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DRAFT GUIDANCE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
Office of Compliance

September 2018
Compounding and Related Documents
Revision 1

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Contains Nonbinding Recommendations

Draft — Not for Implementation

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or the Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed in the title page.

I. INTRODUCTION

Under section 501(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 351(a)(2)(A)), 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 (21 U.S.C. 353a and 353b), compounded human drug products can qualify for exemptions from specified provisions of the FD&C Act if certain conditions are met. However, neither section provides an exemption from section 501(a)(2)(A) of the FD&C Act. Drugs (including biological products) 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 FD&C Act.

This guidance describes examples of insanitary conditions that FDA has observed. This guidance specifically addresses drugs (including biological products) produced by pharmacies, federal facilities, and outsourcing facilities that compound or repackage drugs, or that mix, dilute, or repackage biological products.[3] 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 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 itself need not actually be 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 (21 U.S.C. 351(a)(1)).

[3] FDA generally does not intend to take action under section 501(a)(2)(A) against a physician who is compounding or repackaging a drug product, or who is mixing, diluting, or repackaging a biological product, provided that such activities occur in the physician's office where the products are administered or dispensed to his own patients.

FDA is issuing this guidance to help compounding facilities identify insanitary conditions so that they can implement appropriate corrective actions. This guidance is also intended to help state regulatory agencies understand some examples of what FDA has considered 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 750 cases of infection and 60 deaths. FDA has investigated numerous other serious adverse events, including deaths, associated with contaminated drug products produced by compounding facilities, and it is likely that additional 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 because of those findings. FDA does not inspect the vast majority of compounding facilities in the United States because they generally are not registered with FDA unless they are outsourcing facilities.[4] Therefore, unless FDA receives a complaint, such as a report of a serious adverse event or visible contamination, the Agency is often not aware of these facilities, their conditions and practices, and potential problems with the quality and safety of their drug products. It is critical that compounding facilities avoid 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, both FDA and state regulatory agencies may take action when compounding facilities 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. FDA strongly 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 to take appropriate action, consistent with state laws and regulations and to contact FDA.

III. POLICY

Section III.A of this guidance provides examples of conditions that FDA has observed at one or more compounding facilities it has inspected and has considered to be insanitary conditions under section 501(a)(2)(A) of the FD&C Act. **These examples do not constitute an exhaustive list of insanitary conditions that could be present in a compounding facility; other conditions not described in this guidance may be considered insanitary**.

Section III.B of this guidance describes corrective actions that compounding facilities should take when they identify insanitary conditions. Of note, this section includes a list of particularly concerning conditions that FDA has observed. FDA strongly recommends that a facility immediately recall purportedly sterile drugs and cease sterile operations until these conditions have been remediated.

Finally, section III.C of this guidance discusses regulatory actions FDA may take in response to insanitary conditions we identify. Although FDA expects all insanitary conditions to be remediated in a timely manner, FDA considers the entire set of conditions at the facility, including any aggravating and mitigating factors, as well as evidence of timely and appropriate remediation activities, when determining the type of regulatory action to take against a compounding facility.

Note that the examples of insanitary conditions described in this guidance for products intended to be sterile can exist in cleanroom and associated controlled environments, as well as segregated compounding areas (SCAs), as described in United States Pharmacopeia (USP) Chapter <797> (USP <797>). However, when a compounding facility other than an outsourcing facility produces drugs in a SCA, FDA generally does not intend to take action with respect to certain conditions described in this guidance identified with an asterisk (*), provided that the compounding facility: (1) complies with all criteria for an SCA in USP <797>; (2) assigns beyond-use-dates that do not exceed 12 hours when stored at room temperature and 24 hours when refrigerated or frozen; and (3) does not have any additional insanitary conditions.

A. Examples of Insanitary Conditions[5]

1. Insanitary Conditions Applicable To the Production of Sterile and Non-Sterile Drugs

Although product sterility is not a requirement for non-sterile drugs, it is possible for non-sterile drugs to 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

[5] Note that USP <797> provides descriptions of select terms used in this section, including buffer room and anteroom.

drug components. The following are examples of insanitary conditions that have been observed and are applicable to both sterile and non-sterile drug production.

- Vermin (e.g., insects, rodents) or other animals (e.g., dogs) in the production area[6] or adjacent areas

- Visible microbial contamination (e.g., bacteria, mold) in the production area or adjacent areas

- Sources of non-microbial contamination in the production area (e.g., rust, glass shavings, hairs, paint chips)

- Producing drugs while construction is underway in an adjacent area without adequate controls to prevent contamination of the production area and product

- Standing water or evidence of water leakage in the production area or adjacent areas

- Handling hazardous, sensitizing, or highly potent drugs (e.g., hormones) with inadequate controls to prevent cross-contamination, including:

    - inadequate dedication, segregation, and containment (e.g., a powder-containment hood) of a suite, room, or piece of equipment based on risk;
    - inadequate cleaning of rooms, work surfaces, and equipment (e.g., utensils);
    - inadequate segregation of HVAC systems (as appropriate for the operation);
    - inadequate control over the movement of personnel and materials; and
    - open processing of beta-lactams without complete and comprehensive separation from non-beta-lactam products.

- Using ingredients, both active and inactive ingredients, or processing aides, that have or may have higher levels of impurities compared to compendial or pharmaceutical grade equivalents (e.g., ingredients with potentially harmful impurities, ingredients labeled with "not for pharmaceutical use" or an equivalent statement)

2. Insanitary Conditions Applicable to the Production of Sterile Drugs

a. Gowning and Aseptic Practices

- Engaging in aseptic processing wearing critical gown components (e.g. gloves, masks) that are non-sterile

- Putting on gowning apparel in a way that may cause the gowning apparel to become contaminated, including:

[6] For the purpose of this guidance, FDA regards *production area* with respect to sterile compounding as any International Standard Organization (ISO)-classified area or SCA and with respect to non-sterile compounding as any room or area in which non-sterile compounding occurs.

  - gowning in non-classified areas*
  - allowing gowning apparel (except for foot covers) to touch 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. This includes, for example, gloves exiting and re-entering the International Standard Organization Class 5 (ISO 5) area without changing or sanitizing them, touching a non-sterile object and returning to compounding without first changing or sanitizing gloves, cleaning up after a spill without changing gloves when returning to compounding, and not changing the sterile gloves when glove integrity may have been compromised

- Engaging in aseptic processing after leaving the cleanroom and re-entering from a non-classified area without first replacing gowning apparel (e.g., gowns, mask, goggles, foot covers, gloves)[7]*

- Performing aseptic manipulations with exposed hair or skin (e.g., on hands, wrists, forehead, mouth, or legs)

- Performing aseptic manipulations outside of a certified ISO 5 area (or area of higher quality air)

- Conducting aseptic manipulations in an area where the movement of "first air"[8] in the ISO 5 area is blocked or disrupted (e.g., by equipment, supplies, or operator manipulations)[9,10]

- Exposing sterile drugs and materials to lower than ISO 5 quality air. This would include, for example, exposing partially stoppered drug products or stock solutions in a container/closure system that is not fully closed (airtight), and open packages of sterile wipes.

- Failing to disinfect containers of sterile drug components or supplies immediately prior to opening for any use in operations

[7] Note that personnel moving in and out of the cleanroom without regowning may bring contaminants from non-classified areas into the cleanroom.

[8] *First air* means air that is from a HEPA filter and that has not yet contacted any items/surfaces.

[9] Note that 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 could be introduced to the critical area.

[10] FDA does not intend to object to the temporary blocking or disruption of first air in the ISO 5 area when necessary for the safe handling of radiopharmaceuticals, such as the placement of a shielding material for the radiopharmaceutical in the ISO 5 area.

- Failure to use pre-sterilized or sterilized primary containers and closures to fill sterile products

- Using a non-sterile tool, manually contacting the inner surface of a sterile container or closure, or manually touching a product contact surface

    - This includes, for example, touching the top of an open container, or the lower side or bottom of a closure during manual stoppering (e.g., hand stoppering)[11]

- Moving quickly in a critical area or in an area immediately adjacent to a critical area[12] such that unidirectional airflow is likely to be disrupted[13]

- Staging open sterile vials within the critical area without protective cover longer than needed for the process of filling drug product

b. Equipment/Facilities

- Actionable microbial contamination of the ISO 5 area

- Lack of adequate routine environmental monitoring[14]

    - This includes nonviable airborne particulate sampling; viable airborne particulate sampling; and surface sampling, including but not limited to equipment, work surfaces, and room surfaces

- Lack of adequate personnel sampling (including glove fingertip sampling)

- Lack of routine certification of the ISO 5 area, including smoke studies performed under dynamic conditions[15]

- A facility designed or operated in a way that permits the influx of lesser quality air into a higher quality air area, including:

[11] Note that this could contaminate the drug in the vials even with the use of sterile gloves and appropriate glove sanitization.

[12] 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.

[13] Note that 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.

[14] Note that environmental monitoring provides information on the quality of the aseptic processing environment. If the results reflect a poor quality aseptic processing environment, the compounding facility should promptly identify potential routes of contamination and perform corrective actions.

[15] Note that if the ISO 5 area is not periodically re-certified or does not pass all certification requirements, there is insufficient assurance that the ISO 5 area filters are functioning and delivering the quality of air intended.

  - inadequate pressure differentials between areas of higher quality air and lower quality air*
  - material flow directly from an unclassified area into a room in which sterile compounding is conducted*
  - an ISO 5 area open to the surrounding area with minimal or no physical barriers separating it from non-aseptic activities (e.g., weighing of non-sterile materials, gowning, container labeling)
  - air returns located next to the high efficiency particulate arrestance (HEPA) filter rather than near the floor*
  - an open door or series of open doors between an uncontrolled area and the room in which sterile compounding is conducted*

- Failure to detect and adequately address a change in air quality (e.g, through the environmental monitoring program) of any classified area before there is a loss of environmental control that may impact drug sterility

- No or infrequent measurement of pressure differentials during operations to demonstrate proper airflow (i.e., airflow from areas of higher quality air to adjacent areas with lower quality air)*

- A lack of HEPA-filtered air, or inadequate HEPA filter coverage or airflow, over the critical area

- HEPA filters that are not sealed around the perimeter[16]

- Rooms not properly classified for the activities conducted within them

- Unsealed or loose ceiling tiles in production areas

- Production areas or equipment that are difficult to clean or contain porous, particle-generating, or visibly dirty (e.g., rusty) equipment or surfaces (e.g., shelving, floors, walls, doors, ceilings)

- Buffer room or ISO 5 areas that contain overhangs or ledges capable of collecting dust (e.g., utility pipes and horizontal surfaces, such as windowsills)

- The presence of sinks, drains, or water sources in the buffer room where the ISO 5 area is located; the presence of floor drains in the anteroom[17]

- The presence of equipment unnecessary for aseptic operations, particularly particle-generating equipment, in the ISO 5 area

[16] Note that the air entering the cleanroom needs to be HEPA filtered to remove airborne particles. If HEPA filters are not sealed, air that is not HEPA filtered could enter the cleanroom.

[17] Note that sinks and drains are sources of microbial contamination.

- Equipment within or in close enough proximity to the ISO 5 area that could compromise the air in the ISO 5 area

- Exposing sterile products to non-sterile or non-depyrogenated supplies (e.g., transfer tubing, temporary bulk containers)

  - Using lyophilizers that are not sterilized by routine sterilization cycles and protected from contamination by sterilizing filters on vacuum break air lines/vents

c. Sterilization

  - Using a filter for the purposes of product sterilization that is not certified as both sterilizing-grade and pharmaceutical-grade, or using a sterilizing-grade and pharmaceutical-grade filter in a manner that is not adequate to accomplish sterilization (e.g., using it in excess of its capacity or when it is clogged)

  - Using a filter in drug production whose integrity is compromised; failing to conduct post-use filter-integrity testing on filters used to sterilize products

  - Using a particle-shedding filter in any stage of sterile drug production

  - Using parameters for sterilization (e.g., temperature, pressure, and time) that are not lethal to resistant microorganisms

d. Cleaning and Disinfecting

  - Using non-sterile disinfecting agents and cleaning pads/wipes in ISO-classified areas

  - Lack of, improper, or infrequent use of a sporicidal agent in the facility's ISO 5 areas and other classified areas

  - Failing to appropriately and regularly clean and disinfect (or sterilize) equipment located in the ISO 5 area

  - Lack of disinfection of equipment and/or supplies 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)

  - Using disinfectant in a manner insufficient to achieve adequate levels of disinfection (e.g., using insufficient disinfectant contact time (also known as "dwell time"), concentration, or coverage of the item/surface being disinfected)

  - Using sterile cleaning and disinfecting agents past their expiry date or "discard after opening" date

- Using cleaning and disinfecting agents that may leave residues or not adequately rinsing such agents from containers, closures, or equipment that come into direct contact with drugs

e. Other Insanitary Conditions

- Allowing operators with topical or respiratory infections or with open wounds to work within compounding operations

- Compounding with components, containers, or other materials that have not been verified to assure that they do not contribute endotoxin contamination that may be objectionable given the product's intended use

- Compounding under processing conditions that offer insufficient assurance that the finished product will meet an endotoxin specification appropriate for its route of administration

- Failure to conduct media fill studies to closely simulate aseptic production operations under the worst-case, most-challenging and stressful conditions

B. Corrective Actions for Insanitary Conditions

Upon identifying insanitary conditions, a compounding facility should immediately assess the impact of the insanitary conditions on drug products produced. The compounding facility's assessment should include an evaluation of how widespread the insanitary conditions are and over what period of time the conditions have existed, as well as the lots of drug product that remain on the market that could be affected.

The compounding facility should also determine whether to cease production of drug products until the conditions have been corrected and whether to initiate a recall of all potentially affected lots on the market. Below is a list of insanitary conditions that FDA has observed and considered to be particularly serious. 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 has been corrected.

- Vermin (e.g., insects, rodents) or other animals (e.g., dogs) in ISO 5 areas or areas immediately accessible to production

- Visible microbial growth (e.g., bacteria, mold) in the ISO 5 area or in immediately adjacent areas

- Sources of non-microbial contamination in the ISO 5 area (e.g., rust, glass shavings, hairs, paint chips)

- Performing aseptic manipulations outside of a certified ISO 5 area or area of higher quality air

- Exposing sterile drugs and materials to lower than ISO 5 quality air for any length of time. This would include, for example, exposing partially stoppered drug products or stock solutions in a container/closure system that is not fully closed (airtight), and open packages of sterile wipes.

- Cleanroom areas with unsealed or loose ceiling tiles

- Production of drugs while construction is underway in an adjacent area without adequate controls to prevent contamination of the production area and product

- Consistent and frequent pressure reversals from areas of less clean air to areas of higher cleanliness

- Using a filter for product sterilization that is not certified as pharmaceutical-grade and sterilizing-grade

- Using a certified pharmaceutical-grade and sterilizing-grade filter in a manner that is not adequate to accomplish sterilization (e.g., using it in excess of its capacity, when it is clogged)

- Using parameters for sterilization (e.g., temperature, pressure, time) that are not lethal to resistant microorganisms

If a compounding facility decides to initiate a product recall, it should immediately notify its local FDA Drug Division recall coordinator.[18] 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 identifies insanitary conditions, it should comprehensively assess its operations, including facility design, procedures, personnel, processes, materials, and systems, as applicable. FDA recommends that the facility consider consulting a third party with relevant drug production expertise to conduct this comprehensive evaluation and to help implement appropriate corrective actions.

Compounding facilities producing purportedly sterile drug products under insanitary conditions should not rely upon or cite a passing sterility test result as an indication of product sterility. Microbial contamination, when present, is not uniformly distributed within a batch; therefore, it may not be identified in a sterility test.[19] Compounding facilities must correct all insanitary conditions at their facility regardless of whether the drugs pass a sterility test.

[18] See guidance for industry *Product Recalls, Including Removals and Corrections*.

[19] USP Chapter <71> concerning sterility testing states, "[t]hese 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."

C. Regulatory Action

If a compounding facility produces drugs under insanitary conditions, the facility and responsible individuals may be subject to several regulatory actions, including, but not limited to, a warning letter, seizure of product, 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. The applicable state regulatory agency may also pursue regulatory action against the facility under applicable state authorities.