
Inspection of Injectable Products for Visible Particulates Guidance for Industry

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)**

**December 2021
Pharmaceutical Quality/CMC**

Inspection of Injectable Products for Visible Particulates Guidance for Industry

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1 **Inspection of Injectable Products for Visible Particulates**
2 **Guidance for Industry¹**
3

4
5 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
6 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
7 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
8 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
9 for this guidance as listed on the title page.
10

11
12
13 **I. INTRODUCTION**
14

15 Visible particulates in injectable products can jeopardize patient safety. This guidance addresses
16 the development and implementation of a holistic, risk-based approach to visible particulate
17 control that incorporates product development, manufacturing controls, visual inspection
18 techniques, particulate identification, investigation, and corrective actions designed to assess,
19 correct, and prevent the risk of visible particulate contamination.² The guidance also clarifies that
20 meeting an applicable United States Pharmacopeia (USP)³ compendial standard alone is not
21 generally sufficient for meeting the current good manufacturing practice (CGMP) requirements
22 for the manufacture of injectable products. The guidance does not cover subvisible particulates⁴
23 or physical defects that products are typically inspected for along with inspection for visible
24 particulates (e.g., container integrity flaws, fill volume, appearance of lyophilized
25 cake/suspension solids).
26

27 For the purpose of this guidance:

- 28
29 • *Particulates* refer to mobile, undissolved particles other than gas bubbles that are
30 unintentionally present in an injectable product.⁵ They vary in nature (e.g., metal, glass,

¹ This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, Center for Veterinary Medicine, Office of Regulatory Affairs, and Office of Combination Products in the Office of the Commissioner and in consultation with the Center for Devices and Radiological Health at the Food and Drug Administration.

² Visual detection of a particulate is a probabilistic process that depends on, among other things, the product and the size and shape of the particulate (see United States Pharmacopeia General Chapter <1790> *Visual Inspection of Injections*). Therefore, threshold studies should be conducted to determine the size of visible particulates that can be reproducibly detected by trained personnel with near normal visual acuity. For more information about threshold studies, see section IV in this guidance.

³ USP references in this guidance refer to USP 42–NF 37.

⁴ In general, subvisible particulates are those that cannot be seen with the naked eye. See USP General Chapters <788> *Particulate Matter in Injections* and <787> *Subvisible Particulate Matter in Therapeutic Protein Injections* for information about subvisible particulates control.

⁵ See, e.g., USP General Chapter <788>.

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31 dust, fiber, rubber, polymer, mold, degradant precipitate) and can be divided into three
32 categories⁶:

- 33
- 34 ○ *Inherent particulates* are particulates that are an innate product characteristic.
- 35
- 36 ○ *Intrinsic particulates* are particulates that are derived from the manufacturing
37 equipment, product formulation, or container system.
- 38
- 39 ○ *Extrinsic particulates* are particulates that originate from the manufacturing
40 environment and are foreign to the manufacturing process.
- 41
- 42 ● *Injectable products* generally refer to injectable human drugs approved under section 505
43 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), injectable animal drugs
44 approved under section 512 or conditionally approved under section 571 of the FD&C
45 Act, and injectable biological products licensed under section 351 of the Public Health
46 Service Act. In some cases, the injectable product may be a drug or biological product
47 constituent part of a combination product, such as a drug or biological product prefilled
48 into a syringe (see 21 CFR part 3).⁷
- 49

50 The contents of this document do not have the force and effect of law and are not meant
51 to bind the public in any way, unless specifically incorporated into a contract. This
52 document is intended only to provide clarity to the public regarding existing requirements
53 under the law. FDA guidance documents, including this guidance, should be viewed only
54 as recommendations, unless specific regulatory or statutory requirements are cited. The
55 use of the word *should* in Agency guidance means that something is suggested or
56 recommended, but not required.

II. STATUTORY AND REGULATORY FRAMEWORK

57

58

59

60

61 Under section 501 of the FD&C Act, a drug product, including an injectable product, is deemed
62 adulterated if:

⁶ See USP General Chapter <790> *Visible Particulates in Injections*, which describes inspection procedures used to demonstrate that injectable products are essentially free from particulates, and USP General Chapter <1790>, an informational chapter that provides recommendations on inspection programs for visible particulates covering the injectable product life cycle.

⁷ This guidance generally cites regulatory requirements for drugs and biological products, but where appropriate, also cites relevant requirements for combination products. The regulatory requirements for combination products derive from the statutory and regulatory requirements applicable to their constituent parts, which do not lose their distinct regulatory identity when they become part of a combination product. See, e.g., draft guidance for industry and FDA staff *Principles of Premarket Pathways for Combination Products* (February 2019), which, when final, will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>. See also FDA's Combination Products Guidance Documents web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/combination-products-guidance-documents>.

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- 64 • “It has been prepared, packed, or held under insanitary conditions whereby it may have
65 been contaminated with filth, or whereby it may have been rendered injurious to health”
66 (section 501(a)(2)(A)).
67
- 68 • “It is a drug and the methods used in, or the facilities or controls used for, its
69 manufacture, processing, packing, or holding do not conform to or are not operated or
70 administered in conformity with current good manufacturing practice to assure that such
71 drug meets the requirements of this Act as to safety and has the identity and strength, and
72 meets the quality and purity characteristics, which it purports or is represented to
73 possess” (section 501(a)(2)(B)).
74
- 75 • “It purports to be or is represented as a drug the name of which is recognized in an
76 official compendium, and its strength differs from, or its quality or purity falls below, the
77 standards set forth in such compendium” (section 501(b)).⁸
78
- 79 • It is a new animal drug that is unsafe within the meaning of section 512 (section
80 501(a)(5)).
81

82 Adherence to FDA’s CGMP requirements as set forth in section 501 of the FD&C Act and 21
83 CFR parts 210 and 211 for drug, animal drug, and biological products; §§ 600.10 through 600.15
84 for biological products; and part 4 for combination products⁹ is essential for the control of visible
85 particulates in injectable products.
86

87 Adherence to compendial standards can also assist manufacturers in complying with CGMP
88 requirements (see, e.g., §§ 211.194(a)(2) and 211.165(e)).
89

90 USP General Chapter <1> *Injections and Implanted Drug Products (Parenterals)—Product*
91 *Quality Tests* states that “[t]he inspection process should be designed and qualified to ensure that
92 every lot of all parenteral preparations is essentially free from visible particulates” as defined in
93 USP General Chapter <790> *Visible Particulates in Injections*. Injectable products with a USP
94 monograph are required to meet the applicable criteria from these USP General Chapters (see
95 section 501(b) of the FD&C Act). Noncompendial products should also be “essentially free from
96 visible particulates” as defined in USP General Chapter <790>.
97

98 Applying acceptance criteria, such as the criterion outlined in USP General Chapter <790>, is an
99 important component of the overall visible particulate control program, but meeting these
100 acceptance criteria is not alone sufficient to ensure compliance with the applicable CGMP
101 requirements identified above, which cover a broader array of manufacturing practices than
102 product inspection. Full compliance with CGMP requirements is needed to ensure the continued
103 supply of pure, safe, and effective injectable products.

⁸ *Official compendium* is defined in section 201(j) of the FD&C Act as “the official United States Pharmacopeia, official Homoeopathic Pharmacopeia of the United States, official National Formulary, or any supplement to any of them.”

⁹ 21 CFR part 4 establishes the CGMP requirements and postmarketing safety reporting requirements for combination products. See also guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017).

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104
105 In accordance with USP General Chapter <1>, injectable products should be prepared in a
106 manner designed to exclude visible particulates, and the inspection process should be designed
107 and qualified to ensure that the products are essentially free of visible particulates. Each final
108 container must be inspected (100% inspection) using a qualified method to detect particles
109 within the visible size range, and all units that are found to contain visible particulates must be
110 rejected (§§ 211.160(b) and 211.110(c) and (d); see also USP General Chapter <1>).

111
112 Depending on the clinical risk profile associated with a specific product, FDA may expect that
113 product to comply with stricter standards than those set forth in the compendia in order for those
114 products to meet CGMP requirements.¹⁰ Applicants implementing postapproval changes to their
115 manufacturing processes that are intended to ensure a product is essentially free from visible
116 particulates must follow existing FDA regulations and should follow existing FDA guidance.¹¹

117
118

III. CLINICAL RISK OF VISIBLE PARTICULATES

119
120
121 The clinical manifestations of adverse events caused by particulate contamination vary and may
122 depend on the route of administration (e.g., intravascular, intravisceral, intramuscular), patient
123 population, and nature or class of the particulates themselves (e.g., physical size or shape,
124 quantity, chemical reactivity to certain cells or tissues, immunogenicity, infectivity,
125 carcinogenicity). Particulates in intravascular or intravisceral injections generally can cause more
126 adverse events than those in subcutaneous or intramuscular injections. According to published
127 case reports (Langille 2014; Doessegger et al. 2012), serious adverse events involving injectable
128 products contaminated with visible particulates have included:

- 129
- 130 • At the systemic level, infection and venous and arterial emboli (thrombotic or
131 nonthrombotic).
 - 132 • Microscopic emboli, abscesses, and granulomas in visceral organs.
 - 133 • Phlebitis, inflammatory reactions, granulomas, and infections at injection sites.
- 134
135
136

137 Furthermore, different patient populations may have different risks for developing adverse events
138 after exposure to injectable products contaminated with particulates. Risk factors include age

¹⁰ There are statutory CGMP requirements applicable to products addressed in this guidance. For human drug products, see sections 505(d)(3), 505(j)(4)(A), 505(b)(1)(D), and 505(j)(2)A(vi) of the FD&C Act. For animal drug products, see sections 512(d)(1)(C), 512(c)(2)(A)(i), 512(b)(1)(D), and 512(n)(1)(G) of the FD&C Act. For biological products, see section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)(2)(C)). See also 21 CFR parts 210 and 211, §§ 600.10 through 600.15, and part 4.

¹¹ For approved new drug applications, see 21 CFR 314.70 and guidance for industry *Changes to an Approved NDA or ANDA* (April 2004). For approved biologics license applications, see 21 CFR 601.12 and guidances for industry *Changes to an Approved Application: Biological Products* (July 1997), *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997), and *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (June 2021). For approved new animal drug applications, see 21 CFR 514.8 and guidance for industry *Chemistry, Manufacturing, and Controls Changes to an Approved NADA or ANADA* (May 2007).

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139 (e.g., pediatric and elderly patients), personal or family history of thrombophilia, major surgery,
140 cancer, trauma, underlying infection, autoimmune disease, diabetes-associated late-stage
141 vasculitis, obesity, and smoking.¹²

142
143 Applicants should consider these clinical risk factors when developing their quality target
144 product profile and in establishing an appropriate control strategy and acceptance criteria for
145 visible particulates.¹³

146
147

148 IV. QUALITY RISK ASSESSMENT

149

150 Visible particulates can have a negative effect on overall product quality. To ensure product
151 quality and to limit clinical risk, manufacturers should conduct a risk assessment during product
152 development.¹⁴ During this risk assessment, manufacturers should identify the typical visible
153 particulates that could contaminate the injectable product and characterize their size ranges,
154 quantity, and composition; determine risks for each type; and provide a visual description (e.g.,
155 photographs or drawings of typical defects) to be used for training purposes.¹⁵ Manufacturers
156 should also consider the potential sources of particulates, appropriate analytical methods to
157 monitor them, and mitigation strategies to prevent their presence in the final product.

158

159 Different considerations are relevant depending on the category of particulates found during the
160 risk assessment:

161

162 • **Inherent particulates** are associated with specific products or their formulations—such
163 as proteinaceous particulates, liposomes, or agglomerates—and are considered part of the
164 quality target product profile. Their presence should not be cause for rejection of
165 individual units or product batches if they are a property of the approved product and
166 product release specifications are met. For hard-to-inspect products containing inherent
167 particulates, such as suspensions or emulsions, manufacturers should develop
168 supplemental testing methods to ensure adequate detection of visible particulates (see
169 section V, Visual Inspection Program Considerations). In addition, manufacturers should
170 monitor time-dependent changes during stability testing that may lead to increases in size
171 or number beyond the approved acceptance criteria.

172

173 • **Intrinsic particulates** can be related to the manufacturing process. Such particulates
174 could come from components, containers and closures (e.g., glass vials, rubber stoppers),
175 and product contact processing equipment (e.g., tubing, filters, gaskets). Manufacturers
176 should control such particulates before the actual manufacturing process through careful

¹² The potential clinical risk is further supported by animal studies from the literature (Pesko 1996; Barber 2000; Langille 2014). In animals massively infused with particulates, histopathology findings include endothelial cell injury in pulmonary capillaries, pulmonary capillary microscopic thrombi, pulmonary microscopic granulomata, and inflammatory hepatitis (Liu et al. 1992; Jones and Warren 1992; Bautista et al. 1992).

¹³ See International Council for Harmonisation (ICH) guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

¹⁴ See section II.3 of Annex II in ICH guidance for industry *Q9 Quality Risk Management* (June 2006).

¹⁵ See section V.C in this guidance for information about training.

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177 selection and quality control of components, containers and closures, packaging
178 materials, and manufacturing equipment. Additionally, manufacturers should conduct
179 studies to determine whether their manufacturing processes generate particulates.
180 Similarly, manufacturers should study and understand the impact of handling, washing,
181 and sterilization processes on manufacturing equipment (i.e., wear and tear) that could
182 lead to particulate generation over time. Such process development studies can minimize
183 intrinsic particulates by informing selection of the appropriate handling, washing, and
184 sterilization procedures and establishing equipment life spans. Manufacturers should also
185 evaluate trends in reject data at designated manufacturing facilities and use a life cycle
186 management approach to monitor and control process-related intrinsic particulates in
187 their final products.

188
189 Intrinsic particulates can also be related to the formulation or stability of the product or
190 its container closure (e.g., particulates formed because of precipitation of active
191 pharmaceutical ingredients, glass delamination, or protein-silicone oil interaction). These
192 types of particulates can form after product release and can change in size or number
193 when the product is stored. Manufacturers should study the risk of this type of intrinsic
194 particulate forming under accelerated or stressed conditions in the product development
195 phase to determine particulate characteristics and any time-dependent particulate
196 formation or growth that can occur. In addition, an analytical method suitable for
197 characterizing and monitoring product-specific particulates should be developed. A
198 robust product design achieved through formulation optimization and container closure
199 screening during development is critical to reduce the formation of product-related
200 intrinsic particulates. Information obtained from these studies can be used to support
201 product-specific inspection processes (e.g., particulate seeding for test kits with known
202 product-specific intrinsic particulates, particulate identification, and rejection
203 classification).

204
205 • **Extrinsic particulates** arise from sources other than the formulation's components, the
206 containers and closures, or the manufacturing equipment's product contact surfaces.
207 These particulates, derived from materials not intended to be in contact with the
208 injectable product, can negatively affect product quality and could indicate possible
209 microbial contamination or another CGMP issue. Their presence in the final product can
210 occur because of poor conditions in the manufacturing facility (e.g., poor environmental
211 control; equipment design, age, and maintenance; facility location, construction, and
212 maintenance; material and personnel flows). Manufacturing facilities must be CGMP
213 compliant and of appropriate design to support the manufacture of injectable products
214 (see 21 CFR part 211, subpart C; § 211.63; and part 4).

215
216 Manufacturers should not rely on downstream adjustments during manufacturing to justify a
217 poorly designed product or process. Instead, quality should be built into the manufacturing
218 process, starting with the development phase and continuing during scale-up, process
219 qualification studies, and commercial manufacturing.¹⁶ Successful management of visible

¹⁶ See guidance for industry *Process Validation: General Principles and Practices* (January 2011).

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220 particulates also includes vigilant assessment of the state of control, early detection of poor
221 process performance, and effective process improvement throughout the product’s life cycle.
222

223 Proactively addressing risk is an important part of a life cycle approach to visible particulate
224 control. Formal risk assessments conducted during product development contribute to process
225 understanding and form a foundation for knowledge management. Their results should be used to
226 establish adequate product-specific production controls and clearly defined in-process alert and
227 action limits for particulates. Threshold studies should be conducted to determine the
228 characteristics (e.g., size, shape, color) of visible particulates that can be reproducibly detected
229 by trained personnel. These threshold studies can also be the basis for establishing particulate
230 standards that will be used to establish inspection procedures, help avoid inspection bias, and
231 allow manufacturers to verify their manufacturing processes are in a state of control.
232

233

V. VISUAL INSPECTION PROGRAM CONSIDERATIONS

234

235
236 Visual inspection can be viewed as part of a larger program to ensure that injectable products are
237 essentially free of visible particulates.¹⁷ During injectable product development, manufacturers
238 should establish procedures for inspecting the product, statistical sampling plan(s),
239 acceptance/rejection criteria, and procedures for evaluating inspection results. Inspection
240 procedures carried over from another site or another product may not always be suitable for a
241 new product.
242

243 During process scale-up or transfer to contract manufacturers, the visual inspection methods
244 should be assessed to confirm they are still appropriate and valid at the new scale or
245 manufacturing site. The visual inspection program should allow for appropriate adaptations
246 based on knowledge gained throughout the product’s life cycle. For example, the inspection
247 procedures and/or analytical and statistical methods may need revision if the batch size,
248 manufacturing process, or conditions change.
249

250 In addition to inspection, a visible particulate control program should include the training and
251 qualification of operators and investigation of discrepancies, including root cause analysis,
252 corrective actions, and preventive actions.
253

254 Trained and qualified personnel, automated inspection technology, or a combination of both
255 should be used to inspect each unit of injectable product for visible particulates (hereinafter
256 *100% inspection*). In addition, the quality unit should sample each batch for acceptance quality
257 limit (AQL) testing.¹⁸ A visual inspection program should ensure that any visible particulates
258 present in the batch at the time of release are only those that have a low probability of detection
259 because they are of a size approaching the visible detection limit. This section covers 100%
260 inspection, statistical sampling, training and qualification, quality assurance through a life cycle
261 approach, and actions to address nonconformance.

¹⁷ See, e.g., USP General Chapter <1790>.

¹⁸ *Acceptance quality limit* refers to the “quality limit that is the worst tolerable process average when a continuing series of lots is submitted for acceptance sampling” (see ASTM E456, Standard Terminology Relating to Quality and Statistics).

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A. 100% Inspection

Manufacturers should conduct 100% inspection during the stage at which there is the greatest likelihood that visible particulates will be detected in the final container (e.g., before labeling to maximize container clarity). Manufacturers should ensure that the equipment used and the physical environment where visual inspection will be performed are designed to minimize variability and maximize detectability in the inspection process.

Important factors to consider follow.

1. Components and Container Closure Systems

Visible particulate contamination could be traced to components or container closure systems. To ensure visible particulate control, manufacturers must have written procedures for the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and product containers (including devices and device components that contact injectable products) (§ 211.80; see also part 4). Such procedures must ensure that components and containers and closures are tested or examined and approved, as appropriate, before use in manufacturing (§ 211.84). Containers and closures must not alter the product's safety, identity, strength, quality, or purity (§§ 211.94(a) and 600.11(h); see also part 4).

2. Facility and Equipment

To comply with CGMP requirements, manufacturing facilities must be designed, constructed, and outfitted with equipment to prevent injectable products from being contaminated with particulates. Applicable CGMP regulations include:

- Buildings and facilities (§§ 211.42 through 211.58 and 600.11).
- Equipment design, size, and location (§ 211.63).
- Equipment construction (§§ 211.65 and 600.11).
- Equipment cleaning and maintenance (§§ 211.67 and 600.11).

Inspections can be conducted manually and/or using a range of automated inspection techniques:

- For **manual inspections**, the inspection station should have a backdrop of one or more solid colors (e.g., black and white) to provide adequate contrast and to allow maximum visibility of product contents. 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.
- During **semi-automated inspections**, a machine rotates the product at a constant rate past a trained inspector's field of vision. Rejected products are removed mechanically or by hand.

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- 307 • **Automated inspection technology** can be used as part of an investigation in the
308 inspection process for injectable products, as a replacement for manual inspection, or as
309 an additional quality assurance step. Automated inspection technology can use different
310 wavelengths and sensors to detect hard-to-see particulates in sterile powder, suspensions,
311 or light-protected injection products for which visual inspection is not completely
312 effective.

313
314 Regardless of the technique—manual, semi-automated, or automated—the inspection
315 environment should be free from distractions and extraneous light, and the inspection rate should
316 be qualified and should allow for thorough visual inspection. Manufacturers can operate
317 independent inspection stations as separate units or units that are connected in a series. Some
318 inspection equipment does not require controlled separate facilities for visible particulate
319 inspection.

320
321 For manual and semi-automated inspections, the inspection environment should be
322 ergonomically designed for inspector comfort.

323
324 For semi-automated and automated inspections, equipment must be routinely calibrated,
325 inspected, or checked in accordance with a written program designed to ensure proper
326 performance, and records of those calibration checks and inspections must be maintained
327 (§ 211.68). Equipment should also be properly qualified. See section V.C, Training and
328 Qualification, for more information.

329
330 When compared with manual inspection, automated inspection technology may improve
331 detectability of visible particulates because machine variability is generally easier to control than
332 the variability individual personnel can bring to tasks performed repetitively over time. In some
333 cases, the technology can detect higher levels of specific visible particulates. In others, it can
334 detect particulates at the lower end of the visual inspection range with greater statistical
335 reliability when compared with manual and semi-automated inspection of the same product
336 (Melchore 2010).

337
338 Automated inspection technology may allow manufacturers to better control product quality.
339 Manufacturers may need to adjust in-process action and alert limits if they change from manual
340 to automated inspection. Adjustments should be based on statistical process and batch data
341 analysis obtained during evaluation and validation of automated inspection equipment.

342
343 Among the automated inspection technologies currently in use (e.g., high-speed industrial
344 camera, visible diode array, X-ray, near-field radar, ultraviolet and near infrared spectroscopy),
345 each has its advantages and disadvantages but, if properly implemented, all can substantially
346 improve the accuracy of visual inspection.

347 3. *Process*

348
349
350 Manufacturers should conduct inspection feasibility studies for visible particulate detectability,
351 unit inspection duration, illumination, and fatigue time frame. These studies should be
352 scientifically based and analyzed using appropriate statistical methodology. Depending on the

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353 study results, manufacturers may need to adjust particulate standards or inspection processes or,
354 in some cases, change equipment to improve accuracy and reduce patient risk.

355
356 Manufacturers must implement written procedures for production and process controls (§
357 211.100), which should cover each aspect of the visual inspection process. Such procedures
358 should cover handling of the units (e.g., swirling, inversion, distance from light), maximum
359 length of the inspection period without a rest break, and disposition and documentation of
360 products that were rejected based on the results of the visual inspection.

361
362 A complete program¹⁹ for the control and monitoring of particulate matter must include written
363 procedures for production and process control, sampling and testing of in-process materials, and
364 control of microbiological contamination that are designed to minimize the occurrence of visible
365 particulates, identify affected batches of injectable product, and facilitate investigation to
366 determine the sources of visible particulates (§§ 211.100, 211.110, and 211.113).

367
368 Written procedures should also cover how to conduct 100% inspections to ensure batches are
369 essentially free of visible particulates. All records must be documented in accordance with
370 applicable regulatory requirements (§ 211.188(b)(5); see also § 600.12). Adequate written
371 procedures can contribute to a more thorough understanding of the potential sources and quantity
372 of visible particulates, leading to improvements in process design. The increased level of
373 understanding would also promote a more robust particulate control program and higher quality
374 investigations (see § 211.192).

375
376 *4. Special Injectable Product Considerations*

377
378 **Large volume parenterals** should undergo the same level of inspection as small volume
379 injectable products. In many cases, patient risk from particulate contamination is higher for large
380 volume parenterals than for small volume injectable products because of the volume of product
381 administered and the potential for a patient to receive a continuous administration over many
382 days. Packaging and labeling of large volume parenterals (e.g., overwraps and printing on the
383 flexible bags) can interfere with visual inspection. Large volume intravenous bags that have an
384 outer bag can be particularly challenging to inspect. Manufacturers should take appropriate
385 measures to ensure adequate 100% inspection of these products. Supplemental destructive testing
386 may also be warranted to ensure these products are essentially free of visible particulates if the
387 packaging does not allow for the identification of particulates within the accepted visible size
388 range.

389
390 **Opaque products and containers** (e.g., lyophilized powders, suspension products, tinted vials)
391 present obvious challenges to visual inspection. Using advanced technologies such as those
392 described in section V.A.2 in this guidance (e.g., X-ray spectroscopy) can help, as can
393 supplemental destructive testing after the 100% inspection, which provides additional assurance
394 of product quality. Supplemental destructive testing may not be warranted, however, if the
395 technology used in the 100% inspection is validated to meet or surpass human inspection

¹⁹ USP General Chapter <790> notes that “a complete program for the control and monitoring of particulate matter remains an essential prerequisite,” but it does not describe such a complete program.

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396 capabilities. Manufacturers should conduct a feasibility study to demonstrate the suitability of
397 the technology selected for the specific product.

B. Statistical Sampling

400
401 Following 100% inspection, manufacturers should employ statistically sound sampling plans,
402 validated inspection methods, and appropriate acceptance criteria to ensure that each product
403 batch meets a pre-established AQL for visible particulate contamination. This is consistent with
404 USP General Chapters <1> and <790>; however, a more stringent sampling plan and acceptance
405 criteria may be appropriate for higher risk products.

406
407 A sampling plan allows the user to make a specific statistical quality statement²⁰ about the
408 attribute of interest (e.g., a defect) in a batch based on the sample size and sampling locations.
409 Manufacturers should select their sampling plans in accordance with the risk for a particular type
410 of product defect. CGMP regulations require manufacturers to ensure that batches of injectable
411 products meet appropriate specifications and statistical quality control criteria as a condition for
412 their approval and release (§ 211.165).

413
414 Manufacturers should quantify the following parameters with respect to design and use of
415 sampling plans²¹:

- 416
417 • Operating characteristic curves developed for each defect classification or quality
418 attribute that is being tested.
- 419
420 • Accept/reject criteria, AQL, and unacceptable quality limit (also referred to as *rejectable*
421 *quality limit*, *limiting quality*, or *lot tolerance percent defective*).

422
423 The methodology and acceptance criteria for the statistical sampling plan should consider patient
424 risk, particulate type, and product and container characteristics that may interfere with particulate
425 visibility. For example, an adequate sampling plan with an acceptable AQL for
426 nondestructive/destructive testing could follow ASTM E2234.²² Firms that wish to propose an
427 alternative minimum standard for their specific product should ensure that there is a risk-based
428 justification for the proposed standard.

429
430 Extrinsic particulates identified during 100% inspection or AQL of the batch—which suggests
431 the presence of filth, sterility assurance issues, or other CGMP violations—may result in product
432 that could be considered adulterated, even if the statistical sampling acceptance criteria are met.
433 Likewise, multiple visible particulates (extrinsic or intrinsic) within a single container may be
434 indicative of manufacturing problems and should trigger increased scrutiny of the batch.

435

²⁰ A statistical quality statement could be, for example, “There is 95% confidence that there are no more than X% defects in the batch.”

²¹ See ASTM E2234, Standard Practice for Sampling a Stream of Product by Attributes Indexed by AQL; ASTM E456, Standard Terminology Relating to Quality and Statistics.

²² ASTM E2234 is equivalent to the ANSI/ASQ Z1.4 standards referenced in USP General Chapters <790> and <1790>.

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436 If retained samples are used to evaluate the suitability of product in distribution (such as in the
437 case of product complaints), manufacturers should consider additional factors such as historical
438 data for the facility and/or product when evaluating the suitability of a given product batch.
439

440 According to § 211.194(a)(2), “the suitability of all testing methods used shall be verified under
441 actual conditions of use.” Manufacturers also must validate and document tests used to ensure
442 that each batch of the product conforms to final specifications for release and distribution
443 (§ 211.165(e)).
444

C. Training and Qualification

445
446
447 Only certified inspectors and qualified equipment should be used to inspect injectable products
448 for visible particulates. Personnel conducting inspections (100% inspection and AQL inspection)
449 must be adequately trained (including, as appropriate, periodic retraining or requalification) (§§
450 211.25 and 600.10(b)).
451

452 Formalized training and qualification programs promote consistent performance by individual
453 inspectors or automated inspection machines and help minimize variability among different
454 inspectors or machines (Melchore 2011). The program can include a combination of training
455 materials, standard operating procedures (SOPs), on-the-job training, and testing. Inspector
456 candidates should be trained in the relevant CGMP requirements and should have normal near
457 visual acuity (with or without the use of corrective lenses) and no impairment of color vision
458 (Ricci et al. 1998).
459

460 Regarding inspection equipment:
461

- 462 • The specific backdrop and light intensity selected for manual inspection stations should
463 be qualified.
464
- 465 • Semi-automated inspection equipment should be properly calibrated and qualified at a
466 specific vial-spin and belt speed. Lighting should also be qualified to allow for accurate
467 human detection of defective products.
468
- 469 • Automated inspection machines should be validated to meet or surpass human inspection
470 capabilities and can be qualified using training standards or artificial intelligence
471 technology.
472

473 For personnel qualification and automated inspection systems validation, a mixture of good
474 injectable product units and defective units containing visible particulates should be used
475 (Melchore 2011). This test set should be prepared and approved by quality assurance staff.
476 Manufacturers should develop libraries of defective units from samples collected throughout the
477 product life cycle, samples created to simulate production defects, or samples purchased to be
478 representative of the types of particulates likely to occur for the drug product and its
479 manufacturing process. Quality assurance staff should review the library of defective samples
480 and compare the samples to established standards for proper classification. The library should
481 contain examples from the lower limits of visual detection determined in the threshold studies. If

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482 a new particulate matter defect is identified, it should be analyzed to determine its source and
483 added to the training library.

484
485 Typically, the percentage of defective units in a test set should not exceed 10–20 percent, and the
486 test set quantities should be sufficient to provide an adequate degree of confidence in the test
487 results. Trained inspectors should review defective units before they are included in the test set to
488 determine if the visible particulates in them can be detected under normal conditions, and the
489 identity of defective units should be masked to test subjects. The quality unit should control the
490 test sets to ensure that qualification tests are not manipulated or biased.

491
492 The quality unit should also establish and approve qualification protocols that identify the
493 sample test sets, test duration, grading method for test results, documentation of test results,
494 acceptance criteria for certification, and actions to be taken for test failures. The protocols should
495 also specify requalification testing methods and frequency.

D. Quality Assurance Through a Life Cycle Approach

496
497
498
499 Process performance and product quality monitoring systems should provide information to
500 ensure process control throughout a product's life cycle. Process performance measurements
501 (e.g., deviations, in-process defect results, statistical process control reports, equipment and
502 facility breakdowns) provide information on the state of control during manufacturing. Product
503 quality indicators (e.g., stability test results, complaints, returned product) can help determine
504 whether particulate matter in the product caused an event. Similarly, field alert reports and
505 adverse event reports could reveal possible particulates-related quality issues. This information
506 should be used to evaluate the effectiveness of visible particulate control strategies.

507
508 Trends of increased particulate contamination, identification of new types of particulates, or
509 particulates that exceed alert or action limits may indicate a flaw in product or process design.
510 For example, inconsistent product quality could be caused by any one or a combination of these
511 factors:

- 512
- 513 • Inadequate controls of components, containers, or closures.
 - 514 • A product formulation that is not stable.
 - 515 • Uncontrolled changes to the manufacturing process.
 - 516 • Equipment and facilities that are not suitable for their intended use.
 - 517 • Personnel practices that generate particles.
- 518

519 If an investigation reveals a flaw in product or process design, it is important to redesign the
520 product or process to ensure reproducible product quality and reduction of particulate matter.

E. Actions To Address Nonconformance

521
522
523
524 Manufacturers must investigate quality discrepancies identified through the inspection process,
525 quality control testing, complaints, or as a result of a batch failure and extend their investigation
526 to other batches that may be affected (§§ 211.192 and 211.198). Such investigations should seek

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527 to identify the particulates and categorize them (intrinsic or extrinsic) because the presence of
528 certain categories of particulates could indicate CGMP issues or sterility failures.

529
530 Investigations can include tightened sampling plans, examination of particles to understand their
531 origin, and evaluation of batch release impact. The investigation should determine the sources of
532 the variation and identify appropriate corrective actions and preventive actions. The
533 investigations may also reveal opportunities to enhance the robustness of particle detection (e.g.,
534 improvements to the 100% inspection or AQL inspection program).

535
536 Investigations of manufacturing inspection outcomes should be conducted in situations such as
537 the following:

- 538
- 539 • Individual or total defect limits are exceeded.
 - 540 • A batch fails to meet AQL limits.

541
542 Atypical trends should also be investigated. This includes examining defective units removed
543 from a batch that are within in-process specifications but outside of statistical (historical) trend
544 limits for the manufacturing process or defective units with visible particulates that have not
545 been commonly observed.

546
547 Reinspection of product batches may be permissible with appropriate scientific justification and
548 should be conducted according to approved SOPs with tightened acceptance criteria. FDA does
549 not recommend more than one reinspection in an attempt to release a batch with atypical defect
550 levels. Samples failing the AQL reinspection should be counted along with rejects from any
551 other inspection of the product (e.g., such as 100% inspection and the original AQL visual
552 inspection) in calculations to account for and reconcile all units of final product in the batch.

553
554 Corrective actions, such as reinspection, should be justified based on risk and have quality unit
555 oversight and must be documented consistent with applicable written procedures (§ 211.100(b)).

556
557 Customer complaints must be handled according to applicable CGMP regulations (§ 211.198)
558 and should result in particulate identification whenever possible, an investigation into the
559 potential source of the particulate, corrective actions (if necessary), and analysis of the batch's
560 retain samples for evidence of visible particulate contamination.

561
562 Ensuring the effectiveness, safety, and quality of injectable products is of utmost importance.
563 Therefore, FDA recommends the use of a holistic, risk-based approach to visible particulate
564 control. This approach includes the use of a robust visual inspection program along with the
565 implementation of other relevant CGMP measures to help ensure that injectable products are not
566 adulterated and are essentially free of visible particulates.

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