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Elena Gonikberg, Ph.D.
USP Compendial Science
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via e-mail

Dear Dr. Gonikberg –

PDA appreciates the opportunity to comment on USP's revision of General Chapter <11> *USP Reference Standards*.

PDA supports USP's effort to further clarify the role and applicability of USP's reference standards, specifically introducing language that speaks to both the regulatory and the metrology roles these materials may fulfill. (Re)introducing the concept of reference standards without a direct link to compendial tests and procedures (previously experienced as *USP Authentic Substances*) adds opportunity to provide highly useful materials that can aid the compendial users in the improvement of their measurements. To fulfill this potential, large emphasis should be placed on the availability of sufficient and appropriate characterization data, as well as additional transparency around the general characterization and qualification approaches that USP uses for these materials. Recognizing that <11> as a required Chapter may not be the place for this type of information, perhaps a General Information Chapter as a companion could be considered that lays down key general approaches to the characterization of reference materials with uses that go beyond or are outside of the typical "suitability for use" paradigm of compendial applications. This would allow for consistency in approach beyond individualized qualification schemes and data captured in RS instructions for use or certificates.

Some additional, more specific comments for your consideration:

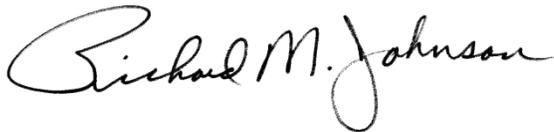
1. Value assignment by primary method: It is suggested that USP provide additional clarity here, particularly with regard to definition of primary method, i.e. if USP is following the CCQM definition of primary method as *a method having the highest metrological qualities, whose operation can be completely described and understood, for which a complete uncertainty statement can be written down in terms of SI units*. A primary direct method: *measures the value of an unknown without reference to a standard of the same quantity*. A primary ratio method: *measures the value of a ratio of an unknown to a standard of the same quantity; its operation must be completely described by a measurement equation*. (see Wielgosz Encyclopedia of Analytical Science, 3rd edition, Volume 8 <https://doi.org/10.1016/B978-0-12-409547-2.14482-8>). Given that most USP chemical reference materials will have been assigned by mass balance approaches, USP may consider additional clarity in setting materials apart that do qualify as true primary standards by meeting the additional metrological rigor above and are not considered primary standards just based on official national regulatory recognition (per *General Notices Section 5.80*).

2. Storage temperature and definition of room temperature: while understanding that the USP interpretation of room temperature is based on the definition in USP Chapter <659>, we would suggest that, especially for newly created materials, USP adopt tighter temperature range definitions for reference materials, more in line with current capabilities and expectations for environmental control. Storage temperature ranges found for reference materials from other providers have been found to be in the +/- 5°C range for room temperature and +/- 3 °C or less for refrigerated or cold storage. It is recognized that with a large inventory of legacy standards, introduction of additional rigor in this area may require significant transition time.

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