VIA ELECTRONIC SUBMISSION

December 17, 2021

Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2021-D-0432 for "Microbiological Quality Considerations in Non-Sterile Drug Manufacturing"

Dear Sir/Madam,

The United States Pharmacopeia (USP)[1] appreciates the opportunity to comment on the Food and Drug Administration's (FDA or the Agency) Draft Guidance for Industry, "Microbiological Quality Considerations in Non-Sterile Drug Manufacturing."

We commend FDA on the issuance of this draft guidance to help ensure the microbiological quality of non-sterile drugs. USP strongly supports the Agency's efforts to minimize the public health risk caused by the contamination of microorganisms and in establishing manufacturing controls to prevent such contamination.

USP supports the draft guidance's reference to the *United States Pharmacopeia-National Formulary* (*USP-NF*) chapters on the microbiological examination of nonsterile products,[2] water activity in nonsterile products,[3] and packaging and storage.[4] In particular, these chapters include: procedures for estimation of total aerobic microbial count and total yeast and mold count (USP <61>); tests for specified microorganisms (USP <62>); tests for *Burkholderia cepacia complex* (*BCC*) (USP <60>); information on recommended acceptance criteria for nonsterile substances and products (USP <1111>); and the importance of water activity in controlling the proliferation of microorganisms (USP <1112>).

[1] USP is an independent, scientific, nonprofit organization dedicated to improving public health for medicines, foods, and dietary supplements. USP public standards are developed through an open, transparent, expert-based process, offering the ability to confront public health emergencies, adapt to new industry practices, and support evolving science and technology.

[2] USP General Chapters <60> *Microbiological Examination of Nonsterile Products: Tests for Burkholderia Cepacia Complex*; <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests*; and <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*.

[3] USP General Chapters <1111> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*; <1112> *Application of Water Activity in Determination to Nonsterile Pharmaceutical Products*; and <1231> *Water for Pharmaceutical Purposes*.

[4] USP General Chapter <659> *Packaging and Storage Requirements*.

USP Headquarters
12601 Twinbrook Parkway | Rockville, MD 20852, USA
+1-301-881-0666 | usp.org

The control of bioburden is mentioned throughout the draft guidance. As such, we recommend that the draft guidance include reference to USP General Chapter <1115> *Bioburden Control of Nonsterile Drug Substances and Products* where FDA deems it is appropriate. This chapter outlines the factors that contribute to microbial proliferation in pharmaceutical manufacturing, using a risk-based approach for bioburden control. The chapter also outlines the concepts and principles necessary to protect products from adventitious microorganisms. This chapter supports current good manufacturing practice requirements in 21 CFR 211.113(a)[5] and states that while microbial sampling and testing play an important role as indicators of microbiological control, testing alone cannot ensure the quality of a substance or product.

Regarding the draft guidance reference to USP <1231> *Water for Pharmaceutical Purposes*, we note the following language (lines 312-315):

> Purified water, USP, that does not exceed 100 CFU/ml is recommended for use in solid oral dosage forms. More stringent microbiological quality standards may be appropriate for other dosage forms [footnote references USP <1231>].

We note that USP <1231> does not include a recommendation for water microbiologic count for solid oral dosage forms[6] and recommend including the second sentence as a separate bullet to help avoid any confusion.

Applicability of USP General Chapters

The draft guidance includes information on the applicability of the USP general chapters. In particular, the draft guidance states (lines 123-131):

> In general, a drug with a name recognized in an official compendium must comply with the United States Pharmacopeia (USP) compendial standards for identity, strength, quality, and purity, or be deemed adulterated, misbranded, or both. If USP has established a monograph for a drug, the USP monograph will identify the official tests, procedures, acceptance criteria, and other requirements. **When USP monographs include a test or specification referencing "Applicable General Chapters," the applicant should ensure that their monograph product complies with the testing requirement, or it could be deemed adulterated. Some of the USP General Chapters that are more commonly referenced in drug monographs, as they apply to controlling microbiological activity in NSDs [nonsterile drugs]** . . . (footnotes omitted; emphasis added).

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[5] 21 CFR 211.133(a) on "Control of microbiological contamination," states that "[a]ppropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed."

[6] Relevant language in USP <1231> includes the following: "Users should establish their own quantitative microbial Specifications suited to their water uses. But these values should not be greater than 100 cfu/mL for Purified Water or 10 cfu/100 mL for Water for Injection unless specifically justified, because these values generally represent the highest microbial levels for pharmaceutical water that are still suitable for manufacturing use [hyperlinks omitted]".

Footnote 20 after “Applicable General Chapters” states, “See USP, Conformance to Standards, 3.10, ‘Applicable general chapters’ means general chapters **numbered below 1000** or above 2000 that are made applicable to an article through reference in General Notices, a monograph, or another applicable general chapter numbered below 1000” (emphasis added). Regarding USP General Chapter <60>, USP is working on clarifying the applicability of this chapter and is looking to engage with FDA and other stakeholders on this important matter. We note that General Chapter <60> on testing for *BCC* is of particular importance due to recent adverse events and recalls of certain nonsterile, water-based drug products.[7]

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USP is committed to helping ensure the microbiological quality of drug products and would welcome engaging further with FDA. We will follow-up with the Agency on any updates to the relevant USP chapters.

Thank you again for the opportunity to comment. For more information, please contact Marissa Chaet Brykman, Esq., Director, U.S. Regulatory Policy, at marissa.brykman@usp.org; (301) 692-3660.

Sincerely yours,

Jaap Venema, Ph.D.
Executive Vice President and Chief Science Officer
jpv@usp.org
(301) 230-6318

[7] FDA Notice, “FDA advises drug manufacturers that Burkholderia cepacia complex poses a contamination risk in non-sterile, water-based drug products,” at https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-drug-manufacturers-burkholderia-cepacia-complex-poses-contamination-risk-non-sterile (July 7, 2021).