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Joint Committee on GMP for Over-the-Counter Drugs

August 20, 2024

Proposed revision to NSF/ANSI 455-4 – *Good Manufacturing Practices for Over-the-Counter Drugs* (455-4i43r1)

Revision 1 of NSF/ANSI 455-4, issue 43 is being forwarded to the Joint Committee for consideration. Please review the proposal and **submit your ballot by September 10, 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 within 21 CFR 211 are included in the 455-4 standard and will add a missing reference to requirement CFR 211.176.

Background

This issue was discussed at the 2023 meeting and it was motioned to go to ballot. Part of that motion was to also create a separate issue paper for definitions of 'cross contamination' and 'sensitizing agent'. Those will be presented in a separate issue paper.

In effort to ensure all the requirements from 211 are included in 455-4, the below reference will be added to 4.2.9. It can be inferred via the audit requirements guidance that the intent of 4.2.9 is for quality to ensure potentially adulterated products are investigated prior to disposition. Unexpected events (potential adulteration) require an investigation per 4.5.29.

Sec. 211.176 Penicillin contamination.
If a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in 'Procedures for Detecting and Measuring Penicillin Contamination in Drugs,' which is incorporated by reference.

4.5.29 Procedures have been established for conducting investigations of unexpected events,

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deviations from procedure, nonconformances, complaints, rejections, and recalls. [21 CFR § 211.100]

From Guidance for Industry Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination

Although FDA has not issued CGMP regulations specific to APIs, the Agency has provided guidance to API manufacturers in the guidance for industry, ICH4 Q7, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (ICH Q7 guidance). Because some APIs are sensitizing compounds that may cause anaphylactic shock, preventing cross contamination in APIs is as important as preventing cross-contamination in finished products. The ICH Q7 guidance recommends using dedicated production areas, which can include facilities, air handling equipment and processing equipment, in the production of highly sensitizing materials, such as penicillins and cephalosporins.

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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4.2 Leadership

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4.2.9 QA operations determine if all specifications have been met (raw material, components, in-process, final product specifications) and assign batch disposition (approve / release or reject) on each finished batch for distribution. [21 CFR § 211.22 & 21 CFR § 211.192, 21 CFR § 211.176]

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