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15 February, 2022

Food and Drug Administration,
Dockets Management Staff (HFA–305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Docket No. FDA-2021-D-0241-0002

Re: Inspection of Injectable Products for Visible Particulates Guidance for Industry

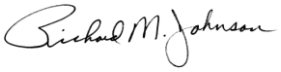
Dear Madam or Sir,
PDA appreciates the opportunity to comment on FDAs draft guidance on Inspection of Injectable Products for Visible Particulates Guidance for Industry. PDA supports FDA's efforts to enhance guidance in this important area of inspection related to visible particulates in parenteral products. PDA agrees the overall guidance is well written and is pleased to see the joint effort across CDER, CBER, and CMV to develop this draft guidance.

However, PDA recommends it would benefit from drawing developed details from additional references that are commonly used to better understand the application of visual inspection to injectable medicine inspection. There are many information sources such as USP General Chapter <1> Injections and PDAs Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products which could serve as supporting resources.

The PDA commenting committee has developed detailed comments which are provided for your consideration in the comments attached to this cover letter.

PDA would be happy to collaborate with FDA in the continued development of this guidance. Like FDA, 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 microbiology 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, PDA
cc: Jahanvi Miller

U.S. Food and Drug Administration Inspection of Injectable Products for Visible Particulates Guidance for Industry
Docket Number: FDA-2021-D-0241-0002; February 2022

General Comments
We welcome the general alignment with USP <790> and <1790>, which includes common particle type definitions, the recognition that the results of visual inspection are probabilistic, and a risk-based approach.
It is a constructive element of this guidance that it has been reviewed and approved jointly by CDER, CBER and CVM. This will help to align agency expectations and response among the centers.
We welcome and agree with support for a lifecycle approach incorporating visual inspection for continuous process improvement and defect reduction.
The guidance would benefit from additional references that are commonly used to better understand the application of visual inspection to injectable medicine inspection. (Visible Particulates in Injections – A History and a Proposal to Revise USP General Chapter Injections <1>, RE Madsen, RT Cherris, JG Shabushnig and DG Hunt, Pharmacopeial Forum, 35(5) pgs. 1383-1387, Sept-Oct 2009. Visual Inspection and Particulate Control D. Scott Aldrich, Roy T. Cherris and John G. Shabushnig, DHI Press ©2016, PDA Bookstore Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products; Bukofzer, S., Ayres, J., Chavez, A., Devera, M., Miller, J., Ross, D., Shabushnig, J., Vargo, S., Watson, H., and Watson, R., PDA J Pharm Sci and Technol 69, 123-139 (2015))

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150-155	To ensure product quality and to limit clinical risk, manufacturers should conduct a risk assessment during product development. … identify typical visible particulates … and characterize their size ranges, quantity, and composition; determine risks for each type; and provide a visual description (e.g., photographs or drawings of typical defects) to be used for training purposes.	While this process can begin during development, the equipment used for clinical manufacturing can differ from that for commercial production and thus the particle profile will also differ. Some of this information may be available when manufacturing clinical supplies but this risk assessment generally requires information not available until later in the scale-up and manufacturing process. Suggest a more general statement on collection and assessment of this information during development with the goal of a more complete risk assessment before commercial manufacture.
256-257	In addition, the quality unit should sample each batch for acceptance quality limit (AQL) testing.	As written, it reads as if the quality unit must physically sample the batch. It may not be practical to have the quality unit perform this sampling in many cases, and it should be sufficient that quality provides oversight. **In addition, the quality unit should oversee sampling of ~~sample~~ each batch for acceptance quality limit (AQL) testing.**

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307-312	"Automated Inspection Technology …"	The primary use is to replace 100% manual inspection when production volume is large enough to justify the high capital and support cost of AVI. It is unclear what is meant here, "as part of an investigation" or "as an additional quality assurance step". Manual inspection is generally preferred for AQL inspection and investigations due to the flexibility of human inspection and its ability to respond to atypical defects (i.e., other than those on which the inspector was previously trained). Instrumental methods may be helpful in further forensic identification of particles but this is not usually referred to as automated inspection. Suggest removing uses as part of an investigation or as an additional quality assurance step unless further information and references can be provided for these uses.
343-344, 392	Among the automated inspection technologies currently in use (e.g., high-speed industrial camera, visible diode array, X-ray, near-field radar, ultraviolet and near-infrared spectroscopy) …	While some research using X-ray, near-field radar, ultraviolet and near-infrared spectroscopy have been performed these techniques have showed limited utility and limited or no commercial availability for pharmaceutical inspection. Suggest removing these examples unless good references can be provided showing practical application.
390	Opaque products and containers	Guideline for opaque products is introduced in Line 390 “Opaque products and containers”. All discussion before this point applies only to non-opaque liquid products, which is not defined as such. It will be beneficial to clarify which part the guidance applies to non-opaque liquid products vs. opaque products such as suspensions, adjuvant-based vaccines, etc.
430-434	Extrinsic particulates identified during 100% inspection or AQL of the batch—which suggests the presence of filth, sterility assurance issues, or other CGMP violations—may result in product that could be considered adulterated, even if the statistical sampling acceptance criteria are met ... and should trigger increased scrutiny of the batch.	This paragraph instructs manufacturers to identify the nature of the particulate found during 100% inspection or AQL. During 100% inspection, due to large quantity of product, there could be many product units found with particulates. It is not practical to isolate and identify each particulate with appropriate analytical technic to differentiate particulates such as intrinsic, extrinsic, or inherent particulates. It is more feasible to do so during AQL inspection. In addition, extrinsic particulates other than those of biological origins are

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		usually found with various frequency (but never zero frequency) during 100% visual inspection of every parenteral drug product batch. To follow the logic in this paragraph, manufacturers will apply increased scrutiny of every single batch produced. Extrinsic particulates of biological origins (e.g., hair, insect parts) identified during 100% inspection and any extrinsic particulates identified during AQL inspection of the batch—which suggests the presence of filth, sterility assurance issues, or other CGMP violations—may result in product that could be considered adulterated, even if the statistical sampling acceptance criteria are met ... and should trigger increased scrutiny of the batch.
470	Automated inspection machines … can be qualified using training standards or artificial intelligence technology.	This suggests that qualification can be done with artificial intelligence alone rather than in combination with trainings standards. This does not appear feasible with current or proposed technologies. Suggest separating discussion of AI from qualification. AI may be used for inspection method development, but qualification/validation of the resulting method's inspection performance should include the use of defect standards.
475	This test set should be prepared and approved by quality assurance staff.	As written, it reads as if the quality unit must develop and approve the test set. Quality may not be the best qualified in all cases to create or develop these test sets. These test sets are also sometimes purchased externally and therefore not made by quality. It should be sufficient to have quality unit approval. **This test set should be ~~prepared and~~ approved by quality assurance staff.**
492-494	The quality unit should also establish and approve qualification protocols that identify the sample test sets, test duration, grading method for test results, documentation of test results, acceptance criteria for certification, and actions to be taken for test failures.	As written, it reads as if the quality unit must author and approve the protocols. Quality may not be best qualified to author these protocols in all cases. It should be sufficient to have quality unit approval of the protocols. **The quality unit should also ~~establish and~~ approve qualification protocols that identify the sample test sets, test duration, grading method for test results, documentation of test results, acceptance criteria for certification, and actions to be taken for test failures.**
549-550	FDA does not recommend more than one reinspection in an attempt to release a batch with atypical defect levels.	While there are risks associated with repeat reinspection that must be considered and controlled, there are some instances where a second

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		reinspection can be reasonably justified. A limit of 2 reinspection would allow for instances where a second reinspection is justified (e.g., the first focused reinspection identifies an unexpected defect that requires a second separate focused reinspection). **FDA does not recommend more than ~~one~~ two reinspection in an attempt to release a batch with atypical defect levels.**