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Desmond G. Hunt, Ph.D.
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Re: USP Stimuli to the Revision Process Filling the Pharmacopeial Gaps of Visual Inspection: Toward Standardization and Consistency of Visible Particle Testing

Dear Dr. Hunt,

PDA appreciates the opportunity to comment on USP's recent stimuli article on visible particle testing. USP has developed several significant chapters providing guidance on the detection and control of visible and subvisible particles in injections. PDA supports USP's efforts to enhance guidance in this important area of product quality. Since this article is not a completed chapter but rather intended to provide discussion on future direction, detailed comments are provided below on the strategic points made therein.

PDA strongly recommends that USP not create a new chapter based on the contents of this article and rather, where appropriate, add content to existing chapters on the topics of visible and subvisible particles. There is a risk of USP introducing contradictory guidance and setting unintended requirements with the recommendations made. Such unintended consequences would not be beneficial for global patients, regulators, or manufacturers.

PDA offers specific feedback for your consideration:

SIGNIFICANT CONCERN – The majority of the contents of the stimuli article overlap with the contents of existing USP chapters <790> and <1790>. If additional content is to be added on this topic it would better be added to the existing <1790> to avoid confusion and conflicts.

SIGNIFICANT CONCERN – A major premise of the article is that there can and should be a standard definition of what is considered visible. This has been discussed on numerous occasions in print and in public conferences. It was further discussed in the creation of the current USP chapters on visual inspection and visible particles with the conclusion that a strict definition is not practical, nor clinically relevant given the wide variety of products and packages covered by these chapters. The stimuli article discusses the point that the size at which particles become visible is dependent on the product properties, the container that is selected, and the particle material (in addition to other factors). It is not accurate to indicate that there is a single size that can be considered visible given the probabilistic nature of the inspection process and there may be considerable confusion created if a new USP chapter is developed to make this point.

SIGNIFICANT CONCERN – The article often shifts focus between visible and subvisible particles despite the title referring to visual inspection. These size ranges have different clinical significance

and regulatory expectations associated with them and therefore should not be intermixed within a single chapter.

SIGNIFICANT CONCERN – The article is not consistent with current USP guidance on “inherent matter” contained in USP <790> and <1790>. The article states that “the proposed chapter specifications should primarily focus on concerns of the inherent particles”. Inherent matter is product specific; the acceptability of these intentionally present and visible product elements is dependent on the product design and use. Practical, universal specifications for this particle category seem very unlikely given the complexity of the factors that must be considered.

MAJOR CONCERN – The article discusses creation of commercially available standards to be used for training and qualification of inspectors. It is not reasonable to establish a new “standard set” as a mandatory requirement, or to build requirements for training and qualification around this set. Such sets are product and container specific, and firms must address this in the qualification of their inspection process(es). Adding an additional testing requirement for production inspectors would not add value to the already extensive qualification process. The type of qualification set discussed is possibly appropriate in a research or development environment but not for routine production.

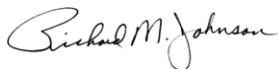
GENERAL CONCERN – The scope of this article is unclear as to application during development or during manufacture for administration to patients (i.e., clinical supplies and commercial products). The expectations at each of these phases is different and thus the methods and criteria used may vary. This article appears to speak more from a development perspective, yet the current USP chapters are intended to address supply of product to patients.

PDA would be happy to collaborate with USP in the continued development of this guidance. Like USP, PDA is also committed to advancing science to support product quality and patient safety, and the topics covered by this guidance are of special interest throughout our organization.

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. Our comments have been prepared by a committee of global experts in visual inspection for parenteral products on behalf of PDA’s Science Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me.

Sincerely,



Richard Johnson
President and CEO

cc: Janie Miller, PDA