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Joint Committee on GMP for Over-the-Counter Drugs

May 9, 2024

Proposed revision to NSF/ANSI 455-4 – *Good Manufacturing Practices for Over-the-Counter Drugs* (455-4i47r1)

Revision 1 of NSF/ANSI 455-4, issue 47 is being forwarded to the Joint Committee for consideration. Please review the proposal and **submit your ballot by May 30, 2024** via the NSF Online Workspace.

Please review all ballot materials. When adding comments, please include the section number applicable to your comment and add all comments under one comment number whenever possible. If you need additional space, please use the attached blank comment template in the reference documents and upload online via the browse function.

Purpose

The proposed revision will ensure all requirements of 21 CFR 211 are included in the standard, as well as missing requirements specific to aseptic processing.

Background

4.5.1 – Process validation; add reference to standard.
4.5.10 – Cleaning validation; add reference to standard.
NEW 4.5.58 – Procedures designed to prevent microbiological contamination; add requirement from CFR 113, not currently in standard. Add ARG guidance for both sterile and non-sterile products.
NEW 4.5.59 – Environmental monitoring not previously in standard. Required for aseptic processing per CFR 113, however it is industry standard for all drug products.

Sec. 211.42 Design and construction features.
(c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures:
(10) Aseptic processing, which includes as appropriate:
(i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;
(ii) Temperature and humidity controls;
(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;
(iv) A system for monitoring environmental conditions;

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(v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;
(vi) A system for maintaining any equipment used to control the aseptic conditions.

Sec. 211.113 Control of microbiological contamination.
(b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.

Sec. 211.167 Special testing requirements.
(a) For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.
(b) For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.

FDA, Oct 2023, Quality Considerations for Topical Ophthalmic Drug Products – Draft Guidance for Industry, https://www.fda.gov/, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-considerations-topical-ophthalmic-drug-products

FDA, Sept 2021, Microbiological Quality Considerations in Non-Sterile Drug Manufacturing – Draft Guidance for Industry, https://www.fda.gov/, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/microbiological-quality-considerations-non-sterile-drug-manufacturing

FDA, Oct 2004, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice – Guidance for Industry, https://www.fda.gov/, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sterile-drug-products-produced-aseptic-processing-current-good-manufacturing-practice

If you have any questions about the technical content of the ballot, you may contact me in care of:

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[Note – the recommended changes to the standard which include the current text of the relevant section(s) indicate deletions by use of ~~strikeout~~ and additions by grey highlighting. Rationale Statements are in *italics* and only used to add clarity; these statements will NOT be in the finished publication.]

NSF/ANSI Standard
for GMP for Over-the-Counter Drugs –

Good Manufacturing Practices for Over-the-Counter Drugs

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4 Audit requirements

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4.5 Operation

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4.5.1 Manufacturing processes ~~have been~~ are validated to produce a product that consistently meets specifications. [21 C.F.R. § 211.100, 21 C.F.R. § 211.110, 21 C.F.R. § 211.111, 21 C.F.R. § 211.113 & U.S. FDA Process Validation Guidelines]

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4.5.10 Procedures have been established for the cleaning and sanitization of all utensils and equipment. Cleaning validation studies have been completed for product contact parts and equipment. [21 C.F.R. § 211.42 & 21 C.F.R. § 211.67]

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4.5.58 Procedures designed to prevent microbiological contamination of drug products shall be established and followed. 211.113

4.5.59 Environmental Monitoring Program shall include controls to mitigate the presence of microorganisms and particulate in processing areas. 211.42, 211.113

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