VIA ELECTRONIC SUBMISSION

September 28, 2022

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2020-N-1383 – Revocation of Methods of Analysis Regulation

Dear Sir/Madam:

On behalf of the United States Pharmacopeia (USP), I am writing to provide comments on the U.S. Food and Drug Administration's (FDA, Agency) proposed rule to revoke the methods of analysis regulation. USP is an independent, scientific, global non-profit organization founded in 1820 and dedicated to building trust where it matters most: in the world's medicines, dietary supplements, and foods through rigorous science and public quality standards.[1] A core pillar of USP's mission is to help strengthen the global supply chain so that the medicines, dietary supplements, and food people rely on for their health are available when needed and meet quality standards as expected and required. USP is governed by more than 500 organizations, including scientific, healthcare practitioner, consumer, and industry communities, as well as dozens of government agencies, who together comprise the USP Convention.[2]

USP appreciates the opportunity to provide comments on the FDA's proposed revocation of the Methods of Analysis Regulation in 21 CFR 2.19 that describes an FDA policy to use certain methods of analysis for FDA enforcement programs when the method of analysis is not prescribed in a regulation. **USP understands the need to modernize regulatory language and is supportive of eliminating unnecessary policy. However, we emphasize the importance of utilizing proper methods of analysis and urge the Agency to maintain updated versions of the Office of Regulatory Affairs Laboratory Procedures Manual, FDA compliance programs, and other resources. To facilitate efficiency and flexibility, we encourage the Agency to ensure preferred methods of analysis in these documents are inclusive of up-to-date public standards from USP and other trustworthy sources.**

Based on USP's extensive experience as a provider of pharmacopeial public standards for over 200 years,[3] the following comments are provided to help inform FDA efforts to ensure methods of analysis included in Agency resources lead to reliable results when assessing quality.

Need for scientifically valid analytical methods:

Lack of uniformity and product quality concerns could result from the use of analytical methods that are not based on validation principles. **Ensuring the inclusion of up-to-**

[1] USP standards are developed by Expert Bodies comprised of more than 750 scientific experts. These experts collaborate to develop USP standards through an open, transparent process, offering the ability to adjust standards to confront public health emergencies, adapt to new industry practices, and keep up with evolving science and technology.
[2] USP's governing bodies in addition to the Council of the Convention include its Board of Trustees and Council of Experts.
[3] 200 Years of Building Trust, The history of medicine quality and a timeline of USP, https://www.usp.org/200-anniversary.

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date public standards from USP and other trustworthy sources as preferred methods of analysis in Agency documents will assist the Agency in its enforcement efforts when the method of analysis is not prescribed in a regulation.

The *USP-National Formulary* (*USP-NF)* and *Food Chemicals Codex (FCC)* contain standards that provide quality specifications consisting of tests that are necessary to ensure quality, including one or more analytical procedures for each test, and acceptance criteria that effectively serve as the goalposts within which the substance or product must fall in order to pass the tests.[4,5,6,7] In order to stay abreast of evolving science and best measurement practices, USP standards in the *USP-NF* and *the FCC* are in a continual state of update or revision in accordance with modern scientific principles.

USP compendial procedures establish the suitability of analytical methods. Specifically, USP General Chapter <1225> *Validation of Compendial Procedures*, which is aligned with ICH *Q2(R1) Validation of Analytical Procedures: Text and Methodology*, provides principles for validation of analytical procedures including establishing accuracy, precision, specificity, quantitation limit, and linearity. Since USP monographs include validated methods, users do not need to validate the methods again; the methods only need to be verified for their specific use.

We note that in the preamble to the 2003 Dietary Supplement CGMP Proposal (68 FR 12157 at 12209), FDA acknowledged that validated methods exist in official compendia for vitamins, minerals, and several botanicals, and recommended the use of validated methods whenever such methods are available. The Preamble notes "We explicitly stated that you may use validated methods that can be found in official references, such as AOAC International, USP, and others."

Public standards as resources for regulators:

Scientifically valid analytical methods are available in the public domain from standards organizations, including USP and AOAC International. Use of public standards—public specifications containing tests, procedures, and acceptance criteria—would reduce the need for repetitive development and review of validation and other data for procedures to ensure identity and quality. Use of public standards can help limit the introduction of potential adulterants and contaminants into an ingredient and/or product and serve as a widely acknowledged quality benchmark in the buying and selling of products and their ingredients.

We recently published a perspective on the use of pharmacopeial standards from USP, American Herbal Pharmacopoeia, European Pharmacopoeia, and Chinese Pharmacopeia as a resource for quality control of botanicals in the United States, noting the number and nature of ingredients covered by these compendia, the process for standard-setting and updates, and the scope of the standards differ among the

[4] Miller RK, Celestino C, Giancaspro GI, Williams RL. FDA's dietary supplement CGMPs: standards without standardization. Food Drug Law J. 2008;63(4):929-42. https://pubmed.ncbi.nlm.nih.gov/19601389/.

[5] Sarma N, Giancaspro G, Venema J. Dietary supplements quality analysis tools from the United States Pharmacopeia. Drug Test Anal. 2016 Mar-Apr;8(3-4):418-23. https://pubmed.ncbi.nlm.nih.gov/26857794/.

[6] USP-NF, https://www.uspnf.com/.

[7] Food Chemicals Codex, https://www.foodchemicalscodex.org/.

compendia.[8] This perspective helps explain the benefits of using methods of analysis in trustworthy pharmacopeial sources, such as those in USP's standards.

The *USP-NF* is an expansive resource that includes more than 4,900 monographs for medicines, dosage forms, drug substances, excipients, biologics, compounded preparations, medical devices, dietary supplements, and other therapeutics. This includes 600 monographs for botanical and non-botanical dietary ingredients (including the native "raw" form of the appropriate plant part, powdered form, and their extracts and processed forms) and finished dietary supplements (dosage forms, including tablets, capsules, etc.) supported by general chapters and Reference Standards. USP non-botanical monographs provide specifications for vitamins, minerals, amino acids, and specialty ingredients, such as fish oil and chondroitin. An elaboration of USP standards for botanicals was recently published.[9] The *FCC* includes over 1,200 monographs to verify the identity, quality, and purity of food ingredients. *FCC* monographs are similarly supported by the General Tests and Assays within the compendium, as well as Reference Standards. *FCC* monographs address a wide range of food ingredients and applications including dietary proteins, fats & oils, amino acids, functional food ingredients, nutrients, flavors, sweeteners, colors, probiotics, and enzymes.

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Thank you again for the opportunity to comment on FDA's proposal. We welcome the opportunity to meet with FDA to discuss how USP approaches can help ensure the quality of FDA-regulated products. For more information, please contact Nandakumara Sarma, PhD, RPh, Director, Dietary Supplements and Herbal Medicines, at (301) 816-8354 or DNS@usp.org.

Sincerely,

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[8] Sarma N, Upton R, Rose U, et al. Pharmacopeial Standards for the Quality Control of Botanical Dietary Supplements in the United States. *J Diet Suppl.* 2021:1-20. Pharmacopeial Standards for the Quality Control of Botanical Dietary Supplements in the United States (tandfonline.com) Accessed July 21, 2022.
[9] Ma C, Oketch-Rabah H, Kim NC, et al. Quality specifications for articles of botanical origin from the United States Pharmacopeia. Phytomedicine : international journal of phytotherapy and phytopharmacology. 2018;45:105-119.