Date of This Update: June 23, 2023

FDA Citations/Recalls/Warning Letters Relevant to Microbiological Issues

Reason for Recall/Warning Letter may be redacted to remove information identifying specific companies.
https://www.accessdata.fda.gov/scripts/ires/index.cfm

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Product Type	Citation [C], Recall [R], Warning Letter [WL]	Reason for Citation/Recall/Warning Letter
Devices	**R**	DuraLife devices instructions for cleaning and sterilization have been determined to be inadequate. Specifically, for the DuraLife product, the IFU does not provide the cleaning method, duration of autoclave cycle or specify the number of cycles the product can be reused on a single patient.
Devices	**R**	Optical Trocars sterility assurance can not be guaranteed
Devices	**R**	3M Attest Steam Chemical Integrators with dates of manufacture between November 6, 2022 and January 17, 2023 have an increased potential to leak ink during a sterilization cycle.
Devices	**R**	The liquid buffer component in the affected test kit lots was determined to have bacterial contamination. User may notice a slight odor when the buffer is brought close to the nose.
Devices	**R**	1. An accessory may be improperly placed during packaging, causing creases and damage to the accessory's sterile pouch. 2. Product packaging may exhibit holes, cracks, dents, and crushed areas.
Devices	**R**	Some catheters had a manufacturing defect where the clear resealing label separating from the product foil pouch, resulting in a possible opening into the product packaging that could impact product sterility.
Devices	**WL**	ii. Your firm has not established adequate procedures for risk analysis, as required by 21 CFR 820.30(g). Specifically, your firm manufactures the OsseoConduct bone graft material which is labeled to be an implantable, sterile, biocompatible, and pyrogen free device. However, the risk analysis documented in your Design History File dated June 1, 2017, does not identify any foreseeable hazards associated with the use of this device. Your November 21, 2022 response is inadequate because the “Risk Management Plan” you provided does not identify reasonably foreseeable hazards with your implantable sterile device. b. Your firm uses a (b)(4) process to sterilize your Oral Bond and Socket Graft devices. Your firm does not have records demonstrating these processes were validated as set forth in your firm’s “Process Validation,” SOP 018 and as required by 21 CFR 820.75(b)(1). c. Your firm uses a (b)(4) sterilization process to sterilize your OsseoConduct device. Your firm does not have records demonstrating this process has been validated as set forth in your firm’s “Process Validation,” SOP 018 and as required by 21 CFR 820.75(b)(1). This is a repeat observation from the FDA inspection conducted December 10-13, 2018, and a violation listed on the Untitled Letter issued to your firm on April 3, 2019. We reviewed your firm’s response dated November 21, 2022, and conclude it is not adequate. Your response is limited to a description of (b)(4) activities purportedly conducted; however, it does not describe the specific processes used or include a protocol indicating critical process parameters to support the process is validated. Additionally, your response does not include a systemic evaluation of your firm’s manufacturing processes to ensure all processes requiring validation have been validated. Finally, your response did not include procedures establishing any specific requirements for the sterilization process validation for each of your devices.
Drugs	**R**	Lack of Assurance of Sterility: Malformed crimped collar seal
Drugs	**R**	Lack of Assurance of Sterility
Drugs	**R**	Lack of Assurance of Sterility: after an FDA inspection called into question the sterility of the products intended to be sterile.
Drugs	**R**	Lack of Assurance of Sterility
Drugs	**R**	Lack of assurance of sterility: The product was potentially exposed to below-recommended storage temperatures, which may cause leaks in the packaging.
Drugs	**R**	Lack of Assurance of Sterility: Tamper Evidence Seal is missing on secondary container.
Drugs	**C**	Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed.

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Product Type	**Citation [C], Recall [R], Warning Letter [WL]**	**Reason for Citation/Recall/Warning Letter**
Drugs	**WL**	1. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes. Your firm also failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups in aseptic processing areas (21 CFR 211.113(b) & 211.42(c)(10)). 3. Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release, and conduct for each batch of drug product, appropriate laboratory testing, as necessary, required to be free of objectionable microorganisms. (21 CFR 211.165(a) and 21 CFR 211.165(b)).
Drugs	**WL**	You failed to adequately establish and follow procedures for growth promotion testing of your microbiological media to assure suitability before use, including failing to establish appropriate challenge conditions and acceptance criteria to ensure the media could support appropriate growth. For example, your growth promotion testing conducted on July 13, 2022, for Salmonella media lot number (b)(4), identified light and moderate growth for the challenge organisms including Escherichia coli. You accepted the lot for use without noting the deviation as required by your established procedure that specifies the growth of Escherichia coli should be inhibited. Further, you also failed to conduct growth promotion for each lot of media received. Additionally, you did not validate your alternative microbial methods used to test drug products to assure the methods were equivalent to or better than USP methods. Specifically, you failed to adequately establish that your microbiological testing methods can reliably detect objectionable microorganisms. For example, Lab Numbers (b)(4) and (b)(4) were samples of (b)(4) drug products marketed for pre- and post-surgical oral care and intended for use with patients who are particularly susceptible to infection. Your microbial method failed to detect Burkholderia cepacia complex (Bcc), and you reported “Not Detected” to your client. Subsequently, you sent microbial subcultures from these samples to another external laboratory that detected Burkholderia contaminans in both samples, a species that is part of Bcc. The ability of microbial testing methods to detect objectionable microorganisms in the presence of each drug product to be tested must be established and validated.

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Product Type	Citation [C], Recall [R], Warning Letter [WL]	Reason for Citation/Recall/Warning Letter
Drugs	**WL**	FDA investigators noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigators observed: 1. An operator rested their hands on the work surface of the hood during aseptic production. 2. An operator placed components and equipment within the ISO 5 work area that had the potential to block the movement of first air to critical in-process operations. 3. Your firm failed to perform adequate smoke studies under dynamic conditions to demonstrate unidirectional airflow within the ISO 5 area. Therefore, your products intended to be sterile are produced in an environment that may not provide adequate protection against the risk of contamination. 4. Your aseptic processing areas included areas that were difficult to clean, including but not limited to, scratches on the work surfaces of all (b)(4) laminar flow hoods. 5. Pools of unidentified liquid on the floors of classified rooms in clean status. 6. Your facility is maintained in a way that may permit the influx of lesser quality air into a higher quality air area and fails to prevent pests from entering classified spaces. Your firm had at least five documented instances where pests were found in the “compounding suite” from June 2020 through September 2021. 7. Multiple air returns in your ISO 7 “compounding room” were observed to be either fully or mostly blocked by your laminar flow hoods. 3. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)). 4. Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42(c)(10)(v)). 5. Your firm failed to maintain buildings used in the manufacture, processing, packing, or holding of drug products in a good state of repair (21 CFR 211.58). 6. Your firm failed to establish an adequate air supply filtered through high-efficiency particulate air filters under positive pressure in the aseptic processing areas (21 CFR 211.42(c)(10)(iii)).
Drugs	**WL**	Your response is inadequate. You fail to provide scientific evidence demonstrating your interim cleaning procedure will sufficiently remove potential contaminants, such as product residues, cleaning and sanitizing agents, and objectionable organisms. You also did not provide your cleaning validation protocol indicating the relevant sources of risk, predetermined acceptance criteria, acceptable amount of time for storing dirty equipment, and other considerations relevant to your equipment cleaning program. Furthermore, you fail to assess the impact of your inadequate cleaning processes on product that is currently on the market and within expiry.

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Drugs	**WL**	The FDA investigator noted that drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigator observed the following: 1. Your firm produced drug products with materials that had not been verified to assure that they did not contribute endotoxin contamination that may be objectionable given the product's intended use. 2. Your facility design allowed the influx of poor-quality air into a higher classified area. 3. Your firm used non-pharmaceutical grade components in the formulation of non-sterile drug products. 4. Your media fills were not performed under the most challenging or stressful conditions. Therefore, there is a lack of assurance that your firm can aseptically produce drug products within your facility. 5. Your ISO-5 classified areas were not certified under dynamic conditions.

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Product Type	Citation [C], Recall [R], Warning Letter [WL]	Reason for Citation/Recall/Warning Letter
Food & Beverages	**WL**	1. You failed to meet the requirement to test spent sprout irrigation water from each production batch of sprouts for E. coli O157:H7 and Salmonella spp. or, if such testing is not practicable, test each production batch of sprouts at the in-process stage (i.e., while sprouts are still growing) for E. coli O157:H7 and Salmonella spp., in accordance with the requirements of 21 CFR 112.147, as required by 21 CFR 112.144(b), using a method described in 21 CFR 112.153(a). Specifically, you stated that you do not conduct spent sprout irrigation water testing or in-process testing for your spicy sprout blend, your broccoli sprouts or your sunflower shoots. Further, you stated you have not conducted any testing on your spicy sprout blend, your broccoli sprouts or your sunflower shoots since April of 2022. From April 21, 2022, to December 23, 2022, you produced your spicy sprout blend (b)(4) times, your broccoli sprouts (b)(4) times and your sunflower shoots (b)(4) times. You sold these sprouts without conducting spent sprout irrigation water testing or any in-process testing. 2. You did not test the spent sprout irrigation water (or sprouts) from each production batch of sprouts for Salmonella spp. using either (1) the method of analysis described in "Testing Methodologies for E. coli O157:H7 and Salmonella species in Spent Sprout Irrigation Water (or Sprouts)," Version 1, October 2015, FDA or (2) a scientifically valid method that is at least equivalent to this method of analysis in accuracy, precision, and sensitivity, as required by 21 CFR 112.153(a). Specifically, on November 22, 2022, following PCR analysis, you received a presumptive positive test result for Salmonella spp. in your spent sprout irrigation water from lot 4211 of alfalfa sprouts. Neither you nor your third-party laboratory conducted a culture confirmation test on the presumptive positive sample by using a method of analysis described in the "Testing Methodologies for E. coli O157:H7 and Salmonella species in Spent Sprout Irrigation Water (or Sprouts)," Version 1, October 2015 or a scientifically valid method that is at least equivalent to this method of analysis in accuracy, precision, and sensitivity, as required by 21 CFR 112.153(a). Rather, you collected a new sample of spent sprout irrigation water for lot 4211 on November 22, 2022, and submitted it for analysis. Following the new sample showing a negative analysis result for Salmonella spp., you released the product for shipment into interstate commerce to your customers, including ones located in Kansas, Iowa, and Missouri. Because the samples were collected from the same production batch as the presumptive positive, that batch should be considered presumptive positive. A negative test result does not negate a previous positive test result from the same batch.
Food & Beverages	**WL**	We reviewed the Food Safety Plan you provided as part of your response and found your plan is inadequate. Despite your recent recall, our Form FDA 483, and our investigator's discussion with you during the closeout meeting about Clostridium botulinum as a known or reasonably foreseeable hazard for the type of animal food manufactured, processed, packed, and held at your facility, your written hazard analysis does not identify and evaluate any hazards associated with the animal food at your facility, as required by 21 CFR 507.33. Furthermore, you allude to hazards in your "Ingredient/Processing Step"; however, you did not specifically identify those hazards and assess the severity of illness or injury to humans or animals if the hazards were to occur or the probability that the hazard will occur in the absence of a preventive control, as required by 21 CFR 507.33(b) and (c). For example, your hazard analysis describes the processing step (b)(4) that are used to remove any foreign object." However, under the column for potential food safety hazards at this step, you have "NO" listed for physical hazards. FDA has resources available online to assist firms in developing food safety plans.9 We encourage you to reevaluate your Food Safety Plan and provide us with any updates and changes you make.
Food/Cosmetics	**R**	*Listeria monocytogenes*
Food/Cosmetics	**R**	Hand soap has the potential to be contaminated with bacteria.
Food/Cosmetics	**R**	Product tested positive for Salmonella
Food/Cosmetics	**R**	Flour has the potential to be contaminated with Salmonella.
Food/Cosmetics	**R**	Possible contamination with listeria monocytogenes
Food/Cosmetics	**R**	The product is being recalled due to Salmonella contamination.
Food/Cosmetics	**R**	Product may be contaminated with Listeria monocytogenes.
Food/Cosmetics	**R**	Product may contain salmonella
Food/Cosmetics	**R**	Dietary ingredient retest is out of specification for Total Yeast and Mold Count
Food/Cosmetics	**R**	Organic Pineapple chunks may be contaminated with Listeria monocytogenes.
Food/Cosmetics	**R**	Product may contain Salmonella

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Foods	**C**	You did not establish a system of process controls covering all stages of processing that was designed to ensure that infant formula does not become adulterated due to the presence of microorganisms in the formula or in the processing environment.
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