Date of This Update: August 25, 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
Biologics	**R**	Whole Blood, Leukocytes Reduced, collected in a manner that compromises the sterility of the collection system, was distributed.
Biologics	**WL**	"2. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, including procedures for validation of all aseptic and sterilization processes [21 CFR 211.113(b)]. For example: a. Your firm failed to validate the aseptic process used to manufacture WJMAX™ (i.e., by performing media fill simulations). By the nature of its route of administration, and per your product labeling, your product purports to be sterile and is expected to be sterile. b. You failed to conduct environmental monitoring for any of the (b)(4) processing runs of WJMAX™ in the aseptic processing areas." "4. Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21CFR 211.160(b)]. For example: a. Sterility samples of WJMAX™ are stored at (b)(4) prior to sterility testing. Freezing in this manner has the potential to destroy any microbial content in the samples before testing; therefore, contamination, if present, may not be detected. b. You have not collected and tested sterility samples that are representative of the lot size. You have tested (b)(4) vials for sterility regardless of lot size, which may consist of as many as (b)(4) vials." "2. In response to FDA-483 Observation 3, you state that storage of sterility samples at **(b)(4)** not affect detection of microbial contamination. FDA disagrees. There is no assurance that microorganisms, which may be weakened by the manufacturing process, would survive freezing and be reliably detected by sterility testing."
Devices	**R**	The STATCLAVE G4 is a dynamic air removal (prevacuum) tabletop steam sterilizer intended for use by a health care provider to sterilize medical products by means of pressurized steam. It is suitable for the sterilization of dental and medical instruments that are validated to be sterilized by steam. The STATCLAVE G4 has not been designed to sterilize liquid loads, bio medical waste or materials not compatible with steam sterilization. The processing of such loads may result in incomplete sterilization and / or damage to the autoclave.
Devices	**R**	Potential for the labeled sterile ultrasound gel component within packs to not meet sterility specifications.
Devices	**R**	Revised OER-Pro, OER-Elite, OER-Mini endoscope reprocessor labeling- the LF-V and LF-P are no longer compatible endoscopes for reprocessing in the OERs. The addendum highlights the following changes: 1. Removal of LF-V and LF-P as compatible with the OER 2. Change conditions for ETO sterilization from 12% ETO to 100% ETO

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Devices	**WL**	"1. Failure to establish and maintain procedures to control product that does not conform to specified requirements, as required by 21 CFR 820.90(a). Specifically: On June 19, 2019, your firm released a lot of Durepair,# 1904005 for distribution that indicated a bacterial endotoxin (BET) result of 9.98 EU/Device. This result exceeded your acceptance criteria of (b)(4) device as specified in your procedure, QCP-037 - Performance of the (b)(4) Endotoxin Assay. The device history record for this lot of product showed that the lot was approved and released by your firm without an investigation or product risk assessment for the BET result that was out of specification (OOS)." "On October 20, 2022, your firm received an internal complaint that alleged quality issues in **(b)(4)** manufacturing areas including your **(b)(4)** inspection process, bacterial endotoxin testing, bovine hide/skin thickness measurements, and control of sterilized devices. As the result of your initial investigation, your firm initiated a production hold on December 14, 2022 and also placed **(b)(4)** lots of product on hold. You initiated a CAPA to address the **(b)(4)** issue, however, CAPAs were not opened to address the remaining **(b)(4)** areas of concern, including endotoxin issues. Your CAPA procedure, GSOP-758, rev 005, indicates that "CAPA investigations and any corrections, corrective and/ or preventive actions should be **(b)(4)**"." "3. Failure to validate with a high degree of assurance, a process whose results cannot be fully verified by subsequent inspection and test, as required by 21 CFR 820.75(a). Specifically: Your firm failed to adequately validate your test method for testing bacterial endotoxin (BET) of finished medical devices, or the (b)(4) used during the manufacture of these devices. Review of your BET test method validation, TMVR-009; revealed the following: o The TMVR-009 assay reports failed to meet (b)(4) testing. ? (b)(4), dated January 28, 2019, excluded (b)(4) with "Sample Descriptions" of "Negative Control", invalidating BET test method verification runs for product lots # (b)(4), and (b)(4). ? (b)(4), dated January 2, 2019, excluded (b)(4) with sample descriptions "Negative Control", invalidating BET test method verification runs for product lots # (b)(4), and (b)(4). ? (b)(4), dated January 29, 2019, excluded (b)(4) with lot sample description "(b)(4)", "Sample (b)(4)", invalidating the BET test method verification for product lot # (b)(4). o Your BET test method protocol, section 7.4 Execution and Documentation of BET Assay, cannot be followed as written, to accurately (b)(4) for BET analysis of device product testing. For example, Section 7.4, step 4., states, "(b)(4)." However, the referenced table lists the (b)(4). o During routine BET testing, your firm introduced a (b)(4), in calculating the Endotoxin Limit which may cause the BET test method to be performed at (b)(4) to detect bacterial endotoxins. The use of this (b)(4) was not included in your endotoxin test method validation, TMVR-009. Your firm failed to adequately validate your test method for bioburden testing of finished medical devices. Review of TMVP-014, Revision 00, Test Method Validation Report for Bioburden Testing; Effective Date April 3, 2020, revealed: o Your report failed to meet the product bioburden recovery Acceptance Criteria (b)(4) to monitor device (b)(4) bioburden loads. Your firm failed to adequately validate your test method for bacterial endotoxin of (b)(4) used in the manufacture of your finished medical devices. Review of (b)(4); Rev 00; Effective Date: April 25, 2019 revealed the following: o For BET Report # (b)(4), Run Date: 3/27/2019, the negative control replicate original data from (b)(4) and (b)(4) were excluded. o (b)(4) sample and negative control results are evident on the BET analytical result printouts in (b)(4), Attachment D. Your firm failed to meet (b)(4), requirement, "Perform re-test for invalid assays/and or samples and document rationale as appropriate."(b)(4)"
Drugs	**R**	Lack of Assurance of Sterility
Drugs	**R**	Lack of assurance of sterility. Validation data for decontamination cycles is lacking.

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Product Type	**Citation [C], Recall [R], Warning Letter [WL]**	**Reason for Citation/Recall/Warning Letter**
Drugs	**WL**	"Aseptic processes should be designed to minimize exposure of sterile articles to potential contamination hazards, including, but not limited to, variation in environmental conditions. It is vital for rooms of higher air cleanliness to have a substantial positive pressure differential relative to adjacent rooms of lower air cleanliness. A suitable facility monitoring system is critical to maintain appropriate environmental conditions throughout all of your cleanrooms. All deviations from established limits should be appropriately investigated to rapidly detect atypical changes that can compromise the facility's environment. Prompt detection of an emerging problem is essential to preventing contamination of your aseptic production operations. Your response is inadequate because you fail to address systemic issues to ensure your facility is suitable for the aseptic processing for sterile drugs. You also do not provide meaningful evidence that your manufacturing environment is under an ongoing state of control."
Drugs	**WL**	"Your firm invalidated multiple endotoxin tests for finished products upon discovery of particulate matter in one or more wells used to perform the kinetic-turbidimetric assay (KTA) method. You failed to characterize the particulate matter and attributed the particulates to environmental and laboratory conditions, such as air ducts and activities being performed by personnel in the immediate vicinity of the analysis. You did not definitively identify the source or sources of the particulate matter, define the scope of potentially impacted operations (including potential manufacturing causes), and implement scientifically justified CAPA in a timely manner." "A written commitment to have all lots of finished products manufactured at your facility analyzed for endotoxins by a qualified laboratory until you have thoroughly investigated each endotoxin test invalidation event since January 1, 2018, and implemented all necessary CAPA to prevent recurrence of endotoxin result invalidations. This should include but not be limited to assuring CAPA effectiveness for your particulate and pipetting issues."

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Drugs	**WL**	"C. Violations of the FDCA Adulterated Drug Products 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 that: 1. Your firm used non-sterile wipes within the ISO 5 aseptic processing area. For example: a. Prior to production, non-sterile wipes were used to sanitize surfaces within the ISO 5 aseptic processing area. b. In preparation for production while removing air from the filling tubing, non-sterile wipes were used to wipe discarded drug product from the (b)(4). c. During production, the filling tubing and barbed fitting (used as a filling nozzle) were placed on non-sterile wipes. 2. An operator blocked first air by placing their gloved hands directly over open sterile containers. 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 firm did not disinfect materials during transfer from the ISO 7 cleanroom into the ISO 5 hood. For example: a. Your filling technician working within your ISO 5 aseptic processing area received vials and stoppers in the ISO 7 buffer room from a support technician who wore non-sterile exam gloves and performed a wipe down of those same components with non-sterile wipes. 5. An operator rested their fingertips on the work surface of the hood during aseptic production. These practices may introduce contamination into the ISO 5 work area. For example: a. Your filling technician did not re-sanitize their sterile gloves between resting fingertips on the ISO 5 work surface during pauses in filling operations and rotating trays of finished drug product vials during filling operations. 6. You did not perform adequate product evaluation and take appropriate corrective action after microbial contamination was recovered within the ISO 5 aseptic processing area. FDA investigators also noted CGMP violations at your facility, that caused your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example: 1. 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)). 2. 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)). 3. 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)). 4. Your firm failed to have buildings used in the manufacture, processing, packing, or holding of drug products of a suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations (21 CFR 211.42(a)). 5. Your firm failed to conduct laboratory testing to determine whether each batch of drug product purporting to be sterile and pyrogen-free conforms to such requirements (21 CFR 211.167(a)). 6. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination (21 CFR 211.28(a)). 7. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv).

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Drugs	**WL**	"Odor Complaints You failed to adequately investigate multiple foul odor complaints for (b)(4). For complaints COMP 20-161 and COMP 20-162, you tested retains of (b)(4), Berry, Lot (b)(4), which failed microbiological testing due to too numerous to count (TNTC) results for total count of yeast and mold (TCYM). Your investigation noted "there was a trend for foul odor complaints for lot (b)(4). The organism which caused of [sic] the odor in this lot was determined to be Staphylococcus epidermis." Your investigation further stated that the organism "is a facultative anaerobic bacteria and poses no health risk to the customer in an oral dose liquid" and "the lot remains fit for use." You failed to adequately assess the microbiological contamination and extend the investigation to additional batches manufactured after Lot (b)(4) that may also have been impacted. The TNTC microbiological testing results for your (b)(4) posed an unacceptable risk to public health, yet you failed to take any market action. Microbiological contamination may not be uniformly distributed, and a sample may not be representative of the type or level of contamination that may exist in other individual units of a batch. Water System Excursions You failed to initiate investigations for multiple microbiological excursions for your purified water system used to manufacture aqueous drug products. For example, you did not investigate several testing results for your water system that indicated the bacteria were too numerous to count (TNTC), and above your total aerobic microbial count action limit of (b)(4) cfu/mL. You also failed to consider how flaws in design, control, and maintenance of your water system contribute to these excessive microbial counts. Furthermore, your procedure for sampling and testing of the water system lacks a mechanism to trigger an investigation in response to severe microbiological excursions from water testing. In addition, your investigation INV-21-051 was inadequate because you failed to identify the microbial species in the water samples and did not extend the impact assessment to other potentially affected products manufactured using the same water system. Indeed, your procedure does not specify the need for microbial identification of water system sample isolates and the level of identification required (e.g., genus or species). Notably, you use water as a component in your aqueous based products, which is the prominent ingredient in your (b)(4) indicated for infants. In your response, you state you are revising your procedures and conducting additional investigations. However, your response is inadequate because your investigations are limited in scope and lack comprehensive review for potentially affected products and root cause determination. You also did not provide any supporting documentation, including details of your corrective actions with your initial 483 response. Well documented, thorough, scientifically sound investigations are necessary to identify the root cause and implement the appropriate CAPA."
Food & Beverages	**WL**	"A knowledgeable person manufacturing/processing food in your circumstances would identify mycotoxins as a hazard requiring a preventive control in this ingredient. Further, a facility that identifies raw materials and other ingredients that require a supply-chain-applied control, such as mycotoxins, must establish and implement a risk-based supply-chain program for those raw materials and ingredients (see 21 CFR § 117.405(a)(1)). The supply-chain program must include using approved suppliers and conducting supplier verification activities (see 21 CFR § 117.410). You do not have this program in place."

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Food & Beverages	**WL**	"You did not identify a process preventive control such as a lethal treatment to significantly minimize or prevent bacterial pathogens, such as Salmonella, associated with the ingredients in your RTE mukhwas products. Process controls include procedures, practices, and processes to ensure the control of parameters during operations such as heat processing. Where appropriate, process controls must also include the parameters associated with the control of the hazard and the minimum and maximum values, or combination of values, needed to significantly control the hazards (see 21 CFR 117.135(c)(1)). These controls must be validated (see 21 CFR 117.160)." "You did not identify a supply-chain program to verify control of bacterial pathogens, such as Salmonella, in seed and spice ingredients before your receipt. A facility that identifies raw materials and other ingredients with hazards such as Salmonella that require a supply-chain-applied control must establish and implement a risk-based supply-chain program for those raw materials and ingredients (see 21 CFR 117.405(a)(1)). The supply-chain program must include using approved suppliers and conducting supplier verification activities (see 21 CFR 117.410). Salmonella in RTE ingredients is a hazard that can cause serious adverse health consequences or death. Therefore, an annual onsite audit is the appropriate supplier verification activity unless there is a written determination that other verification activities and/or less frequent onsite auditing of the supplier provide adequate assurance that the hazard is controlled (see 21 CFR 117.430(b)). The audit must be conducted before using the raw material or other ingredient from the supplier and at least annually thereafter (see 21 CFR 117.430(b)(1)(ii)). Your February 2 response included a revised Food Safety Plan and Preventive Control Plan dated January 19, 2023. However, your revised hazard analysis did not identify bacterial pathogens, such as Salmonella, in ingredients such as seeds and spices as requiring a preventive control. It also does not appear that a (b)(4) step has been identified. Your revised food safety plan indicates that "(b)(4)", which appears to indicate this is not a (b)(4) step. Further, you did not identify any process or supply-chain preventive controls to address the hazard of Salmonella in these ingredients."
Food/Cosmetics	**R**	Possible microbiological contamination, specifically Listeria monocytogenes.
Food/Cosmetics	**R**	potential contamination with E coli
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Rapidmicro biosystems®		https://www.rapidmicrobio.com

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STERIS®		http://www.sterislifesciences.com/
vai VELTEK ASSOCIATES, INC.		http://www.sterile.com
rapid microbiology FOCUSED ON MICROBIOLOGY		https://www.rapidmicrobiology.com/subscribe
Giles Scientific, Inc.		https://www.biomic.com/trinity-v3.html
Special Process Services, LC		https://www.linkedin.com/in/joseph-connaghan-b663929