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31 March 2020

Jessica Simpson
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via e-mail

Dear Ms. Simpson –

PDA welcomes the opportunity to comment on USP's proposed revision of *General Notices and Requirements* as published in *Pharmacopeial Forum (PF) 46(1).*

Section 1. Title and Revision: PDA supports USP's continuing efforts to transition the USP and NF compendia to a fully electronic format, with the latest revisions to the General Notices completing this timely effort.

Section 3.10 Applicability of Standards: PDA appreciates and supports USP's intent to clearly delineate informational from required language in the *USP-NF*. As users of the *USP-NF*, PDA members have concerns about the clarity of the current delineation. Although USP may intend for certain compendial text to be merely informational, regulators can and do make different choices about enforceability. With that in mind, the more clarity and consistency USP can provide with regard to text hierarchy and intended use, the more helpful the resulting standards can be.

PDA offers the following specific comments on this section:

1. First, PDA does not support USP's proposal to indicate that Chemical Information is informational. A growing number of analytical tests rely on correct primary structure or sequence information as part of a specification or calculation. If the Chemical Information is presented for mere informational purposes, it cannot be referenced directly by a test or specification elsewhere in the monograph. PDA is not certain that the Chemical Information is especially helpful if presented only for informational purposes. Yet as mentioned above, regulators may still interpret the Chemical Information as mandatory, creating additional levels of confusion.

With that in mind, it is critically important that (1) all chemical and structural information in the monograph receives the same high level of review during initial proposal and revision as any other aspect of the monograph and (2) USP's intent in graphically representing chemical structures is clear.

Therefore, PDA recommends that USP revise the USP Preface to require PF publication and opportunity for comment on changes to Chemical Information in any monograph. At present, the Preface allows Chemical Information to be updated on an ongoing basis without going through the regular compendial revision process. By requiring PF publication and

opportunity for public comment on any change to Chemical Information, USP would gain the benefit of thorough review while also reducing the impact of the information's location in the monograph.

In order to try to prevent misunderstanding, USP might consider including in the General Notice the language from the Preface that the graphical representation of the chemical compound structure in the monograph is understood to represent one of many possible ways to depict the molecule.

2. PDA urges USP to revise this sentence for clarity: "*In either format, information outside of these sections that state requirements—including Chemical Information—is provided for informational purposes."* USP might consider revising it to read, for instance: *"In either format, information that appears before the double arrow symbol, before the section titled "Definition," or in or after the section titled "Auxiliary Information" is provided for informational purposes.*" If USP takes PDA's suggestion regarding the Chemical Information above, of course, this would need to be edited further.

3. PDA encourages USP to continue to advance the completion of the redesign for all remaining "classic style" monographs through the compendial revision process, thus eliminating the need for delineation between informational and required information via the double-arrow symbol (previously known as the chevron).

4. As USP continues to develop and revise monographs in the recently redesigned format, PDA encourages USP to consider that, in many instances, the Definition contains specification information without providing an associated compendial procedure or referencing a procedure in a relevant General Chapter. This creates compliance challenges in practice, as manufacturers are left to determine, and justify to regulators, the procedure used to meet the compendial specification.

Section 3.10.40 Applicability of Global Health Monographs: PDA supports the creation of a section for Global Health Monographs in the compendia via the newly added GN provision 3.10.40, in keeping with the organization's ongoing efforts to provide quality standards for essential medicines in the global market.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality, and is an ANSI-accredited standards development organization. Our comments have been prepared by a committee of experts in regulatory affairs and standards-setting on behalf of our Regulatory Affairs and Quality Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me via email at johnson@pda.org.

Sincerely,

Richard Johnson
President and CEO

cc: Tina Morris, PDA; Ruth Miller, PDA