Visible Particulates in Injections—A History and a Proposal to Revise *USP* General Chapter *Injections* ⟨1⟩

Russell E. Madsen,[a] Roy T. Cherris,[b] John G. Shabushnig,[a] and Desmond G. Hunt[c,d]

ABSTRACT This *Stimuli* article provides a history of visual inspection practices and requirements for parenteral products in the United States. It includes a sampling plan and test for products that have been 100% inspected as part of the manufacturing process and criteria by which a product can be considered ''essentially free'' from visible particulates. The proposed test alone is insufficient for batch release testing—a complete program for the control and monitoring of particulate matter remains an essential prerequisite. The proposal is generally harmonized with the Particulate Contamination: Visible Particles section of the *European Pharmacopoeia* and the Foreign Insoluble Matter Test for Injections in the *Japanese Pharmacopoeia*. The objectives of this *Stimuli* article are to initiate discussion and to solicit public comments that will be considered by the Ad Hoc Advisory Panel—Visual Inspection of Parenterals and subsequently the Parenteral Products: Industrial Expert Committee. The Expert Committee will consider recommendations from the Advisory Panel regarding the proposed revision.

THE NEED TO INSPECT

Visual inspection of parenteral products is driven by the need to minimize the introduction of unintended particulate matter to patients during the delivery of injectable medications. Such inspection also offers the opportunity to reject nonconforming units, such as those with cracks or incomplete seals, that pose a risk to the sterility of the product. The desire to detect these defects at a very low frequency and the randomness of their occurrence have resulted in the current expectation that each finished unit be inspected (100% inspection).

Human visual performance is critical to the assessment of visible particles. The threshold for human vision is generally accepted to be 50 μm. The detection process is probabilistic; i.e., the probability of detection increases with increasing particle size. Analysis of inspection results pooled from several studies involving different groups of inspectors shows that the probability of detection for a single 50-μm particle in clear solution in a 10-mL vial with diffuse illumination between 2000 and 3000 lux is slightly greater than 0%. This probability increases to approximately 40% for a 100-μm particle and becomes greater than 95% for particles 200 μm and larger (*1*).

Many animal studies have been conducted to determine the fate of intravenous particles of differing size and composition (*1–4*). Most studies have focused on subvisible particles that have a diameter of less than 50 μm. The smallest of these particles (approximately 1 μm in diameter) are often trapped in the liver, lungs, and spleen. Intravenous infusion of particles larger than the internal diameter of capillaries may be clinically significant because the particles may increase the risk of foreign particle embolism (*5*, *6*). Larger particles generally do not migrate far from the injection site. The most common response observed is the formation of emboli and granulomas. Although they help explain the physiological response to particulate matter, the large number of particles employed in these studies (e.g., 10^9 particles/kg/injection) provides little guidance about the risk of delivering small numbers of particles to patients.

Several reviews describe the effect on patients of particles in parenterals (*7–13*). Garvin and Gunner were among the first to express concern about the effects of particles in patients (*14*, *15*). Ethical considerations preclude controlled human studies on the effect of particulates in human patients. Some anecdotal information can be obtained from studies that involve intravenous drug abusers (*16–18*). In these case studies, solid oral dosages often are ground up and injected as a slurry. Pulmonary foreign body emboli and granulomas were observed in these patients. Again, the clinical risks of particles administered in other settings are difficult to infer from these observations because of the large number of foreign particles and the uncontrolled conditions in which they were administered.

Even though an estimated 15 billion injectable doses of medicines are dispensed each year (*19*), no reports of adverse events associated with the injection of individual visible particles have been found. Although zero defects is the desired goal and should drive continuous process improvement, it is not a workable acceptance criterion for visible particulate matter because of current packaging components and processing capability. The US Pharmacopeial Convention (USP) has adopted the terminology of ''essentially free'' to recognize this current state. As we move forward, a more precise definition is desirable to prevent misunderstanding and to aid in communication of this important quality attribute.

[a] Member, USP Parenteral Products—Industrial Expert Committee

[b] Member, USP Ad Hoc Advisory Panel—Visual Inspection of Parenterals

[c] Documentary Standards Division, USP

[d] Correspondence should be addressed to: Desmond G. Hunt, PhD, Scientist, US Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852-1790; tel. 301.816.8341; fax 301.816.8373; e-mail dgh@usp.org.

HISTORY OF INSPECTION STANDARDS

In 1915 *USP IX* described the need for injectable compounds to be true solutions. In 1916, the *National Formulary* (*NF IV*) included six monographs for parenteral products and specified the method of preparation, but neither Compendium provided guidance with respect to solution clarity.

The first appearance of ''solution clarity'' and freedom from contaminants for parenterals occurred in 1936 in *NF VI*. A requirement for clarity in injectable solutions specified: ''Aqueous ampule solutions are to be clear; i.e., when observed over a bright light, they shall be substantially free from precipitate, cloudiness or turbidity, specks or flecks, fibers or cotton hairs, or any undissolved material.''

The requirement for visual clarity of parenteral products began in 1942. This was before USP's acquisition of *NF* and required coordination between USP and the American Pharmaceutical Association, the publisher of *NF* at that time. The two compendia that were official at the time,*NF VII* and *USP XII*, were coordinated in response to the need to define and control the quality of injectable products purchased in support of the military during World War II. Together, the compendia introduced the term ''substantially free'' to describe the need for control of particle contamination. *NF VII* stated: ''Aqueous solutions are to be clear; i.e., when observed over a bright light, they shall be substantially free from precipitate, cloudiness, or turbidity, specks or flecks, fibers or cotton hairs, or any undissolved material. Substantially free shall be construed to mean a preparation which is free from foreign bodies that would be readily discernible by the unaided eye when viewed through a light reflected from a 100-watt Mazda lamp using as a median a ground glass and a background of black and white'' (*20*).

USP XII stated ''Appearance of Solutions or Suspensions—Injections which are solutions of soluble medicaments must be clear, and free of any turbidity or undissolved material which can be detected readily without magnification when the solution is examined against black and white backgrounds with a bright light reflected from a 100-watt Mazda lamp or its equivalent'' (*21*).

Both *USP* and *NF* used the same test procedure; however the *USP* procedure was more rigorous because it omitted the qualifying adverb ''substantially.'' These directives were used by FDA in its role as the Quality Control Office for all pharmaceuticals purchased by the Armed Forces during World War II. On the basis of these requirements, FDA rejected many lots of injectable solutions offered to fulfill government contracts.

In 1947, *USP XIII* published requirements for clarity of solutions (*22*): ''Clarity of Solutions—Water for Injection, pharmacopeial Injections or pharmacopeial Solutions of medicament, intended for parenteral administration, unless exempted by individual monographs, must be substantially free of any turbidity or undissolved material which can be detected readily without accessory magnification (except for such optical correction as may be required to establish normal vision), when the solution is examined against a black background and against a light which at a point ten inches below the source provides an intensity of illumination not less than 100 and not more than 350 foot candles. This intensity of illumination may be obtained from a 100-watt, inside-frosted incandescent lamp operating at rated voltage, or from fluorescent lamps, or from any equivalent source of light.''

Following adverse observations during an FDA inspection of Bristol Laboratories, a finding of particle contamination in ampules was tested in court (*23*). The FDA inspector, guided by the ''clarity'' requirement as described in *USP XIII*, found particle-contaminated ampules in six accepted stocks from Bristol Laboratories. As a result of this inspection, the company was served with an FDA injunction and request for recall.

Bristol Laboratories challenged the results of the test by preparing a blinded test group of 150 ampules containing 1.5 mL sterile saline. This test group included 38 ampules that the FDA inspector had rejected as contaminated with particles. The case came to trial in 1949. At the conclusion of the government's testimony, the court granted the defendant's motion for dismissal. When on the witness stand, the FDA expert witness was asked to replicate the inspection using the test group and passed 36 out of 38 previously rejected containers. The case was dismissed on the grounds ''1) that the standards involved were indefinite and 2) that the evidence was insufficient to show such violation of the Act as would warrant the granting of the relief prayed for (destruction of the ampules)''(*23*).

From 1955 through 1970, *USP XV* through *USP XVIII* provided guidance about visual inspection of injections. For example, *USP XV* noted: ''Every care should be exercised in the preparation of injections to prevent contamination with micro-organisms and foreign material. Good pharmaceutical practice also requires that each Injection, in its final container, be subjected individually to visible inspection.'' *USP XVI* and *USP XVII* said: ''Every care should be exercised in the preparation of injections to prevent contamination with micro-organisms and foreign material. Good pharmaceutical practice also requires that each Injection, in its final container, be subjected individually to visible inspection whenever the nature of the container permits.''

In 1959, Fed. Std. No. 00142, Parenteral Preparations, was issued by the United States Navy Bureau of Medicine and Surgery (BuMed) and became mandatory for all Federal agencies. The standard was applicable to sterile parenteral preparations in final containers intended for human consumption. The standard was superseded in 1966 by Fed. Std. No. 142a. The standard provided requirements for clarity of solutions as well as limits for visible particulate matter as follows:

Section S6.2.1 *Clarity of solutions*. Applicable to type I, class 1; type II, class 1; type II, class 3; and solutions of dry solids (type IV, class 1). Solutions of parenteral preparations shall be clear and free from undissolved or particulate matter within the limits permitted in the classification of defects and the applicable acceptable quality level (AQL), when examined without accessory magnification (except for such optical correction as may be required to establish normal vision) against a black background and against a white background and

illumination from a light which at a point 25.4 centimeters (10 inches) from its source, provides an intensity of illumination of not less than 100 and not more than 350 foot-candles. Some biological products need not be clear and entirely free from turbidity, provided this is characteristic of the product. The clarity standards for such products shall be judged on an item-for-item basis with the characteristic properties of the product considered in each case.

NOTE—This standard was applied as a final test to samples of finished products, not to 100% on-line inspection, and the sampling was in accordance with MIL-STD-105.

For aqueous solutions (type I, class 1), the ''solution not clear'' defect was classified as Major A, Inspection Level II and the AQL (percent defective) as 1.0. Therefore, in a 30,000 unit batch, 315 units would be inspected; if only 7 or fewer contained visible particulate matter, the batch would pass the Clarity of Solution Test. Thus, at the time, agencies of the Federal government, including FDA, would deem this level to be acceptable and in compliance with the meaning of the USP term ''essentially free.''

Fed. Std. No. 142a was amended in 1970. It is not known when this standard was abandoned, but the significance of Fed. Std. No. 142a is that it provided government-endorsed acceptance limits for the presence of ''visible'' particles. Parenteral product quality acceptance levels were based on the limitations of sterile-product manufacturing capability at that time. Solomon Pflag, BuMed director in 1968, noted, ''Within the framework of the technology available on the subject of particulate matter, Military Services have been highly successful in the procurement of quality parenterals'' (*24*).

Fed. Std. No. 142a could serve as a model on which to frame a practical visible particulate matter acceptance level reflecting the improvement in present parenteral manufacturing technology.

USP XIX, Supplement 1, initiated the philosophical requirement for a zero-defect quality standard for foreign matter and particles (*25*): ''Every care should be exercised in the preparation of injections to prevent contamination. Good pharmaceutical practice also requires that each Injection, in its final container, be subjected individually to a physical inspection, whenever the nature of the container permits, and that every container whose contents show evidence of contamination with visible foreign material be rejected.'' This requirement was repeated verbatim in *USP XX* in 1980 (*26*).

In 1995, *USP XXIII* repeated the requirement for a zero-defect quality standard for foreign matter and particles (*27*): ''Every care should be exercised in the preparation of all products intended for injection, to prevent contamination with microorganisms and foreign material.'' This revision returned to the view expressed in *USP XIX Revision 1* that the response to particle contamination in injectable fluids must be a graded one. Only one phrase was changed: The previous use of the term *substantially free* was replaced by the term *essentially free*. In response to various publications and comments since 1980, a graded response to the inspection for visible particles appeared in *USP XXIII*, *Particulate Matter in Injections* ⟨788⟩: ''Particulate matter consists of mobile, randomly sourced, extraneous substances...that cannot be quantitated by chemical analysis due to the small amount of material that it represents and to its heterogeneous composition. Injectable solutions, including solutions constituted from sterile solids intended for parenteral use, should be essentially free from particles that can be observed on visual inspection.'' This requirement remains basically unchanged since the printing of *USP XIV* (*28*).

The requirements regarding ''visible particulates'' in the pharmacopeias of countries that participate in the International Conference on Harmonization are somewhat different, as shown below.

General Chapter ⟨1⟩ in *USP 31* states: ''Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter (hereafter termed 'visible particulates') in its contents. The inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates'' (*29*). No inspection method is specified.

The *Japanese Pharmacopoeia* states: ''Unless otherwise specified, Injections meet the requirements of the *Foreign Insoluble Matter Test for Injections* ⟨6.06⟩'' (*30*). Two inspection methods are described. Method 1 ''is applied to injections either in solutions, or in solution constituted from sterile drug solids'' and contains the following instructions: ''Clean the exterior of containers, and inspect with the unaided eyes at a position of light intensity of approximately 1000 lux under an incandescent lamp: Injections must be clear and free from readily detectable foreign insoluble matter. As to Injections in plastic containers for aqueous injections, the inspection should be performed with the unaided eyes at a position of light intensity at approximately 8000 to 10,000 lux, with an incandescent lamp at appropriate distances above and below the container.'' Method 2 ''is applied to injections with constituted solution'' and contains the following instructions: ''Clean the exterior of the containers, and dissolve the contents with constituted solution or with water for injection carefully, avoiding any contamination with extraneous foreign substances. The solution thus constituted must be clear and free from foreign insoluble matter that is clearly detectable when inspected with the unaided eyes at a position of light intensity of approximately 1000 lux, right under an incandescent lamp.''

The *European Pharmacopoeia* states ''Solutions for injection, examined under suitable conditions of visibility, are clear and practically free from particles'' (*31*). The inspection is described as follows: ''Gently swirl or invert the container...and observe for about 5 s in front of the white panel. Repeat the procedure in front of the black panel. Record the presence of any particles.''

BASIS FOR THE PROPOSAL

The proposal (see Draft Text for Consideration, below) is based on Fed. Std. No. 142a, which was used successfully for more than a decade to ensure the quality of sterile parenteral products delivered to the US government, and on the results of Parenteral Drug Association (PDA) surveys that assessed current practices in the inspection

of parenteral products. Fed. Std. No. 142a classified the defect as Major A, Inspection Level II and the AQL (percent defective) as 1.0. From the 2008 PDA Survey of Visual Inspection Practices (2), the median value for the AQL for Major defects (most often associated with particulate matter) is 0.65%.

The proposed inspection conditions have been harmonized with those specified in the *European Pharmacopeia*, with a recommendation to use a high-frequency ballast with the fluorescent lamps to reduce flicker and associated inspector fatigue.

The proposal uses a General Inspection Level II sampling plan, as found in American National Standards Institute/American Society for Quality (ANSI/ASQ) Z1.4, as a release test for product that has been 100% inspected during manufacturing and a fixed sample size of 60 units when there is a need to re-evaluate a batch that has been released and is in distribution (*33*). The re-evaluation, or ''field'' sample size is applicable to batch sizes greater than 600 units. The 60-sample plan is similar to an ANSI/ASQ Z1.4 Special Level S-4 inspection with an AQL of 0.65%, covering sample size code letters G (n = 32) for batches between 1201 and 10,000, H (n = 50) for batches between 10,001 and 35,000, or J (n = 80) for batches between 35,001 and 500,000. It has an AQL of 0.60%. A batch with 2.8 defective units per hundred would be accepted 50% of the time. For comparison, an ANSI/ASQ Z1.4 General Level II inspection at a comparable AQL (0.65%) would accept a batch with 1.3 defective units per hundred 50% of the time. The re-evaluation sampling plan does not require abnormally high levels of retained samples, and, with the exception of powders and/or freeze-dried products, it is nondestructive.

DRAFT TEXT FOR CONSIDERATION

Definitions

ESSENTIALLY FREE *[Insert at the end of the Definitions section of* ⟨1⟩ *Injections]*:

Where used in this Chapter, the term essentially free *means that when the batch of Injection is inspected as described herein, no more than the specified number of units may be observed to contain visible particulates.*

Visible Particulates in Injections *[Insert as a subheading under Foreign and Particulate Matter]*:

This test is intended to be applied to product that has been 100% inspected as part of the manufacturing process; it is not sufficient for batch release testing alone, and a complete program for the control and monitoring of particulate matter remains an essential prerequisite. This includes dry sterile solids for injection when reconstituted as directed in the labeling. Other methods that have been demonstrated to achieve the same or better sensitivity for visible particulates may be used as an alternative to the one described below.

Injections shall be clear and free from visible particulates when examined without magnification (except for optical correction as may be required to establish normal vision) against a black background and against a white background with illumination that at the inspection point has an intensity between 2000 and 3750 lux. This may be achieved through the use of two 15-W fluorescent lamps (e.g., F15/T8). The use of a high-frequency ballast to reduce flicker from the fluorescent lamps is recommended. Higher illumination intensity is recommended for examination of product in containers other than those made from clear glass.

Before performing the inspection, remove any adherent labels from the container and wash and dry the outside. The unit to be inspected shall be gently swirled, ensuring that no air bubbles are produced, and inspected for approximately 5 s against each of the backgrounds. The presence of any particles should be recorded.

For batch-release purposes, sample and inspect the batch using ANSI/ASQ Z1.4 General Inspection Level II, single sampling plans for normal inspection, AQL 0.65. Not more than the specified number of units contains visible particulates.

For product in distribution, sample and inspect 60 units. Not more than one unit contains visible particulates.

REFERENCES

1. Shabushnig JG, Melchore JA, Geiger M, Chrai S, Gerger ME. A proposed working standard for validation of particulate inspection in sterile solutions. Paper presented at: DIA Annual Meeting; 1994; Philadelphia, PA.
2. Brewer JH, Dunning JHF. An in vitro and in vivo study of glass particles in ampules. *J Am Pharm Assoc*. 1947;36:289–293.
3. Schoenberg MD, Gillman PA, Mumaw V, Moore RD. Proliferation of the reticuloendothial system and phagocytosis. *Exp Mol Pathol*. 1963;2:126.
4. Hozumi K, Kitamura K, Kitade T, Iwagami S. Localization of glass particles in animal organs derived from cutting of glass ampoules before intravenous injection. *Microchemical J*. 1983;28:215.
5. Brekkan A, Lexow PE, Woxholt G. Glass fragments and other particles contaminating contrast media. *Acta Radiol*. 1975;16:600.
6. Parikh MJ, Dumas G, Silvestri A, Bistrian BR, Driscoll DF. Physical compatibility of neonatal total parenteral nutrient admixtures containing organic calcium and inorganic phosphate salts. *Am J Health-Syst Pharm*. 2005;62:1177–1183.
7. Newton DW, Driscoll DF. Calcium and phosphate compatibility: revisited again. *Am J Health-Syst Pharm*. 2008;65:73–80.
8. Thomas WH, Lee YK. Particles in intravenous solutions. *N Z Med J*. 1974;80:170.
9. Borchert SJ, Abe A, Aldrich DS, Fox LE, Freeman JE, White RD. Particulate matter in parenteral products: a review. *J Parenter Sci Technol*. 1986;40:212.
10. Turco S, Davis NM. Clinical significance of particulate matter: a review of the literature. *Hosp Pharm*. 1973;8:137.
11. Groves MJ, deMalka SR. The relevance of pharmacopeial particulate matter tests. *Drug Dev Commun*. 1976;2:285.
12. Groves MJ. *Parenteral Products: The Preparation and Quality Control of Products for Injection*. London, UK: Heinemann Medical Books; 1973.

13. Groves MJ. *Particulate Matter: Sources and Resources for Healthcare Manufacturers*. Buffalo Grove, Illinois: Interpharm Press; 1993.
14. Garvin JM, Gunner BW. Intravenous fluids: a solution containing such particles must not be used. *Med J Aust*. 1963;2:140.
15. Garvin JM, Gunner BW. The harmful effects of particles in intravenous fluids. *Med J Aust*. 1964;2:1.
16. Burton JF, Zawadzki ES, Wetherell HR, Moy TW. Mainliners and blue velvet. *J Forensic Sci*. 1965;10:466.
17. Richman S, Harris RD. Acute pulmonary edema associated with Librium abuse. *Radiol*. 1972;103:57.
18. Douglas FG. Foreign particle embolism in drug addicts: respiratory pathophysiology. *Ann Intern Med*. 1971;75:865.
19. Injectable Drug Delivery: Probing the Route to Growth. *Datamonitor*; January 2004.
20. American Pharmaceutical Association. *NF VII*. Washington, DC: American Pharmaceutical Association; 1942.
21. USP. *USP XII*. Philadelphia, PA: Mack Publishing; 1942.
22. USP. *USP XIII*. Philadelphia, PA: Mack Publishing; 1947.
23. Kleinfeld VA, Dunn CW. United States vs Bristol Labs., Inc. *Federal Food Drug and Cosmetic Act: Judicial and Administrative Record*. 1938–1949;310–314.
24. Pflag SC. Large volume parenteral solutions procured by the military. Paper presented at: FDA National Symposium, Safety of Large Volume Parenteral Solutions; July 28–29; 1968.
25. USP. *USP XIX*, Supplement 1. Rockville, MD: USP; 1975.
26. USP. *USP XX*. Rockville, MD: USP; 1980.
27. USP. *USP XXIII*. Rockville, MD: USP; 1995.
28. USP. *USP XIV*. Rockville, MD: USP; 1971.
29. USP. *USP 31*. Rockville, MD: USP; 2008.
30. Japanese Pharmacopoeia. *Japanese Pharmacopoeia, Fifteenth Edition, General Rules for Preparations, 11. Injections*. Tokyo, Japan: Japanese Pharmacopoeia; 2006:11.
31. European Medicines Evaluation Agency. *European Pharmacopoeia 6.0, Parenteral Preparations, Injections, European Directorate for the Quality of Medicines & HealthCare*. Strasbourg, France: EMEA; 2008:736.
32. Leversee RL, Shabushnig JG. A survey of industry practice for the visual inspection of injectable products (preliminary report). Paper presented at: PDA Visual Inspection Forum; 2008; Berlin, Germany.
33. ANSI/ASQ. *Z1.4-2003 Sampling Procedures and Tables for Inspection by Attributes. American Society for Quality*. Milwaukee, WI: ASQ; 2003.