Docket number: FDA-2021-D-0241*:* Inspection of Injectable Products for Visible Particulates (FDA), Guidance for Industry, December 2021

Comments submitted by International Society for Pharmaceutical Engineering (ISPE)

General Comments on the Document

The content of the guidance includes more topics than the title suggests. The title only refers to visual inspection. The content comprises additional topics, e.g. manufacturing and product lifecycle considerations, investigations. We suggest improving the title to reflect the full content of the document. (e.g., reference to pharmacopoeia, product design and GMP topics such as facilities design, equipment design…)

Specific Comments on the Text

ISPE indicates text proposed for deletion with ~~strikethrough~~ and text proposed for addition with **bold and underlining**.

Line Number	Current Text	Proposed Change	Rationale or Comment
34 – 40 and 162 - 231	Definition of inherent, intrinsic, and extrinsic particulates	For the definition of inherent, intrinsic, and extrinsic particulates, please refer to the definitions in USP chapter <1790> section 4.1 OR The explanation given in this chapter should be copied. We suggest using the USP definition in this document for more clarity or refer to pharmacopoeia monograph N°.	Definition of the different kinds of particles should be aligned with the USP definition in chapter <1790> section 4.1 Different definitions lead to different interpretations.
123	(e.g., physical size or shape)	~~(e.g., physical size, shape or others …)~~ We suggest not considering examples (e.g.,) as being requirements.	We consider this part as just general information to explain why we need to make visual inspection on sterile injectable products and further detail is not required.

Line Number	Current Text	Proposed Change	Rationale or Comment
227 - 228	Threshold studies should be conducted to determine the characteristics (e.g., size, shape, color) of visible particulates that can be reproducibly detected	Threshold studies should be conducted to determine the characteristics (e.g., size, ~~shape~~ color) of visible particulates that can be reproducibly detected	Not every type of shape can be quantified or described sufficiently to allow detection by a trained operator by an instrument Therefore, the word shape should be deleted
243	During process scale-up or transfer to contract manufacturers, the…	During process scale-up, **transfer to other sites** or transfer to contract manufacturers, the….	The inspection methods should also be assessed when transferred with different VI processes a company. This could be part of the change management process.
271 - 293	1. Components and Container Closure Systems… 2. Facility and Equipment…	We suggest removal of lines 271 to 293 since these sections are not strictly relevant to Inspection. They are important cGMP requirements.	These two chapters are not related to the 100% inspection process.
299 - 301	The light intensity of the inspection station is also critical to achieving maximum visibility. Manufacturers should consider container color, size, and shape as well as product characteristics when determining the ideal intensity.	The light intensity of the inspection station is also critical to achieving maximum visibility **and should be established using USP <790>.** Manufacturers should consider container color, size, ~~and shape…~~	Light intensity is defined in the USP. A uniform approach is needed. We suggest staying with the content of the monograph pharmacopoeia
315	Regardless of the technique - manual, semi-automated, or automated - the inspection environment should be free from distractions and extraneous light, and…	Regardless of the technique - manual, **or** semi-automated~~, or automated~~ - the inspection environment should be free from distractions and extraneous light, and…	Automated inspection equipment does not necessarily need to stand isolated from extraneous light, since, e.g., cameras are covered within the machine and not influenced by light sources outside of the machine
315 - 316	and the inspection rate should be qualified and should allow for thorough visual inspection	and the inspection rate should be ~~qualified~~ **verified** and should allow for thorough visual inspection	Inspection rate cannot be qualified, only the process.
350 - 354	Manufacturers should conduct inspection feasibility studies for visible particulate	Manufacturers should ~~conduct~~ **consider** inspection feasibility studies for visible	There should also be the possibility that manufacturers rely on other scientifically

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	detectability, unit inspection duration, illumination, and fatigue time frame. These studies should be scientifically based and analyzed using appropriate statistical methodology. Depending on the study results, Manufacturers may need to adjust particulate standards or inspection processes or, in some cases, change equipment to improve accuracy and reduce patient risk	particulate detectability, unit inspection duration, illumination, and fatigue time frame. These studies should be scientifically based and analyzed using appropriate statistical methodology. Depending on the study results, Manufacturers may need to adjust particulate standards or inspection processes or, in some cases, change equipment to improve accuracy and reduce patient risk	based studies performed independently. There is no rationale why each manufacturer has to perform similar studies on its own.
362 - 365	A complete program for the control and monitoring of particulate matter must include written procedures for production and process control, sampling and testing of in-process materials, and control of microbiological contamination that are designed to minimize the occurrence of visible particulates, identify affected batches of injectable product, and facilitate investigation to determine the sources of visible particulates (§§ 211.100, 211.110, and 211.113).	We suggest modifying the title of the document - see general comment.	This section is not part of the Visual Inspection Process – see general comment.
370 - 374	Adequate written procedures can contribute to a more thorough understanding of the potential sources and quantity of visible particulates, leading to improvements in process design. The increased level of understanding would also promote a more robust particulate control program and higher quality investigations (see § 211.192).	We suggest modifying the title of the document - see general comment.	These sentences are not directly related to the inspection process itself; it is part of an investigation process. See general comment.

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430 - 432	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.	Extrinsic particulates ~~identified during 100% inspection or AQL of the batch—which suggests~~ **that indicate** the presence of filth, sterility assurance issues, or other CGMP violations **identified during 100% inspection or AQL of the batch** may result in product that could be considered adulterated, even if the statistical sampling acceptance criteria are met. **Investigation should be carried out to assess product quality impact.**	Better delineation between the terms "adulterated" and "extrinsic particulates"; there might also be extrinsic particulates that do not indicate the presence of filth, sterility assurance issues, or other CGMP violations.
433 - 434	Likewise, multiple visible particulates (extrinsic or intrinsic) within a single container may be indicative of manufacturing problems and should trigger increased scrutiny of the batch.	Sentence should be deleted. Batches with unusual level defects when compare with routine defect numbers should lead to an investigation	Not only a single container with multiple visible particulates can indicate manufacturing problems but also multiple containers containing one particulate. Elevated levels in the lot may implicate a broader contribution from the same source with higher risk than a single multiple visible particulates event in one unit.
436 – 438	If retained samples are used to evaluate the suitability of product in distribution (such as in the case of product complaints), manufacturers should consider additional factors such as historical data for the facility and/or product when evaluating the suitability of a given product batch.	See general comment on the title	The content is not aligned with the title. See general comment.
447 - 448	Only certified inspectors and qualified equipment should be used to inspect injectable products for visible particulates.	Only certified inspectors and ~~qualified~~ **suitable controlled** equipment **and environment** should be used to inspect injectable products for visible particulates.	Meaning of qualified equipment? The equipment has to be suitable for use (light intensity, inspection station) and controlled.

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462 - 463	The specific backdrop and light intensity selected for manual inspection stations should be qualified.	The specific backdrop and light intensity selected for manual inspection stations should be specified **and controlled**.	Meaning of qualification in the context of light intensity or inspection station? The correct parameters for these types of equipment have to be specified and controlled to ensure suitability for use.
465 - 467	Semi-automated inspection equipment should be properly calibrated and qualified at a specific vial-spin and belt speed. Lighting should also be qualified to allow for accurate human detection of defective products.	Semi-automated inspection equipment should be properly calibrated and qualified at a specific vial-spin and belt speed. Lighting should also be ~~qualified~~ **specified and controlled** to allow for accurate human detection of defective products.	Meaning of qualification in the context of lighting? The correct parameters for the lighting have to be specified and controlled to be suitable for use.
469-471	Automated inspection machines should be validated to meet or surpass human inspection capabilities and can be qualified using training standards or artificial intelligence technology	We suggest incorporating AI development requirement.	AI should also be qualified using training standards (test kits). AI should be developed using good practices standards for development, learning and production to keep the system under control.
475	This test set should be prepared and approved by quality assurance staff.	This test set should be prepared **by competent personnel and** approved by quality assurance staff.	Preparation of test is usually set by knowledgeable personnel and approved by QA.
479	Quality assurance staff should review the library of defective samples and compare the samples to established standards for proper classification.	It should be ensured by QA that the defective samples in the library are properly classified according to established standards.	Allow quality unit to delegate this activity.
489 - 490	The quality unit should control the test sets to ensure that qualification tests are not manipulated or biased.	It should be ensured by QA that test sets are not manipulated or biased.	We suggest making additional clarity and allow quality unit to delegate this activity
492	The quality unit should also establish and approve qualification protocols that identify the sample test sets, test duration...	The quality unit should also ~~establish and~~ approve qualification protocols that identify the sample test sets, test duration **prepared by knowledgeable personnel**. ...	Establishment of qualification protocol is usually performed by knowledgeable personnel.

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547 - 550	Reinspection of product batches may be permissible with appropriate scientific justification and should be conducted according to approved SOPs with tightened acceptance criteria. FDA does not recommend more than one reinspection in an attempt to release a batch with atypical defect levels.	Suggested modified text for the last sentence: "FDA does not recommend more than one reinspection in an attempt to release a batch with atypical defect levels, **however, based on a thorough route case investigation and justification supported by a risk assessment and application of AQL testing more than on reinspection could be considered.**	