TO: Joint Committee on GMP for Over-the-Counter Drugs

FROM: Dan Klassen, Chair of the Joint Committee

DATE: February 25, 2020

SUBJECT: Proposed revision to NSF/ANSI 455-4 – Good Manufacturing Practices for Over-the-Counter Drugs (455-4i15r1)

Revision 1 of NSF/ANSI 455-4, issue 15 is being forwarded to the Joint Committee for consideration. Please review the proposal and submit your ballot by March 17, 2020 via the NSF Online Workspace <www.standards.nsf.org>.

When adding comments, please use the comment template provided in the ballot and upload it online via the browse function.

Purpose

The proposed revision will harmonize the standard format to match 455-2 GMP for Dietary Supplements, and 455-3 GMP for Cosmetics under the ISO Format.

Background

The numeration of section 4.5 is different from 455-2 and 455-3. Other scopes do not have subsection under support. Request to remove OTC has 3 subsections 4.5.1 Resources, 4.5.2 Infrastructure, 4.5.3 Environmental Controls, 4.5.4 Documentation. These Subsections change the numeration of the element to 4 numbers (i.e. 4.5.1.1) which can be confused with the ARG numeration structure.

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

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

Good Manufacturing Practices for Over-the-Counter Drugs

4 Audit requirements

4.5 Support

4.5.1 Resources

4.5.1.1 Adequate resources (human, financial, materials, facilities, and equipment) are provided to implement, maintain, and improve the quality system. [ICH Q10]

4.5.2.1 There shall be written procedures assigning responsibilities for cleaning and sanitization of buildings and facilities. [21 CFR § 211.25 & 21 CFR § 211.56]

4.5.3 Consultants used to advise on the manufacture, processing, testing and holding of drug substance and drug product shall have the qualifications for the type of service they provide. [21 CFR § 211.34]

4.5.2 Infrastructure

4.5.2.1 Building and grounds have been properly maintained through removal of litter and waste, cutting of grass and weeds adjacent to the plant, maintenance of roads and parking lots, providing adequate drainage, etc. [21 CFR § 211.42, 21 CFR § 211.56, & 21 CFR § 211.58]

4.5.2.5 Waste disposal is adequate and does not provide a source of potential contamination. [21 CFR § 211.50]

4.5.2.6 Production facility is maintained in a clean and sanitary condition and in a proper state of repair. [21 CFR § 211.58]

4.5.2.7 Entrances to the facilities are properly controlled and maintained to prevent contamination. [21 CFR § 211.42]

4.5.2.8 Cleaning and sanitizing compounds have been established for cleaning the facility. These agents are safe and adequate under the conditions of use. [21 CFR § 211.56]
4.5.2.6 \textbf{4.5.9} Cleaning and sanitizing agents, pesticide chemicals, and fungicides have been identified, used, held and stored in a manner that protects against adulteration of raw materials and in-process or finished products, and protects against contamination of processing equipment, utensils, and packaging materials. [21 CFR § 211.56]

4.5.2.7 \textbf{4.5.10} Physical barriers have been installed to prevent pest, rodent, bird and insect intrusion, including screens and rodent barriers, rodent traps, insect traps or lights, etc. [21 CFR § 211.56]

4.5.2.8 \textbf{4.5.11} Pest control procedures have been established for the appropriate use of any insecticides, fungicides, fumigants, rodenticides, etc. [21 CFR § 211.56]

4.5.2.9 \textbf{4.5.12} The water supply is safe and sanitary and under suitable temperature and pressure. At a minimum, water used in processing areas shall meet WHO Guidelines for Drinking Water. Water used as a component of a non-parenteral drug product shall meet USP purified water Standards, and the water purification system shall be validated. [21 CFR § 211.48]

4.5.2.10 \textbf{4.5.13} Water sources do not act as a potential source of contamination of the drug products, either due to water purity or due to the configuration and construction of the water delivery system. [21 CFR § 211.42 & 21 CFR § 211.48]

4.5.2.11 \textbf{4.5.14} Plumbing is of adequate size and design for intended usage. [21 CFR § 211.42 & 21 CFR § 211.48]

4.5.2.12 \textbf{4.5.15} Sewage and waste disposal piping is properly designed and installed to prevent contamination. [21 CFR § 211.50]

4.5.2.13 \textbf{4.5.16} Floor drainage allows immediate and continuous drainage, no pooling, proper drain covers. [21 CFR § 211.48]

4.5.2.14 \textbf{4.5.17} Air breaks, backflow and cross-connection prevention is in place. [21 CFR § 211.48]

4.5.2.15 \textbf{4.5.18} Bathrooms are provided and are of adequate number and location. [21 CFR § 211.52]

4.5.2.16 \textbf{4.5.19} Bathrooms and wash facilities are kept clean and are not a potential source of contamination to components, products, contact surfaces, etc. [21 CFR § 211.52]

4.5.2.17 \textbf{4.5.20} Solid waste and trash are disposed of appropriately and not allowed to accumulate. [21 CFR § 211.50]

4.5.2.18 \textbf{4.5.21} Solid waste and trash does not provide a potential source of contamination to components, products, contact surfaces, etc. [21 CFR § 211.50]

4.5.2.19 \textbf{4.5.22} Hazardous waste is properly controlled to prevent contamination of components, products, contact surfaces, etc. [21 CFR § 211.50]

4.5.2.20 \textbf{4.5.23} Procedures have been established for cleaning of the facility. [21 CFR § 211.56]

4.5.2.21 \textbf{4.5.24} All facilities are of adequate size, construction, and design for their intended use.
4.5.2.22 There is adequate space for performing all operations and to prevent mix-ups, contamination, and cross-contamination during manufacturing, packaging, labeling, or holding. [21 CFR § 211.42]

4.5.2.23 Areas have been clearly defined or separated for receiving, inspecting and identifying, holding and withholding from use components, drug products, packaging, and labels designated for production and packaging use. [21 CFR § 211.42]

4.5.2.24 Areas have been provided for quarantine and release of materials to be used in the manufacture, packaging, or labeling of drug products. [21 CFR § 211.42]

4.5.2.25 Areas have been provided to separate the manufacturing, packaging, labeling, and holding of different product types (i.e., foods, cosmetics, dietary supplements) from drug products. [21 CFR § 211.42]

4.5.2.26 Separate or defined areas exist for laboratory analysis and holding of laboratory supplies, reference samples, in process, product and stability samples associated with the manufacture, packaging and labeling, of drug products. [21 CFR § 211.42]

4.5.2.27 Walls, floors, ceilings can be adequately cleaned and kept in good repair. [21 CFR § 211.42]

4.5.2.28 Fixtures, ducts, piping, etc. are kept clean, do not drip or leak or provide a source of condensation that could contaminate components, products, or contact surfaces. [21 CFR § 211.42]

4.5.2.29 Adequate ventilation and airflow is provided in all areas of the facility. [21 CFR § 211.42]

4.5.2.30 Provisions are in place for power backup or uninterruptable power supply (UPS) for critical equipment, or written procedures, or both, for recovery from power failure.

4.5.3 Environmental control

4.5.3.1 Temperature and humidity control equipment (HVAC) is of adequate design for its intended function and is functioning properly. [21 CFR § 211.42]

4.5.3.2 Adequate lighting is provided in all production and laboratory areas, inspection and sampling rooms, and in those areas where equipment is cleaned and examined. [21 CFR § 211.44]

4.5.3.3 Lighting that is suspended or located above areas where materials or equipment are exposed is of adequate construction or lighting type to prevent contamination with the use of safe-lights, fixtures, etc. [21 CFR § 211.42 & 21 CFR § 211.44]

4.5.3.4 Closed processing is preferred. In areas where tanks are required to be open for charging or mixing, there is adequate protection against contamination, i.e., vertical or horizontal HEPA airflow across the vessel opening or use of protective coverings. [21 CFR § 211.42]

4.5.4 Documentation

4.5.4.1 All documents related to drug manufacture are prepared, reviewed, approved, and distributed according to written procedures. [21 CFR § 211.180 & 21 CFR § 211.22]
4.5.4.2 4.5.39 Drug product production and control records shall be reviewed and approved by the quality unit before a batch is released and distributed. [21 CFR § 211.180]

4.5.4.3 4.5.40 The issuance, revision, superseding, and withdrawal of all documents is controlled, and records of these activities are maintained in revision histories or equivalent. [21 CFR § 211.180 & 21 CFR § 211.22]

4.5.4.4 4.5.41 Procedures exist describing GMP recordkeeping practices, i.e., permanent ink, identification of "who" and "when" for all entries, and procedures for correcting entries by signing, dating, explaining, and not obscuring the original entry. [21 CFR § 211.180]

4.5.4.5 4.5.42 Procedures have been established that describe the requirements for record retention. [21 CFR § 211.180]

4.5.4.6 4.5.43 Batch records shall be maintained for one year after the expiration date or three years beyond the date of distribution of the last batch associated with those records. [21 CFR § 211.180]

4.5.4.7 4.5.44 All records are maintained as original record, as verified true copies or as electronic records. [21 CFR § 211.180]

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