Insanitary Conditions at Compounding Facilities

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Compliance

August 2016
Compounding and Related Documents

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TABLE OF CONTENTS

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I. INTRODUCTION

Under section 501(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act), a drug is deemed to be adulterated "if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health."[2] Drug products prepared, packed, or held under insanitary conditions could become contaminated and cause serious adverse events, including death.

Under sections 503A and 503B of the FD&C Act, compounded human drug products can qualify for exemptions from specified provisions of the FD&C Act if certain conditions are met. However, neither section 503A nor section 503B provides an exemption from section 501(a)(2)(A) of the FD&C Act. Drugs prepared, packed, or held (hereinafter referred to as "produced") under insanitary conditions are deemed to be adulterated, regardless of whether the drugs qualify for exemptions set forth in sections 503A or 503B of the Act.[3] Any drug that is produced under insanitary conditions is adulterated under the Act, including compounded human and animal drugs; repackaged drug products; compounded or repackaged radiopharmaceuticals; and mixed, diluted, or repackaged biological products. The policies described in this guidance document specifically address pharmacies, Federal facilities, physicians' offices (including veterinarians' offices), and outsourcing facilities that compound or repackage human or animal drugs (including radiopharmaceuticals); or that mix, dilute, or repackage biological products. For purposes of this guidance, we refer to such entities as "compounding facilities."

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research, in consultation with the Office of Regulatory Affairs and the Center for Veterinary Medicine at the Food and Drug Administration.

[2] Insanitary conditions are conditions that could cause a drug to become contaminated with filth or rendered injurious to health; the drug need not be actually contaminated. A drug that is actually contaminated with any filthy, putrid, or decomposed substance is deemed to be adulterated under section 501(a)(1) of the FD&C Act.

FDA is issuing this guidance to assist compounding facilities in identifying insanitary conditions so that they can implement appropriate corrective actions. This guidance is also intended to assist State regulatory agencies in understanding some examples of what FDA considers to be insanitary conditions that could cause a drug to become contaminated or rendered injurious to health.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Public Health Risk of Insanitary Conditions

FDA has investigated numerous outbreaks of infections and deaths found to be the result of drug products that were contaminated because they were produced under insanitary conditions. Most notably, in 2012, injectable drug products produced by a compounding facility and shipped across the country caused a fungal meningitis outbreak that resulted in more than 60 deaths and 750 cases of infection. FDA has investigated numerous other serious adverse events, including deaths, associated with contaminated drug products produced by compounding facilities, and it is likely that such adverse events are underreported.

Since the 2012 fungal meningitis outbreak, FDA has identified insanitary conditions at many of the compounding facilities that it has inspected, and numerous compounding facilities have voluntarily recalled drug products intended to be sterile and temporarily or permanently ceased sterile operations as a result of those findings. However, FDA does not inspect the vast majority of compounding facilities in the United States because they generally do not register with FDA unless they elect to become outsourcing facilities.[4] Therefore, FDA is often not aware of these facilities and potential problems with their drug products, or conditions and practices, unless it receives a complaint, such as a report of a serious adverse event or visible contamination. It is critical that compounding facilities avoid the presence of insanitary conditions and identify and remediate any insanitary conditions at their facilities before the conditions result in drug contamination and patient injury.

In addition, to protect the public health, it is critical that both FDA and State regulatory agencies take appropriate action when compounders produce drugs under insanitary conditions. Based on its inspections, FDA determines whether compounding facilities produce drugs under insanitary conditions in violation of section 501(a)(2)(A) of the FD&C Act, and if so, the Agency may initiate regulatory action. However, compounding facilities that are not registered with FDA as outsourcing facilities are primarily overseen by the States and, as explained above, generally are not routinely inspected by FDA. Therefore, FDA encourages State regulatory agencies to assess during inspections whether compounding facilities that they oversee engage in poor practices,

[4] *See* section 503B of the FD&C Act.

including those described below, and if so, to take action, as appropriate, consistent with State laws and regulations, and to contact FDA.

III. POLICY

Section III.A of this guidance describes examples of conditions that would be considered insanitary conditions under section 501(a)(2)(A) of the FD&C Act. FDA has observed each of these conditions in one or more of the compounding facilities it has inspected. **These are only examples and are not an exhaustive list. Other conditions not described in this guidance may be considered insanitary**.

Section III.B of this guidance describes procedures that compounding facilities should employ to ensure that they do not have insanitary conditions and that they are capable of producing sterile drug products, and section III.C describes actions that compounding facilities should take if they identify insanitary conditions at their facilities. Finally, section III.D of this guidance describes potential FDA regulatory actions if insanitary conditions are not adequately corrected.

FDA intends to consider the entire set of conditions at the facility, including whether the facility engages in the procedures described in section III.B, when prioritizing regulatory action against a compounding facility for producing drugs under insanitary conditions.

A. Examples of Insanitary Conditions[5]

1. Insanitary Conditions Applicable to the Production of Sterile and/or Non-Sterile Drugs

Although maintaining sterility is not a requirement for non-sterile drugs, non-sterile drugs can become contaminated with microorganisms of a type or at a level that can cause patient harm. Non-sterile aqueous solutions are particularly susceptible to microbial growth if contaminated. Contamination may also include non-viable filth and the presence of unintended drug components. The following are examples of insanitary conditions that are applicable to both sterile and non-sterile drug production.

- Vermin (e.g., insects, rodents) observed in production areas or areas immediately adjacent to production.
- Visible microbial contamination (e.g., bacteria, mold) in the production area.
- Non-microbial contamination in the production area (e.g., rust, glass shavings, hairs).
- Handling beta-lactam, hazardous, or highly potent drugs (e.g., hormones) without providing adequate containment, segregation, and cleaning of work surfaces, utensils, and personnel to prevent cross-contamination.
- Production of drugs while construction is underway in an adjacent area without adequate controls to prevent contamination of the production environment and product.

[5] For definitions of some of the terms used in this section, refer to United States Pharmacopeia (USP) Chapter <797>.

2. Insanitary Conditions in a Sterile Operation

a. Aseptic Practices

- Putting on gowning apparel improperly, in a way that may cause the gowning apparel to become contaminated. This includes, for example, gowning in non-classified areas, gowning apparel touching the floor, or putting on sterile gloves improperly (e.g., touching the outside of a glove with bare hands).
- Failing to disinfect or change gloves frequently enough given the nature of the operations to prevent contamination.
- Engaging in aseptic processing wearing non-sterile gloves. This could contaminate the critical area.[6]
- Engaging in aseptic manipulations with exposed hands, wrists, legs, hair, or mouth, for example.
- Performing aseptic manipulations outside of an International Organization for Standardization Class 5 (ISO 5) area.
- Exposing unprotected sterile product, including stock solutions, to lower than ISO 5 quality air (e.g., removing it from the ISO 5 area without a robust and intact container closure system).
- Engaging in aseptic processing after leaving the cleanroom and re-entering from a non-classified area without first replacing gowning apparel (e.g., sterile gloves, gowns, mask, foot covers). Movement of personnel in and out of the cleanroom without regowning may bring contaminants from the non-classified areas into the cleanroom.
- Moving quickly in the vicinity of open containers or instruments (e.g., needles). While conducting aseptic manipulations, ISO 5 airflow must be unidirectional to protect the product from contaminating particles. Quick movement of personnel disrupts the airflow and increases the risk of bringing lesser quality air into the ISO 5 area.
- Conducting aseptic manipulations or placing equipment/supplies in an area that blocks the movement of first pass air around an open container, whether before or after it is filled with sterile product. If unidirectional air over the critical surface is blocked, the area is no longer protected. If it is blocked by personnel conducting aseptic manipulations, contamination on personnel, particularly on exposed skin, could be introduced to the critical area.
- Using a non-sterile tool or manually contacting the inner surface of the container or closure. For example, during manual stoppering (e.g., hand stoppering), personnel touching the top of open containers, or the lower side or bottom of closures. This could contaminate the drug in the vials.
- Touching equipment or other surfaces (e.g., walls, telephone, floors) located outside of the ISO 5 area with gloved hands and then proceeding with aseptic manipulations without changing or sanitizing gloves.

[6] A *critical area* is an area designed to maintain sterility of sterilized materials. Sterilized product, containers or closures, and equipment may be exposed in critical areas. The ISO 5 area is the critical area, and the terms are used interchangeably throughout this guidance.

- Storing open sterile vials within the critical area without protective cover longer than needed for the process of filling drug product. The longer a vial is open to the environment, the greater the risk of contamination.
- Failure to disinfect container closure systems of sterile drug components immediately prior to opening for use.

b. Equipment/ Facilities

- Actionable microbial contamination of the ISO 5 area or in adjacent areas.
- Cleanroom with unsealed, loose ceiling tiles.
- ISO classified areas with difficult to clean (e.g., porous), particle-generating, or visibly dirty (e.g., rusty) equipment or surfaces such as shelving, floors, walls, doors, window sills, and ceilings. For example, wood is both difficult to clean and particle-generating.
- Classified areas and segregated production areas surrounding the ISO 5 area that contain dust-collecting overhangs (e.g., utility pipes or ledges, such as windowsills).
- ISO 5 area open to the surrounding cleanroom with minimal or no physical barriers separating it from non-aseptic activities (e.g., non-aseptic weighing materials, gowning, container labeling).
- ISO 5 area open to non-classified rooms (segregated production area). Lower quality air from the surrounding room entering the ISO 5 area increases the risk of introducing microbial contamination into drug products being manipulated.
- A facility designed and/or operated in a way that permits poor flow of personnel or materials, or allows the influx of poor quality air into a higher classified area. Examples include:
  - materials flow into the ISO 7 area directly from an unclassified area;
  - air return located next to the high efficiency particulate arrestance (HEPA) filter rather than near the floor;
  - an air vent between classified and unclassified areas;
  - a door opened between the unclassified area and the ISO 8 anteroom while the door between the ISO 7 and ISO 8 areas is also open;
  - inadequate pressure differentials between areas of higher quality air and lower quality air.
- A lack of HEPA-filtered air, or inadequate HEPA filter coverage or airflow, over the area to which sterile product is exposed.
- HEPA filters that are not sealed around each perimeter to the support frame. The air entering the cleanroom must be HEPA filtered to remove airborne particles. If HEPA filters are not sealed, air that is not HEPA filtered could enter the cleanroom.
- The presence of sinks or drains in the cleanroom where the ISO 5 area is located. Sinks and drains are sources of microbial contamination.
- Use of non-sterilized or non-depyrogenated equipment (e.g., transfer tubing, temporary bulk containers). Use of such equipment can introduce or increase bioburden and endotoxins.
- Use of non-sterilized or non-depyrogenated final containers/closures. Use of such container/closures could contaminate the drug product after it has been sterilized.

c. Sterilization

- The "sterilizing filter" is not adequate to accomplish sterilization and is not pharmaceutical grade.
- Temperature and time conditions used for heat sterilization are not lethal to heat-resistant microorganisms.

d. Cleaning and Disinfecting

- Non-sterile disinfecting agents and cleaning pads or wipes are used in the aseptic processing areas, especially the ISO 5 area. Non-sterile cleaning and disinfecting items could spread microbial spores.
- No, improper, or infrequent, use of a sporicidal agent in the facility's cleanrooms and ISO 5 area.
- No disinfection of equipment and/or supplies entering the aseptic processing areas. Disinfection should occur at each transition from areas of lower quality air to areas of higher quality (e.g., from non-classified to first classified room, from anteroom to buffer room, from buffer room to ISO 5 area).
- Disinfectant contact time (also known as "dwell time") and coverage of the item being disinfected are insufficient to achieve adequate levels of disinfection. The use, including contact time, of commercially-obtained disinfectants should follow the manufacturer's instructions.

B. Identifying Insanitary Conditions

Certain procedures are critical to ensuring that compounding facilities do not have insanitary conditions that could compromise drug sterility and that they are capable of producing sterile drug products. FDA recommends that compounding facilities that produce drugs that are intended to be sterile routinely employ these procedures to help ensure that they can produce sterile products. A non-exhaustive list of such procedures follows.

1. Conduct routine[7] environmental monitoring, including a) nonviable airborne particulate sampling; b) viable airborne particulate sampling; c) personnel sampling (including glove fingertip sampling); and d) surface sampling, including but not limited to equipment, work surfaces, and room surfaces. Environmental monitoring provides information on the quality of the aseptic processing environment and, if problematic, the compounding

[7] For compounding facilities that are not registered with FDA as outsourcing facilities, see USP Chapter <797>. For outsourcing facilities, see FDA's draft guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* ("interim CGMP draft guidance"). Once final, this guidance will represent FDA's current thinking regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until FDA promulgates CGMP regulations that are more specific to outsourcing facilities.

This interim CGMP draft guidance states that outsourcing facilities should conduct environmental monitoring of the ISO 5 area at least daily. FDA recommends that compounding facilities that are not registered as outsourcing facilities also conduct daily environmental monoitoring during operations.

facility should promptly identify potential routes of contamination and perform corrective actions.

2. Certify the ISO 5 area every six months. If the ISO 5 area is not certified every six months or does not pass all certification requirements, there is no assurance that the ISO 5 area is working properly (e.g., generating unidirectional ISO 5 airflow). Smoke studies should be conducted as part of the certification to assess the airflow patterns necessary to maintain unidirectional flow from areas of higher air quality (e.g., ISO 5) to areas of lower air quality (e.g., ISO 7) to prevent microbial contamination of the sterile drug products during processing. Conducting smoke studies under dynamic conditions helps to ensure that unidirectional airflow is maintained while personnel are working in the ISO 5 area.

3. Measure pressure differentials during operations to help ensure proper airflow (i.e., from areas of higher quality air to adjacent areas with lower quality air).

4. Conduct media fill studies to closely simulate aseptic production operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations.

C. Corrective Actions

A compounding facility should immediately assess the impact of insanitary conditions on drug products produced, which should include an evaluation of how widespread the insanitary conditions are and over what period of time the conditions existed.

The compounding facility also should determine whether to cease production of drug products until the conditions have been corrected and initiate a recall of all potentially affected lots on the market.

For example, FDA considers the following insanitary conditions to be particularly serious, and if any one of these conditions exists, FDA strongly recommends that a compounding facility immediately initiate a recall of purportedly sterile drugs and cease sterile operations until the condition(s) have been corrected:

- Vermin (e.g., insects, rodents) observed in ISO 5 areas or in immediately adjacent areas.
- Visible microbial contamination (e.g., bacteria, mold) in the ISO 5 area or in immediately adjacent areas.
- Non-microbial contamination in the ISO 5 area (e.g., rust, glass shavings, hairs).
- Performing aseptic manipulations outside of the ISO 5 area.
- Exposing unprotected sterile product, including stock solutions, to lower than ISO 5 quality air (e.g., removing it from the ISO 5 area without a robust and intact container closure system).
- Cleanroom areas with unsealed, loose ceiling tiles.

- Production of drugs while construction is underway in an adjacent area without adequate controls to prevent contamination of the production environment and product.
- Consistent and frequent pressure reversals from areas of less clean air to areas of higher cleanliness.
- The "sterilizing filter" is not adequate to accomplish sterilization and is not pharmaceutical grade.
- Temperature and time conditions used for heat sterilization are not lethal to heat-resistant microorganisms.

If a compounding facility decides to initiate a recall, it should notify its local FDA District recall coordinator as soon as the decision to recall is made.[8] The compounding facility should also notify the applicable State regulatory body in the State(s) to which the facility ships drugs, consistent with State laws and guidance.

In addition to the immediate actions recommended above, if a compounding facility has insanitary conditions, it should undertake a comprehensive assessment of its operations, including, as applicable, facility design, procedures, personnel, processes, materials, and systems, and should consider consulting a third party with relevant drug production expertise to conduct this comprehensive evaluation and to assist in implementing appropriate corrective actions.

Compounding facilities producing purportedly sterile drug products under insanitary conditions should not rely on a passing sterility test as an indication of sterility assurance because microbial contamination, when present, is not uniformly distributed within a batch and may not be identified by a sterility test. Furthermore, compounding facilities must correct all insanitary conditions at their facility,[9] regardless of whether the drugs pass a sterility test.[10]

D. Regulatory Action

If a compounding facility produces drugs under insanitary conditions, the facility and responsible individuals may be subject to Federal regulatory actions including, but not limited to, a warning letter, seizure of product, and/or injunction. FDA may also recommend that the facility initiate a recall of some or all of its drugs and cease operations until the insanitary conditions have been adequately addressed. In addition, the applicable State regulatory agency may pursue regulatory action against the facility under applicable State authorities.

[8] *See* the FDA guidance, *Product Recalls, Including Removals and Corrections*.

[9] *See* section 501(a)(2)(A) of the FD&C Act.

[10] USP Chapter <71> concerning sterility testing states, "these Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by validation of the sterilization process or of the aseptic processing procedures."