthritis Associated With Intra-Articular Injections at an Outpatient Practice—New Jersey, 2017," *Morbidity and Mortality Weekly Report* 66, no. 29 (2017): 777-779, http://dx.doi.org/10.15585/mmwr.mm6629a3.

7 U.S. Food and Drug Administration, "FDA Notifies Health Care Professionals That Becton-Dickinson Replaced Problematic Rubber Stoppers in Its Syringes," accessed Jan. 2, 2019, https://www.fda.gov/Drugs/DrugSafety/ucm458952.htm.

8 U.S. Food and Drug Administration, "FDA Alerts Drug Makers of a Recall of Porcine Thyroid API From Sichuan Friendly Pharmaceutical Co., Limited, China," accessed Oct. 22, 2018, https://www.fda.gov/Drugs/DrugSafety/ucm617287.htm.

9 Centers for Disease Control and Prevention, "Deaths From Intravenous Colchicine Resulting From a Compounding Pharmacy Error—Oregon and Washington, 2007," *Morbidity and Mortality Weekly Report* 56, no. 40 (2007): 1050–52, https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5640a3.htm.

10 American Society of Health-System Pharmacists, "Compounding Suppliers Issue Recalls of Products Tested by Front Range Laboratories," news release, Aug. 28, 2013, https://www.ashp.org/news/2013/08/28/compounding_suppliers_issue_recalls_of_products_tested_by_front_range_laboratories.

11 U.S. Food and Drug Administration, "Pharmakon Pharmaceuticals 5/21/15," accessed Nov. 15, 2018, https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2015/ucm448642.htm.

12 U.S. Food and Drug Administration, "FDA Announces Pharmakon Pharmaceuticals' Nationwide Voluntary Recall of Purportedly Sterile Drug Products," accessed Oct. 23, 2018, https://www.fda.gov/Drugs/DrugSafety/ucm496346.htm.

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