PDA
Parenteral Drug Association

Connecting People, Science and Regulation®

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European Directorate for the Quality
of Medicines & HealthCare (EDQM)
European Pharmacopoeia Department
Council of Europe
7 allée Kastner
CS 30026
F-67081 STRASBOURG
FRANCE

Reference: Proposed European Pharmacopeia Chapter 5.17.2.
Recommendations on testing of particulate contamination: visible particles

Dear European Pharmacopeia Members:

PDA believes that visual inspection for particles is a critical element of providing high quality parenteral medicines. We are encouraged to see the development of additional guidance for industry on this topic and appreciate the opportunity to provide comments to the newly proposed Chapter 5.17.2. *Recommendations on testing of particulate contamination: visible particles* published in Pharmeuropa Issue 30.4.

Overall concerns and observations:

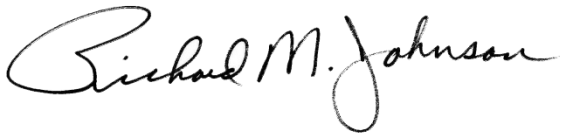
1. **Naming conventions and terminology:** The draft document is establishing new naming conventions that are different than existing compendia and industry naming conventions. If this is intentional, further explanation should be provided for these changes as they are expected to lead to confusion across the industry. For example, the definition of "extrinsic" and "intrinsic" on Page 1, Lines 24-29 utilize the exact terms previously introduced in USP General Chapter ⟨1790⟩ Visual Inspection of Injections and PDA Technical Report 76 Identification and Classification of Visible Nonconformities in Elastomeric Components and Aluminum Seals for Parenteral Packaging, however the definitions in the proposed draft document are not aligned to the existing publications.
2. **Document structure:** The document aims to give guidance on different types of testing required for lyophilized versus liquid products, but it is not always clear and hence difficult to follow which guidance applies to which product type. It is also often unclear if guidance relates to 100% routine inspection, or the non-destructive testing of an AQL sample, and/or the destructive testing of an AQL sample.
3. **Exemption for products administered using in-line filters from practically-free particle requirements:** This concept raises significant

concern, since it is not aligned with other current regulatory views and industry practice.

4. **Example of Quality Control confusing:** The example of Quality Control found on Page 3, Lines 16-19 is confusing as to what quantity of particle(s) may be acceptable. Reference to a Quality Risk Management (QRM) approach may make this discussion clearer.

A table with additional comments referenced to specific page and line numbers is also attached for your consideration.

Sincerely,



Richard Johnson
President, PDA
Cc: Tina Morris, Janie Miller, Ruth Miller

Submission of comments on EP proposed Chapter 5.17.2. Recommendations on testing of particulate contamination: visible particles

Comments from:

Parenteral Drug Association (PDA)

1. General comments

Naming conventions and terminology: The draft document is establishing new naming conventions that are different than existing compendia and industry naming conventions. If this is intentional, further explanation should be provided for these changes as they are expected to lead to confusion across the industry. For example, the definition of "extrinsic" and "intrinsic" on Page 1, Lines 24-29 utilize the exact terms previously introduced in USP General Chapter ⟨1790⟩ Visual Inspection of Injections and PDA Technical Report 76 Identification and Classification of Visible Nonconformities in Elastomeric Components and Aluminium Seals for Parenteral Packaging, however the definitions in the proposed draft document are not aligned to the existing publications.

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Exemption for products administered using in-line filters from practically-free particle requirements: This concept raises significant concern, since it is not aligned with other current regulatory views and industry practice.

Example of Quality Control confusing: The example of Quality Control found on Page 3, Lines 16-19 is confusing as to what quantity of particle(s) may be acceptable. Reference to a Quality Risk Management (QRM) approach may make this discussion clearer.

Specific comments on text

Line number(s) of the relevant text	*(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 1, Lines 8-9	It would be helpful to clarify the link to EU Annex 1 Manufacture of Sterile Medicinal Products; either the current version or chapters 8.26 to 8.29 in the proposed revision published December 20, 2017 if a final version is published before publication of this EP chapter.
Page 1, Lines 9-11	Please clarify the scope of this document regarding 100% inspection, non-destructive acceptance sampling (or AQL inspection) and/or laboratory (QC) appearance or destructive testing. All of these topics appear to be addressed, however it is not always clear which of these topics is being discussed in each section of the document.
Page 1, Line 14	Please clarify which liquid preparations this document is applicable to. For example, does it apply to topical ophthalmic preparations?
Page 1, line 16-19	There is no clinical evidence to support the statement that visible particles present a potential safety concern and as a result their presence should be minimized and represents an unsupported assertion that detracts from the desired substantive information that follows. Suggest the following edit: "Visible particles should be minimized as far as possible in any product intended for parenteral administration to humans or animals. As visible particles can be assumed…"
Page 1, Lines 21-22	Unclear if all particles found should require an investigation. If this is the intent than this seems an unnecessarily burdensome requirement. Better to emphasize identification and investigation of atypical particles and when an AQL limit is exceeded or warranted by trending. The intent may better be achieved through routine tracking and trending of inspection results.
Page 1, Lines 24-27	The definitions and examples of "extrinsic" and "intrinsic" particles does not agree with current compendial guidance found in USP <1790> and PDA TR 76. The examples further confuse the intent since they are not consistent with the source of the particle. It is suggested that existing definitions be adopted here, or further explanation given as to why they need to be different.
Page 1, Lines 28-29	"Fatty acid particles "from degradation appears to be a very specific case and it seems would still require a safety assessment for the product(s)in question.
Page 1, Line 33-36	It is suggested that the use of "inherent particles" terminology be introduced as found in USP <1790> to better describe intended particles from the active substance itself.
Page 1, Line 47	These recommendations are confusing because they mix 100% inspection (e.g., light intensity and inspection time) and supplemental or destructive testing in the laboratory (e.g., dilution). Clarification of scope and improved structure of the document would be helpful. Specifically, separate paragraphs for actions suitable for 100% and those for destructive testing would help clarify the intended guidance here.
Page 2, Lines 8-9	All containers where extrinsic and/or intrinsic particles are observed should be removed during visual inspection, however those that contain inherent or intended particles (e.g., active drug substance) may be accepted depending on the nature of the particles. Please clarify which units with particles are to be removed to avoid confusion.
Page 2, Lines 11-12	While acceptance sampling (AQL inspection) provides a good check on the 100% inspection process and batch quality, it can not guarantee that all defective containers are eliminated. This is based on the limits of the statistical sample and the probabilistic nature of the visual inspection performed at each stage (100% and acceptance sample).
Page 2, Lines 18-19	The term "cross validation" is not a widely used term for this process. Most would require a validated process that is demonstrated to achieve inspection results equivalent of better than the manual compendial method.
Page 2, Lines 27-28	Recommend removing magnification or providing further guidance on when it may be appropriate since it is not recommended in the EP, USP or JP inspection methods.

Line number(s) of the relevant text	*(If changes to the wording are suggested, they should be highlighted using 'track changes')*
Page 2, Lines 33-36	Recommend not suggesting removal of “all” visible particles, but rather use the term “practically free” or “essentially free” as found in the EP and USP chapters.
Page 2, Lines 45-47	Suggest reference to the special sampling plans in ISO 2859 for destructive testing.
Page 3, Line 1-3	Again, clarification of the scope of this chapter would be helpful. Application of visual inspection to stability studies might be better discussed separately. While some of the visual attributes observed for stability samples are the same as those during routine 100% inspection, the goals are different in that the emphasis is on stability indicating attributes such as precipitation, agglomeration, discoloration, glass delamination and not the more typical extrinsic and intrinsic particles. Methods discussed in this and other inspection chapters are certainly a useful reference for inspection of stability samples, but modification of these methods and inspection conditions may be desirable.
Page 3, Lines 13-15	The use of supplemental or destructive testing here may make this clearer as quality control testing is a very broad term with many applications.
Page 3, Lines 16-17	The example of quality control is confusing as to what quantity of particle(s) may be acceptable. Recommend removing this sentence and adding a reference to a Quality Risk Management (QRM) approach to make this discussion clearer.
Page 3, Lines 27-32	The use of in-line filters may be justified in some situations where the utility of the filter has been appropriately supported by clinical evidence, but current regulatory and industry practice does not support a general exemption from the requirements to be “practically free” of visible particles as found in 2.9.20 or other compendial guidance.