BRIEFING

⟨1790⟩ Visual Inspection of Injections. The General Chapters—Dosage Forms Expert Committee proposes this new chapter to provide guidance on the inspection of injectable drug products for visible particles. The methods discussed are also applicable to detection of other visible defects that may affect container integrity or cosmetic appearance of the product.
(GCDF: D. Hunt.)
Correspondence Number—C160024
Comment deadline: January 31, 2016

Add the following:

▲⟨1790⟩ VISUAL INSPECTION OF INJECTIONS

1. SCOPE

1.1 Introduction

This chapter provides guidance on the inspection of injections for visible particles. The terms particle, particulates, and particulate matter are equivalent and do not have different meaning when used in this chapter. Particulate matter is defined in *Particulate Matter in Injections ⟨788⟩* as “mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions.” Visual inspection is a probabilistic process and the specific detection probability observed for a given product for visible particles will vary with differences in product formulation, particle characteristics, and package design. The methods discussed in this chapter are also applicable to the detection of other visible defects not the subject of *Visible Particulates in Injections ⟨790⟩*, but critical to a qualified, comprehensive inspection process. These include, but are not limited to, container integrity defects such as cracks, misplaced stoppers, or incomplete seals, any of which may compromise the sterility of the product. Additional container defects (1), as well as other product characteristics such as fill level, discoloration, or clarity may also be detected during visual inspection, and non-conforming units should be rejected using the methods described in this chapter. Inspection for these other quality attributes often occurs at the same time as the inspection for particles. The primary focus of this chapter is a manual reference inspection method; however, semi-automated and automated methods are also discussed and permitted by the pharmacopeia.

1.2 Related Chapters

Injections and Implanted Drug Products ⟨1⟩ provides an overview of injectable dosage forms and the quality tests associated with them. Another chapter, *⟨790⟩*, has been added to the USP–NF to provide a clear definition of routine inspection procedures for injectable products; the goal is to comply with the expectation that products be essentially free of visible particulate matter. Additionally, information on the detection of subvisible particulates is provided in *Subvisible Particulate Matter in Therapeutic Protein Injections ⟨787⟩*, *⟨788⟩*, and *Particulate Matter in Ophthalmic Solutions ⟨789⟩. Measurement of Subvisible Particulate Matter in Therapeutic Protein Injections ⟨1787⟩* and *Methods for the Determination of Particulate Matter in Injections and Ophthalmic Solutions ⟨1788⟩* provide additional supporting information on measurement methods for subvisible particles.

1.3 Defect Prevention

Although this chapter focuses on detection and removal of product units that show evidence of visible particles, the need for preventing such contamination should not be overlooked. No inspection process, manual or automated, can guarantee complete removal of all visible particulate matter or other visible defects; thus, prevention of such defects is an important consideration. Good process and product design, along with environmental control, are necessary to ensure the reliable production of products with a low particle burden. To ensure the control of defects throughout the process, manufacturers should consider an inspection life-cycle approach (2). This approach begins with developing quality attributes based on incoming component specifications, followed by component-level acceptance testing. It extends to component preparation and product-filling procedures, followed by 100% in-process inspection of filled product, and concluding with final acceptance sampling and testing of the finished product. The approach must extend to purchased, ready-to-use components such as containers or closures, where there is no opportunity for subsequent particle removal after receipt and before filling. Stability and retention sample inspection, customer complaint evaluation, and in-house investigative procedures support this integrated approach. The inspection life-cycle is composed of, and supported by, sub-cycles involving qualification, maintenance, personnel training, defect characterization by forensic analytical methods, and the use of standards within each of the critical areas. The final element of the life-cycle is a feedback loop of trending and data review from each of these process areas, resulting in a mechanism that supports continuous process improvement.

2. INTRODUCTION

2.1 Inspection Process Capability

Visual inspection of injections is necessary to minimize the introduction of unintended particles to patients during the delivery of injectable medications. Such inspection also offers the opportunity to reject containers whose integrity has been compromised, such as those with cracks or incomplete seals, which pose a risk to the sterility of the product. The desire to detect these defects, despite their very low frequency and the randomness of their occurrence, has resulted in the long standing expectation that each finished unit will be inspected (100% inspection). Although zero defects is the goal and this should drive continuous process improvement, zero defects is not a feasible specification for visible particles given current packaging components, processing capability and the probabilistic nature of the inspection process.

The detection process is probabilistic: the likelihood of detection is a cumulative function of visible attributes such as particle size, shape, color, density, and reflectivity. Understanding human performance is therefore critical to establishing visual inspection criteria. Individual receptors in the eye have a theoretical resolution of 11 µm, but typical resolving power is reported as 85–100 µm (3). Analysis of inspection results pooled from several studies (4–6) conducted with standards prepared with single spherical particles show that the probability of detection for a seeded sample with a single 50-µm particle in a clear solution contained in a clear 10-mL vial utilizing diffuse illumination between 2,000 and 3,000 lux is only slightly greater than 0%. The detection probability increases to approximately 40% for a seeded standard with a 100-µm particle and the threshold for routine, reliable detection (≥70% probability of detection) of individual visible particles is often near 150 µm in diameter (4) and typically exceeds 95% for

particles that are 200 µm and larger. Thus, in a qualified visual inspection system, the vast majority of particles that might go undetected and be introduced into the pharmaceutical supply chain will be smaller than 200 µm. Changes to the container (e.g., increasing size and opacity), formulation (e.g., color and clarity), fill level, and particle characteristics beyond size (e.g., color, shape, and density) will all affect the probability of detection which can be achieved for a specific product and package (6).

2.2 Patient Risk

A complete review of the medical literature is beyond the scope of this chapter, but the effect of extraneous particles on the patient must be considered. A number of reviews on this subject are available (7–13). The clinical implications of extraneous particulate matter in injections are determined by many factors, including the size and number of particles, the composition of the material, the potential for microbiological contamination, the route of administration, the intended patient population, and the clinical condition of the patient. For example, an otherwise healthy individual receiving a subcutaneous or intramuscular injection containing sterile, inert particulates would likely experience no adverse effect or at worst would develop a small granuloma. On the other hand, a critically ill premature infant receiving a particle-laden infusion directly through an umbilical catheter might suffer considerable pathophysiologic sequelae (14,15).

Garvin and Gunner were among the first to report a concern about the effects of particles in human patients (16,17). For obvious ethical reasons, there is a lack of controlled clinical studies on the effects of particles in human patients. Some anecdotal information about human patient safety may be obtained by examining case reports of intravenous drug abusers (18–20). In these cases, solid oral dosages are often ground up and injected as a slurry; pulmonary foreign body emboli and granulomas were observed in these patients (21). Unfortunately, the clinical risks to human patients posed by small numbers of particles are difficult to infer from these observations due to the extreme number of insoluble particles and the uncontrolled conditions in which they were administered.

Numerous animal studies have been conducted to determine the fate of intravenous particles with different sizes and composition (22–25). Most studies have focused on subvisible particles with a diameter of <50 µm. In these studies, a massive infusion of particles has been accompanied by histologic evidence of injury to pulmonary capillary endothelial cells (26), microscopic thrombi in the pulmonary capillaries (27), pulmonary microscopic granulomata (28), and hepatic inflammatory effects (29). Although useful for understanding the pathophysiologic response to particulate matter, the large number of particles used in these studies (e.g., 109 particles/kg/injection) provides little insight into the risk to humans posed by small numbers of macroscopic particles. Arterial embolization using materials such as polyvinyl alcohol (PVA), collagen-coated acrylic microspheres, and gelatin spheres also provides some insight into the potential human pathophysiologic implications of non-target embolization of extraneous-particle intravenous infusions. In these cases, massive particle loads moving from the arterial injection site into the venous circulation were also reported (30–34).

In a review of the hazards of particle injection, it has been found that the primary contributor of particulate matter in vial presentations is the rubber closure, a risk that is present with almost every injection. In addition, case reports have documented injury associated with infusion of significant quantities of precipitated admixtures or therapeutic use of particles for embolization (14,15,35). Despite the administration of an estimated 15 billion doses of injectable medicines

each year (36), no reports of adverse events associated with the injection of individual visible particles have been found.

Ultimately, the safety considerations related to particulate matter in injections must be assessed for each drug product, intended patient population, and method of administration. No single set of inspection criteria can adequately anticipate all of the potential risks to the patient. The methods outlined in *⟨790⟩*, should serve as essential requirements when assessing the adequacy of the visual inspection procedure, but alternative acceptance criteria (for example, the use of tightened sampling plans) should be implemented when the patient population and intended use of the product warrant these additional measures.

2.3 History of Compendial Inspection Standards

The requirement for injections to be “true solutions” appeared in USP IX in 1915, and the first appearance of “solution clarity” for parenterals occurred in 1936 in NF IV. Since then, there have been numerous modifications to the compendia in this regard. A comprehensive history of compendial inspection standards is available in the Pharmacopeial Forum (37).

3. TYPICAL INSPECTION PROCESS FLOW

3.1 100% Inspection

Chapter *⟨790⟩* establishes the expectation that each unit of injectable product will be inspected as part of the routine manufacturing process. This inspection should take place at a point when defects are most easily detected; for example, prior to labeling or insertion into a device or combination product. Each unit may be examined manually with the unaided eye, or by using a conveyor to transport and present the containers to a human inspector (semi-automated inspection), or by means of light obscuration or electronic image analysis (automated inspection). Manual and semi-automated inspection should only be performed by trained, qualified inspectors. Inspection may also be enhanced by means of a device that holds more than a single unit at one time for examination. This inspection may be performed in-line with filling or packaging or in a separate, off-line inspection department. The intent of this inspection is the detection and removal of any observed defect. When in doubt, units should be removed (see Figure 1).

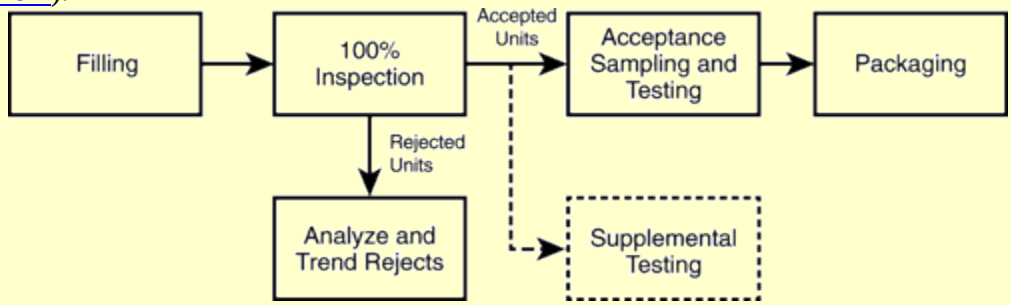

Figure 1. Typical process flow chart.

[Note—100% inspection refers to the complete inspection of the container–closure system and its contents. Inspection may be accomplished in a single operation or in multiple steps using a combination of technologies. See additional discussion in 3.3 Remediation and Alternative Practices and 6. Inspection Methods and Technologies.][Note—Supplemental testing is required

when the nature of the product or container limits visual inspection of the contents (e.g., with a lyophilized cake or powder or with an amber glass or opaque container). See additional discussion in 5.2 Unique Product and Container Considerations. Samples for supplemental testing may be taken from any point in the process after 100% inspection.]

During 100% inspection, limits on typical rejection rates should be established to identify atypical lots (38). These limits may be established for categories of defects (e.g., critical, major, and minor) or for specific types of defects (e.g., particles). A review of historical performance is useful in establishing these limits, and the review may include grouping products similar in appearance and manufacture. Periodic reassessment of these limits is recommended to account for expected process improvements and/or normal fluctuations in process baseline (39). If a limit is exceeded, it should trigger an investigation. The investigation may include additional inspection or it may determine whether additional inspection is necessary.

3.2 Acceptance Sampling and Testing

After 100% inspection, a statistically valid sample is taken from the units accepted by the inspection process. This may be a random sample or a representative sample (e.g., at fixed time intervals or a fixed number per tray). Defects may not be distributed equally over the lot, and therefore a sampling process that represents the whole lot is required. Typical sampling plans used for this purpose can be found in the ANSI/ASQ Z1.4 standard (40). Equivalent plans may also be found in the ISO 2859 (41) or JIS Z9015 (42) standards. For batch release, the sampling plans listed as Normal II are typically used. Tightened sampling plans may be appropriate when an atypical result is observed or reinspection is performed. These plans specify a sample size for a range of batch sizes and require selection of an acceptable quality limit (AQL). The AQL is the defect rate at which 95% of the lots examined will be accepted and is a measure of falsely rejecting good batches. Critical defects (those that pose the greatest risk to the patient) should be assigned an AQL with a very low value. Often, the accept number (the number of defective units allowed in the sample) for a critical defect is zero. Major and minor defects, which pose less risk to the patient, will have increasing (less stringent) AQL values and accept numbers greater than zero. Table 1 shows the range of AQL values typically used for visual inspection processes (43).

Table 1. Typical AQL Values for Visual Inspection Processes

Defect Category	AQL Range (%)
Critical	0.010–0.10
Major	0.10–0.65
Minor	1.0–4.0

[Note—When selecting a sampling plan for AQL testing after 100% inspection using ANSI/ASQ Z1.4, ISO 2859 or JIS Z9015, choose the sample size to satisfy the AQL value for the most critical category (e.g., critical) of defects being evaluated. Then use the accept numbers for this sample size for the AQL values chosen for the other defect categories (e.g., major and minor). This assures that the sample size will produce a statistically valid result for all defect categories examined. The defect categories shown here represent a common basic approach to grouping defects by risk; however additional categories may be added to these for more detailed analysis.]

The unacceptable quality limit (UQL) for the sampling plan used should also be known. The

UQL is the defect rate at which 90% of the lots examined will be rejected and is a better measure of the customer or patient risk. The protection afforded by any sampling plan is represented by its operational characteristic (OC) curve. This is a plot of the probability of lot acceptance versus the defect rate in the lot. The AQL and UQL are two points on this curve. Sampled units should be manually inspected under controlled conditions by trained inspectors. Inspection conditions should be aligned with the 100% inspection process.

Acceptance sampling should be performed after any type of 100% inspection process, including manual, semi-automated, and automated inspection processes. It provides a measure of the performance of the overall inspection process and the quality of a specific lot, compared with predefined acceptance criteria. Although automated systems are validated before use and are routinely challenged to ensure acceptable performance, the use of acceptance sampling detects unexpected defects that were not included in the development and training of the automated system by the manual inspection process.

Acceptance criteria are comprised of the product specifications and acceptance/rejection criteria, such as the AQL and UQL values, with an associated sampling plan that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units) as described in 21 CFR 210.3 (44). If the acceptance criteria of the sampling plan are not met, an investigation should be conducted. Depending on the nature of the failure, this investigation should include examinations of the manufacturing process, the raw materials, and the packaging materials, as well as the inspection process. If, after investigation, the inspection process is deemed capable of detecting the defect(s) in question, the batch may be reinspected. An alternative inspection process, better suited to detection of a specific defect may also be chosen for reinspection. After reinspection, a new sample of the accepted units is taken and compared against established acceptance criteria. It is a good practice to use a tightened sampling plan and acceptance criteria under these circumstances because of the atypical nature of this process step.

3.3 Remediation and Alternative Practices

REINSPECTION

As discussed in the preceding section, reinspection may be appropriate if the initial 100% inspection is not successful. This includes instances when the established 100% inspection failure rate(s) and/or the accept/reject number(s) associated with the chosen AQL values have been exceeded. Reinspection should only be conducted using a prior-approved procedure that addresses key parameters such as the inspection conditions (e.g., same as primary inspection or modified to enhance detection of a specific defect type), the number of times reinspection may be performed (this should be limited, and justified), and the acceptance criteria (e.g., same as primary inspection or tightened). If reinspection is required often, consideration should be given to improving the sensitivity of the primary inspection process. Frequent and routine reinspection is not recommended. Reinspection is not considered rework and is more closely associated with reprocessing as defined in 21 CFR 211.115 (45), where a qualified or validated processing step is repeated.

TWO-STAGE INSPECTION

In cases where an assignable cause, such as formation of air bubbles or specific container or closure variation, results in a high false-rejection rate (rejection of acceptable units), the use of a

second inspection step may be considered. This is more common with automated inspection systems, where there is less ability to tolerate normal variation in product or container. Under these circumstances, the inspection system is adjusted to ensure acceptance of good units. Those not accepted are considered of uncertain disposition until inspected by another means (e.g., manual inspection following automated inspection). Inspection conditions may be adjusted to provide greater sensitivity in this second inspection step (e.g., additional inspection time) to ensure a high probability that true defective units will be rejected. The limitations of the first inspection and the reason for conducting a second stage of inspection should be clearly defined and documented. The second inspection of these units by the same method (e.g., automated inspection after automated inspection) is generally not recommended, because the same limitation in inspection method is present for both inspections. However, it may be suitable when the root cause is air bubbles in the solution and a study has been performed to establish an appropriate holding time to allow the bubbles to dissipate before performing the second inspection. It is recommended that each inspection stream (those accepted by the first stage and those accepted by the second stage) be sampled separately and evaluated against the sampling plan acceptance criteria before they are confirmed as accepted and recombined into a single batch.

4. INSPECTION LIFE-CYCLE

4.1 Extrinsic, Intrinsic or Inherent Particles

Particles may originate from many sources. These are discussed here, as well as in other chapters in the USP (e.g., *⟨1787⟩*). Those that are foreign to the manufacturing process are considered to be exogenous or “extrinsic” in origin; these include hair, non-process-related fibers, starch, minerals, insect parts, and similar inorganic and organic materials. Extrinsic material is generally a one-time occurrence and should result in the rejection of the affected container in which it is seen; however, elevated levels in the lot may implicate a broader contribution from the same source. These particles may carry an increased risk of microbiological or extractable contamination, because less is known about their path prior to deposition in the product container or their interaction with the product.

Other particles are considered “intrinsic”, from within the process, or “inherent”, which are known to be or intended to be associated with specific product formulations. The determination of whether the particulate is inherent or intrinsic to the process is based upon appropriate characterization of the particle's physicochemical properties. Intrinsic particles may come from processing equipment or primary packaging materials that were either added during processing or not removed during container preparation. These primary product-contact materials may include stainless steel, seals, gaskets, packaging glass and elastomers, fluid transport tubing, and silicone lubricant. Such particles still pose the risk of a foreign body, but generally come from sterile or sanitized materials and more is known about their interactions when in contact with the product. Any process-related intrinsic particles should have controls established based on the use of a life-cycle approach as outlined in 1.3 Defect Prevention. Another group of particles considered intrinsic is interrelated with the stability of the product. These product stability-related particles come from container–closure interaction, changes to the drug formulation (insoluble degradation products), or temperature sensitivity over time. Stability-related intrinsic particles should be identified and addressed as early in the product development process as

possible.

The physical form or nature of inherent particles varies from product to product and includes solutions, suspensions, emulsions, and other drug delivery systems that are designed as particle assemblies (agglomerates, aggregates). Product formulation-related particulate formation should be studied in the development phase and in samples placed on stability to determine the normal characteristics and time-based changes that can occur. Use of automated particle counting or image analysis in the subvisible (for particle sizes ≥2 μm) and visible ranges may be required to fully characterize inherent formulation-related particles. In biologics, protein particles are considered inherent when their presence may be measured, characterized, and determined to be part of the clinical profile. Inherent particles may be accepted if the drug product has a control strategy showing that this particulate category is part of the product clinical profile. The manufacturer may allow inherent particles if the product appearance specification also allows their presence or if the product is an emulsion or suspension.

An evaluation of the potential impact of particles identified from any of these sources may be enhanced by incorporating a clinical risk assessment. This assessment may include factors such as the intended patient population, route of administration, source of the particles, and implications for product sterility. For intrinsic or inherent particulate matter sources, a risk assessment may be useful in developing product-specific control strategies. Given the probabilistic nature of particle detection, it is important to assess the possible implications of particles identified through the product life-cycle to better ensure the product's safe use.

4.2 Prevention of Particulates

The manufacturing process is designed to keep the final container and its contents clean within the control parameters established for process-related particulates. Once the container is filled, the stability of the product needs to be maintained throughout its shelf life. Changes that occur as the product ages during its normal shelf life must be characterized. Avoidance of intrinsic particle sources that may affect final product stability depends on careful consideration of the entire product system. If these intrinsically sourced changes occur, and they affect stability, particles ranging from sub-visible to visible may develop. Typically, these particles result from change mechanisms that slowly affect the on-shelf product.

ROBUST DESIGN DURING DEVELOPMENT

To anticipate potential sources of instability that yield intrinsic particles, the product design is evaluated from many perspectives, beginning with a literature review of similar formulae/packages. Points to consider include the reported sensitivities of the active, the formulation type, and the final container–closure system needed for delivery. Knowledge of how glass containers are fabricated, controlled, sterilized, and tested is important as this may affect the tendency to form glass lamellae (46,47). Obtaining further information on residual extracts, possible leachates, metals, or solubility-edge conditions is important as these factors may promote formation of solid material in the aging solution. Several additional key factors for successful product design are the product concentration, solution pH, critical micelle concentration, oligomerization content/potential, package effects (large surface area, product volume, head space, light/oxygen transmission), and compatibility of the formulation with the package. Some key formulation design factors include the formula components chosen and their purity; the solubilities of the active ingredient(s) and excipients, and consideration of potential salt forms. Finally, to maximize product stability, consider the final product preparation for

delivery, product dilutions, and shelf stability of the commercial product or its therapeutic preparations.

To examine the appropriateness of the product design for maintaining product stability, there are two levels of evaluation. Both levels examine retained containers for visible changes using methods described in this chapter, but neither level dwells on low percentage defects.

For the first level of stability study, bench trials consisting of visual inspection of trial containers in the formulation lab will show general compatibility of the chosen components over time with regard to clarity, color, and particle formation. Careful product assembly in clean containers, with consideration of the container type, headspace, and sealing, will yield a beneficial first-pass trial of stability over several months' time. Detection of extrinsic particles at this stage of development is generally not significant, as the particles do not reflect on the formulation under development.

The second, more refined level of stability study involves conducting visual inspections of the injection in defined, International Conference on Harmonisation (ICH)-relevant trials. This may include periodic inspection of the same containers over time if the product does not require reconstitution or is not affected by frequent temperature changes. Detection of minor or subtle differences in these containers is not the goal at this stage of development. Catastrophic change and the occurrence of intrinsic product-related visible particles should be the focus. Typically, a set of containers is carefully prepared to exclude extrinsic particles and is then inspected to cull out any units with visible defects. Next, a numbered set of containers appropriate for the batch size is placed on trial and visually inspected periodically; a typical sample size is 80–100 units. Additional sets of containers stored at selected extremes of ICH temperatures can be followed to aid discovery of solubility-edge phenomena. When unwanted changes are detected, such as particle formation, solution color change, solution haze, and package changes, the process of isolation, characterization, and identification can commence. Identification of the material making up the changes aids in determination of the cause, as well as development of improvements for future use.

COMMON SOURCES OF INTRINSIC PARTICULATES

Process-related intrinsic particles originating from product contact materials tend to be stable and unchanging (e.g., glass, rubber, or metal). In contrast, there may also be particles resulting from product stability-related change mechanisms within the final product. It is very important to understand that these changes only have to be slight in certain cases, far below the detection limit of most release or stability assays, to result in visible changes to the product. The threshold levels for the formation of visible change for certain substances may be only 10–100 ppm (0.001%–0.01%). However, if all of this insoluble material were contained in a single visible particle, it would likely cause rejection of the container.

FORMULATION COMPONENTS

The active ingredient may also contribute to the presence of stability indicating intrinsic particles. For example, significant haze and particles have manifested in aqueous formulations due to extraction of plasticizers from filtration media during bulk drug production (5). Metal content in the active ingredient has contributed to organometallic salt formation and has also been observed as precipitated inorganic salts, blooming long after product release. The active ingredient and related degradation products may also be relatively insoluble and may grow to

form visible particles. The particulate material must be analyzed to determine its chemical nature and possible identification.

Monomers or single molecules may join together through chemical processes to form dimers, trimers, and oligomers (a limited assemblage of monomers, short of polymerization). Such changes are not unexpected (48). In high-concentration and/or saturated formulations, and especially for micellar drug associations, the solubility of related forms is significant when the aging formulations contain progressively higher concentrations of these substances. Larger molecules may have a greater effect on solution integrity due to their inherent insolubility, especially if the active drug is in a micellar formulation.

Polymorphs are unique crystalline forms of identical chemical entities. Although uncommon in solutions that have been mixed homogeneously and filtered, small seed crystals of a relatively stable polymorph may form over time, especially at nucleation sites such as container-surface defects. More common than formation of polymorphs is formation of a modified crystal lattice containing an integral liquid, typically water or solvent. The lattice may form slowly, promoted by evaporation, nucleation, and temperature extremes (49,50).

PACKAGING COMPONENTS

Extractables and leachables are terms commonly used to describe the potential for primary packaging materials to contribute unwanted agents to the product. Extractables represent all of the materials that could be contributed, and leachables represent the practical contribution upon contact between packaging components and drug formulation (51). These substances can also contribute to the formation of subvisible and visible particles.

Formulation attack of the container is a dramatic change and most often occurs in glass container systems. Glass containers undergo corrosion that is 25 times greater at pH 8 than at pH 4 (52). A formulation pH above 7, especially with high-ionic strength solutions, promotes attack of the inner glass surface, resulting in particle generation.

Silicone oil is added to pre-filled glass syringe systems to enhance lubricity for closure insertion and/or syringe movement. Silicone may also come from tubing used for fluid transfer and a variety of polymeric fittings and seals that are used in the processing equipment. All of these components must be compatible with the formulation to minimize leachates. Although silicones are processed to be sterile and are widely used, their use must still be controlled. Silicone can cause container sidewall droplets and a variety of visible semi-solid forms. No more than the minimum quantity should be used during processing. Silicone and other hydrophobic substances have the capacity to coalesce and agglomerate with other particles, reaching a visible size.

4.3 Particulate Removal by Component Washing

GLASS CONTAINERS

Each step of the glass-container washing and rinsing process should be evaluated for particle-reduction capability. The washer validation studies should demonstrate a reduction in naturally occurring particles or should use seeded containers to demonstrate such reduction capability. The use of statistical sampling plans with light obscuration and/or membrane microscopic particle-counting methods can provide a means to demonstrate reduction of both subvisible and visible particles during washing cycle development and validation. During process development, validation, and routine use, container-washing procedures should include periodic visual operational checks. This routine verification ensures that effective draining of all containers is

occurring during all washing and rinsing steps. Review the wash-water recirculating filter maintenance procedures to ensure that particle overloading or breakthrough is being prevented. Glass breakage that occurs during the component washing process could affect surrounding containers and the washing cycle should be evaluated for possible glass particle generation and distribution. Effective, written container-clearance procedures following these occurrences should specify the number of containers to be removed from the affected portion of the line. Removing units that could potentially contain glass particles aids in minimizing particle transfer to the downstream process.

ELASTOMERIC CLOSURES

Each step of the elastomeric-component washing and rinsing process should be evaluated for particle-reduction opportunities. Utilize statistical sampling plans to collect meaningful test units. Light obscuration or other automated particle counting and membrane microscopic particle-counting methods may be used to demonstrate reduction of both subvisible and visible particles during washing validation. During process development and validation and in routine use, container-washing procedures should include visual checks to ensure that stoppers are not routinely sticking together. Such sticking surfaces reduce cleaning efficacy and entrap particles. Periodic assessment of component cleanliness and supplier washing capabilities should be included as part of the supplier qualification program when using purchased, ready-to-sterilize, or ready-to-use components.

Evaluate any current siliconization process used, whether in-house or by the supplier, to minimize excess silicone levels while maintaining machinability of the stoppers. Light obscuration or other automated particle-counting method may be used to compare overall particle level reduction (background silicone oil droplets) during process development or validation. The level of residual silicone oil will affect the particulate quality of the final filled product, observed as dispersed droplets and particle-forming matrices.

GLASS HANDLING

Processes that use racks or trays for transporting and holding samples, as are typically used in batch ovens, should be monitored for metal particle generation. The racks or trays should have a formal maintenance program associated with their routine use. Trays should be inspected for wear and scoring, which can be sources of particulates. Periodic cleaning, polishing, and/or resurfacing may be warranted to effectively control particles. Tunnels used for depyrogenation should also have a routine maintenance program for periodic cleaning, inspection, and replacement of parts that may wear and generate particles. Routine process observation for glass breakage allows for clearance of any potentially affected surrounding containers and minimizes the occurrence of glass particles being carried downstream to filling. Glass-to-glass and glass-to-metal contact should be minimized where possible to reduce weakening of the glass surface and increasing the risk of subsequent fracture. The use of polymeric facing on guides can help in reducing such damage.

EQUIPMENT PREPARATION

It is important to minimize redeposition of particles on product contact surfaces after cleaning. Cleaned and sterilized equipment should be protected by HEPA-filtered, unidirectional airflow until transferred to, and installed on, the filling line. For cleaned equipment that needs to be

wrapped or bagged prior to sterilization, utilize low-shedding, non-cellulose (synthetic) wrapping materials. Cellulose fibers are one of the most common particles found in the injections-manufacturing environment and injectable products and their origin will be a prime concern (43).

FILLING LINE

The transfer of open containers should be evaluated and reviewed to mitigate particle contamination. For example, for aseptically filled products the transfer should be conducted in Grade A (ISO 5, Class 100), unidirectional air flow to minimize particle contamination. The air in critical zones should be monitored continuously during operation to confirm compliance. Routine checks to detect particles and potential particle-generation locations should be explained in the procedures. Effective, written container-clearance procedures to be used after glass breakage should specify the number of containers to remove from the affected portion of the line. Note that improper set-up and adjustment of the filler can lead to “needle strikes” where the filling needles make contact with the container being filled. This can generate either stainless steel or glass particles.

Filling pump design and the pump's compatibility with the filling solution are important considerations. Metal-on-metal piston pumps have a greater potential for generating metal particles, compared with other types of piston pumps. Pump maintenance is essential and includes a requirement to resurface the cylinders and pistons periodically. Peristaltic-action pumps must be monitored for generation of silicone tubing particles, especially with aggressive, near-saturated solutions or suspensions. Friction in the peristaltic roller area can break down the tubing, resulting in the generation of particles.

Stopper bowl surfaces should have a formal maintenance program, and stopper handling or replenishment by operators should be specifically designed to minimize particle transfer to the stoppers. Proper operator positioning and avoidance of open containers is important in good, aseptic filling practices, to avoid microbial contamination. These same principles help reduce particle transfer to the open containers and exposed elastomeric closures.

Careful selection of cleaning and gowning materials will help reduce contamination from extrinsic particles and fibers. These clean-room materials should be selected for their superior non-shedding and low-particle properties.

4.4 Trending

Data obtained from the inspection process are used for batch release. These data should also be analyzed for adverse trends on a periodic basis, typically at least once per year. High-volume products may generate sufficient data to allow quarterly analysis, whereas a longer period of time may be necessary to accumulate data for products that are produced infrequently. Data from component inspection, production 100% inspection, and the AQL inspections should be evaluated based upon sound statistical principles to determine whether the current action levels are accurately reflecting the current process capability. Alert levels may be introduced and/or adjusted accordingly if the statistical analyses indicate that lower defect levels are being observed consistently.

When establishing new action or alert levels, a preliminary value may be used until sufficient production experience is obtained. Consideration should be given to planned improvements in the manufacturing and inspection processes. If significant improvements are planned, the

reduction of the action/alert level should not be instituted until the impact of the improvement is measured over sufficient time to establish the validity of the new value.

5. INTERPRETATION OF INSPECTION RESULTS

5.1 Defect Classification

Defects are commonly grouped into classifications based on patient and compliance risk (1). The most common system uses three groups: critical, major, and minor. Critical defects are those that may cause serious adverse reaction or death of the patient if the product is used. This classification includes any nonconformity that compromises the integrity of the container and thereby risks microbiological contamination of the sterile product. Major defects carry the risk of a temporary impairment or medically reversible reaction, or involve a remote probability of a serious adverse reaction. This classification is also assigned to any defect which causes impairment to the use of the product. These may result in a malfunction that makes the product unusable. Minor defects do not impact product performance or compliance; they are often cosmetic in nature, affecting only product appearance or pharmaceutical elegance.
For visible particles, particle motion aids in detection. Stationary particles are difficult to detect. Upon 100% inspection, visible extrinsic and intrinsic particles should be reliably removed. The test method allows inherent particles to be accepted if the product appearance specification allows inherent particle types. The size of particles reliably detected (≥70% probability of detection) is generally 150 µm or larger (4). This Probability of Detection (POD) is dependent on the container characteristics (e.g., size, shape, transparency), inspection conditions (lighting and duration), formulation characteristics (color and clarity), and particle characteristics (size, shape, color, and density). The POD at 70% or greater is known as the Reject Zone described in Knapp's methodology (53,54) which is used worldwide as an industry common practice for rejecting particle defects. Test sets characterized by repeated inspections, as described in 7.4 Rejection Probability Determination, are used to “calibrate” the inspection method's POD, inspector performance or automated inspection systems, and to demonstrate the sensitivity to threshold particle size at the Reject Zone of >70% POD. It should be understood that the limitation of the Reject Zone at 70% detection is that at this size threshold particles of the same size may routinely be missed or go undetected up to 30% of the time. These undetected units may contain some amount of threshold sized particles or sub-visible particles at a lower POD. It is therefore important to characterize any particles recovered from AQL testing, retention sample inspection and product returned from distribution to understand how it could have gone undetected originally during the initial 100% in-process inspection.

5.2 Unique Product and Container Considerations

LYOPHILIZED PRODUCT

Lyophilized products receive 100% inspection after the freeze-drying step has been completed and each unit has been sealed. However, the solid, lyophilized cake can mask the presence of visible particles because they cannot be seen within the solid matrix. The cake surface is visible during inspection but accounts for only a small fraction of the cake volume. Because of these challenges in evaluating acceptability, a small sample of units is reconstituted and inspected for visible particles in addition to the 100% inspection of the cakes for visible particles. Care must

be taken during reconstitution of these samples to avoid contamination that can lead to false-positive results. Sample preparation should be done in a clean environment with appropriate particle-control measures. Reconstituted samples should be inspected using the same conditions as those for visible particles. The destructive nature of this test limits the size of the sample; however, the resultant fluid allows visible particles to be more readily detected. Typical sampling plans for this type of test can be found in the special sampling plans S-3 and S-4 in ANSI/ASQ Z1.4 (40). The S-plans offer a practical compromise between sample size and statistical power and for most batch sizes between 3,201 and 150,000 suggest a sample size of 20 with an accept number of 0 (based on an AQL of 0.65%). Alternative plans are acceptable, but care should be taken to examine the UQL of such plans to assess their sensitivity. Once inspection of these reconstituted samples has been performed, they may be used for other required testing, such as that for subvisible particles, potency, impurities, or other specified tests. If particles are detected in this relatively small sample, additional units may be reconstituted as part of an investigation and to assess the compliance of the entire batch.

POWDER PRODUCT

Sterile powders are difficult to inspect for particles due to powder flow and the occlusion of white or light-colored particles by the drug product itself. Sterile powders should be reconstituted and inspected for visible foreign particles using an approach similar to that for lyophilized products, as discussed above.

EMULSION AND SUSPENSION PRODUCT

The manufacturer may allow inherent particles if the product is an emulsion or suspension. For suspension products, a test dissolving the suspension or disruption of the emulsion that provides for extrinsic and intrinsic particle detection is also recommended as part of destructive supplemental testing of a small sample as described above for lyophilized products.

AMBER CONTAINERS

Inspecting amber containers is challenging because selected elements have been added to mask UV light penetration into the Type I glass container. Light transmission is blocked below 500 nm, and thus increased light intensity (e.g., 8,000–10,000 lux) may be required to observe visible particles during inspection. Directional lighting from behind the container may also be beneficial. At the extreme, filled solution in practically opaque containers may be audited via sampling and transfer to clear, clean containers.

TRANSLUCENT PLASTIC CONTAINERS

Plastic or translucent containers are chosen for break resistance or other properties that glass cannot offer, such as injection molding into shapes that minimize hold-up volume or for use in a combination product. Plastic containers may have optical properties that require significantly more light (e.g., 8,000–10,000 lux) to illuminate any visible particles against black and white backgrounds. Directional lighting from behind the container may also be beneficial.

LARGE-VOLUME CONTAINERS

Large-volume containers (>100 mL) may require additional time to complete a thorough

inspection. For flexible bags, the semi-transparent nature of the PVC film used to manufacture these containers may require the use of additional light intensity to enhance the visibility of particles. Directional lighting from behind the container may also be beneficial.

COMBINATION PRODUCTS

When inspecting the unlabeled primary drug container for a combination product, the inspection considerations should be the same as those specified for a conventional drug product in a vial or syringe. This inspection should be performed before assembly into the device. Where there are critical attributes that are only visible after assembly (such as alignment with a fill-level window), a second inspection after assembly may also be required.

6. INSPECTION METHODS AND TECHNOLOGIES

6.1 Manual Visual Inspection

Manual visual inspection (MVI) is the reference inspection method described in all of the major pharmacopeias (55,56). It consists of viewing filled and sealed containers under controlled conditions. This process may be aided by the use of a tool to allow consistent examination of more than one container at a time. The quality decision, to either accept or reject the container, is made by a trained person. Inspection is a probabilistic process, and detection rates <100% are to be expected, especially for smaller or low-contrast defects.

CRITICAL PROCESS PARAMETERS IN MVI

Light intensity: The results of the manual inspection process are influenced by the intensity of the light in the inspection zone. In general, increasing the intensity of the light that illuminates the container being inspected will improve inspection performance; *⟨790⟩* recommends light levels NLT 2,000–3,750 lux at the point of inspection for routine inspection of clear glass containers. Special attention should be given to assure that inspection is not performed below the lower limit of 2,000 lux. Increased light levels are recommended for plastic containers or those made from amber glass. Under these circumstances, light levels as high as 10,000 lux may prove beneficial. The final inspection condition will depend on measured performance.

Light should be diffuse and even across the inspection zone, and it is a good practice to clearly identify this zone within the inspection station where the intensity meets the required levels. Fluorescent lamps have often been used as the light source for inspection. When fluorescent lamps are used, high-frequency ballasts are recommended to reduce visible flicker (and associated inspector fatigue). Incandescent lamps have also been used successfully for this purpose, but they generate significant heat during use. Light-emitting diodes (LED) offer an energy efficient, stable source of light without the added heat of incandescent lamps.

Light intensity in each inspection station should be measured periodically to ensure continued compliance within the specified range. The frequency of monitoring should be based on historical experience with the type of light source in use. A lower light-intensity action limit should be established to trigger corrective action before inspection is performed below the lower limit of the range.

Background and contrast: Contrast between the defect of interest and the surrounding background is required for detection, and increased contrast improves detection. The use of both black and white backgrounds is described in *⟨790⟩*, as well as other global pharmacopeias. The

use of both backgrounds provides good contrast for a wide range of particulate and container defects, which can be light or dark in appearance.

Inspection rate: Sufficient time must be provided to allow for thorough inspection of each container; chapter *⟨790⟩* specifies a reference time of 10 s/container (5 s each against both black and white backgrounds). Larger or more complex containers may require additional time for inspecting all attributes. Increased time may facilitate detection of defects near the threshold of detection, but studies by Wolfe, et al. (57,58) suggest that there are diminishing gains with increasing inspection time. Time spent per container may be controlled through the use of a pacing device such as a light or tone, or these may be used during training only, much as a musician uses a metronome during practice to learn the tempo of a musical piece for later performance. Recording the time spent inspecting each batch and then calculating a nominal inspection rate is a good way to confirm that the rate of inspection was within established limits. Correction can be made for non-inspection activities performed during this time by the inspectors to better document the nominal inspection rate.

Container handling and movement: When observing objects, the human eye is very sensitive to movement. Good techniques for manual inspection include a careful swirl or inversion of the liquid product within the container. This rinses any particles from the upper inner surfaces of the container and the closure and puts them into motion. A technique that minimizes the introduction of air bubbles is important, as air bubbles can appear as particles and interfere with detection of offending particles. A tool that holds multiple containers for consistent presentation can be useful when performing inspection. Holding many containers by hand at once should be avoided, as it is difficult to obtain a complete view of all container surfaces and contents. Container motion is also helpful for identifying small container defects such as cracks or chips.

Magnification: Some inspection processes use a large magnifier to increase image size and thus increase the probability of detecting and rejecting containers with defects near the threshold of detection. Although magnification can be useful for critical examination of a portion of the container, it does not often lead to increased overall detection rates for defects of interest. This may be due, in part, to the added eye strain that often results from use of magnification. As such, it is not recommended as part of the reference inspection method described in *⟨790⟩* or in other global pharmacopeias (55,56). Although not recommended for use during routine inspections, magnification can be helpful for critical examination of a small number of units, as may be needed during an investigation.

INSPECTOR FATIGUE AND ERGONOMIC CONSIDERATIONS

Inspecting for extended periods of time can cause inspector fatigue and a decrease in inspection performance. Based on industry experience (43), it is recommended that inspectors be given a break from performing inspection at least every hour. This break should allow time to rest the eyes and mind, and may be achieved with a short rest (e.g., 5 min) or a longer meal break. This need for regular breaks may also be met through rotation to a non-inspection function, such as material handling or documentation.

Inspection stations should be designed and operated in a manner that minimizes the inspector's risk of repetitive-motion injury. Adjustable chairs and careful positioning of light sources as well as incoming and inspected product can reduce the risk of such injury. These adjustments can also reduce inspector fatigue and discomfort, both of which can be distracting and thus can decrease performance.

The inspection room environment should also be considered. Temperature and humidity should

be controlled for inspector comfort. Reduced ambient lighting is recommended to focus the inspection process and to reduce distraction from extraneous reflections. Special care should be given to inspection rooms with exterior windows that allow daylight into the room and thus changing ambient lighting throughout the day and with changing seasons.

6.2 Semi-Automated Visual Inspection

Semi-automated visual inspection combines automated material handling of the containers to be inspected with human vision and judgment to make the decision to accept or reject. These systems often use a conveyor equipped with rollers to transport the containers in front of the inspector inside an inspection booth or station. For inspection of liquids, the booth can be equipped with a high-speed spin station to set particles in motion. The rollers are also used to slowly rotate the containers in front of the inspector as they traverse the inspection zone. These systems offer a means to control the presentation of the vials and can offer additional lighting options, such as Tyndall lighting, which may enhance the appearance of some defects such as cracks or small particles. Mirrors may also be used to provide a clear view of the top and bottom of each container. Rejected units may be removed from the rollers by hand, and some systems are equipped with a remote rejection system that can be triggered by the inspector. Care should be taken in the qualification and operation of these systems to ensure full rotation of vials in the inspection zone; this allows examination of all surfaces. In addition, studies should be conducted to ensure the detection of heavy particles, which may not be lifted from the bottom of the container, and to ensure that the rate of inspection produces an acceptable detection rate for defects of interest.

With semi-automated visual inspection, performance is similar to that with MVI. Some increase in throughput may be achieved because the inspector spends all of the available time viewing the containers, rather than splitting the time between inspection and material handling.

CRITICAL PROCESS PARAMETERS FROM SEMI-AUTOMATED INSPECTION

Light intensity must be controlled, as with MVI. The rate of inspection is controlled by the speed of the roller/conveyor. Spin speed for liquid products and rotation rate for all containers should be established during validation/qualification and maintained within the validated range for routine inspection. The background color is controlled by the color of the rollers selected and the color of the background seen through the spaces between the rollers. Qualification of inspectors and validation of the inspection equipment should be based on comparison with the compendial manual inspection process with an expectation that alternative methods such as semi-automated inspection demonstrate equivalent or better performance.

6.3 Automated Visual Inspection

Automated visual inspection (AVI) combines automated material handling of the containers with electronic sensing of product appearance. Containers that do not meet pre-programmed acceptance criteria are automatically rejected by the machine. Early machines performed inspection for particles and fill level, but manual or semi-automated inspection was required for the container and closure system. Newer models have the capability to inspect all attributes of the containers, along with the contents. As with MVI, machines often spin the containers to set particles in motion and make them easier to detect. Multiple cameras are used to image various regions on the container in great detail. Each camera is coupled with unique lighting to highlight

specific defects in the region of interest. Light-field and dark-field lighting techniques offer the same benefits as white and black backgrounds as discussed above, offering contrast for a full range of light- and dark-colored defects. A defect found by any camera is tracked through the machine to allow accurate ejection by the reject system. These machines also offers detailed reporting of defects observed in a specific production lot.

AVI offers advantages in the areas of throughput and consistency, compared with MVI (4). AVI may also offer enhanced sensitivity for some defects, compared with MVI, but may suffer from higher false rejection rates due to the inability to tolerate normal variation in containers or product. This is especially true for molded glass containers and flexible bags.

Validation of the automated inspection equipment should be based on comparison with the compendial manual inspection process with an expectation that alternative inspection methods demonstrate equivalent or better performance.

LIGHT-OBSCURATION METHODS

Some systems use an optical sensor to detect the shadow of particles in solution products. This method requires particles to be in motion, typically using a high-speed spin and rapid braking of the container to achieve this motion. Spin conditions must be optimized to provide sensitivity for heavier particles while minimizing false rejections due to bubbles. Some biological products experience shear-induced agglomeration, so care should be taken with regard to agitation of these products.

Light obscuration methods are optimized for sensitivity to moving particles, and can thus be made less sensitive to minor container imperfections. This technique can be used with both tubing and molded containers. Results are generally robust in detecting particles that are 100 µm in diameter and larger.

These systems can also detect fill height by detecting the shadow of the solution meniscus. Generally, this process is not sensitive enough to ensure compliance with dose or fill-weight specifications, but it can provide a secondary check of gross fill. Sensitivity is a function of the container shape, with greater sensitivity achieved in small-diameter containers.

IMAGING METHODS

Continuing advances in camera technology now allow the rapid capture of high-resolution images for inspection. When coupled with high-speed processors that have ever-increasing computational capability, a powerful inspection tool can result. Images are divided into inspection windows, and an array of tools such as image subtraction, pixel counting, intensity analysis, and others are used to assess the images against programmed quality attributes. Significant amounts of time are required to train inspectors to test the performance of such systems against a range of known defects, as well as acceptable containers.

Imaging systems can detect particles and fill level, as well as other container and closure attributes. Inspection in this manner can provide 100% inspection of all visual attributes. These systems can offer high sensitivity, but may also have high false-rejection rates if container and product attributes are not tightly controlled.

OTHER TECHNOLOGIES

Container–closure integrity can also be assessed using non-visual methods such as electrical conductivity and capacitance, vacuum decay, or mass extraction, for example (59). Laser-based

gas headspace analysis can also be used if there is a modified headspace such as vacuum or inert gas. Generally, such nondestructive container-integrity inspection methods offer greater sensitivity than visual detection with the potential to reduce false rejection of acceptable product. See *Sterile Product Packaging—Integrity Evaluation ⟨1207⟩* for further information regarding package integrity testing by these and other test methods.

X-ray imaging has also been explored as a means to detect particles within freeze-dried cakes, powders, or suspensions (60).

These technologies may be used alone or in combination with other inspection methods to provide a comprehensive assessment of product quality before labeling and packaging.

7. QUALIFICATION AND VALIDATION OF INSPECTION PROCESSES

7.1 Standards

The use of standards for visual inspection has been described by Melchore and Berdovich (61). Development of inspection standards begins with identification or characterization of the defect types that will be represented in the test set(s). This information typically comes from the manufacturing area, where naturally occurring defective units can be identified from rejected product. The defects are categorized as critical, major, or minor. These defects must be further characterized to allow for 1) selection from naturally occurring particulate and physical or cosmetic production rejects removed from product lots, and/or 2) re-creation of equivalent defect types in a controlled laboratory environment. Characterization information on defects should include, where appropriate, the range of sizes typically observed and the specific location on the container. If feasible, a photograph of the defect should be included. All information that could support consistent re-creation of the defect standards should be included in the characterization description.

7.2 Preparing Defect Standards

Visual inspection standards may be identified from known production rejects, or may be created manually with characterized particulate material. A single particle/seeded container should be used when determining detection thresholds.

7.3 Particle Types

The primary packaging materials that directly contact the product and the potential environmental contaminants can be divided into specific particle groups such as glass, stainless steel, elastomeric closure, plastic, and fibers (synthetic or natural). Naturally occurring particles from rejects should be no smaller than the visible particle (measured in situ) in the container. Measurement can be accomplished with a wide field microscope or loupe with a calibrated reticle. Physically prepared particles can be sieved initially to target a specific size, and then the individual particles are measured using optical microscopy. These materials, or production defects, are preferred for inspector training and qualification, as well as machine validation as they better represent actual inspection performance. Spherical standard particles may be utilized as surrogates for naturally occurring particulates; however, these are best used for routine machine calibration rather than validation or inspector qualification, as they do not move or look like actual production defects.

7.4 Rejection Probability Determination

Once a well-defined defect standard is available, it is assigned a detection frequency or probability of detection (POD) by conducting a documented, manual human inspection qualification that is accomplished by repeated manual inspection. This repeated inspection is the basis for qualifying the defect standard. This approach has been described by Knapp and Kushner (53,54). The Knapp methodology recognizes that the detection of particles is probabilistic, and repeated inspections with strict controls on lighting and inspection pacing/sequencing generate the statistical confidence to assign a reject probability to each standard unit. A manual, visual inspection POD of ≥0.7 or 70%, is required to assign the container to the Reject Zone for subsequent calculation of the reject zone efficiency (RZE). Secure probabilistic data for particulate standards can be achieved with 30–50 inspections of each container. This is best achieved with multiple inspectors. Inspection reject probability is calculated for the defect as follows:

POD = (Number of times rejected)/(Number of times inspected)

7.5 Test Sets

These qualified defect standard units are then assembled into test sets, which may be used to specifically challenge the particle detection technique of human inspectors, used as part of a defect test set (including container–closure defects) for human qualification, or for comparison during automated equipment qualification and validation. When possible, the test set should be prepared with duplicate product units per particle type and size to ensure that backup units are available in the event that a standard container is broken or the particle is trapped or lost within the container. When using test sets, it is a good practice to verify the presence of particles before and after use, as particles may become lodged between the container and the closure. When a freely moving particle cannot be verified, the unit should not be used and the data should be excluded from subsequent calculations. When this happens, it may be possible to free the particle with the use of an ultrasonic bath. If this is not possible, the unit should be replaced. The number of defective units in each test set should be limited to approximately 10% to prevent rejection bias (57). The accept containers will be identified as having a pre-determined manual, visual inspection POD of <0.3 or 30%. Any particle standards found to fall within the acceptable “grey zone”, indicating a manual inspection rejection probability ≥30% and <70%, may be included as an “acceptable unit” in a test set, if desired.

It is important to prepare a written procedure for the creation and maintenance of standards. This procedure should define the qualification criteria, appropriate storage conditions, periodic examination and requalification, expiration, and sample custody during use. Test sets should be approved by the quality unit. The container in which the specific particle set is stored must be clearly labeled with the test set identification information.

7.6 Types of Test Sets

The particle detection threshold can be determined for a specific inspection method and product/package combination. It is a standard curve of detection probabilities at various particle types and sizes in an approximate range of 100–500 µm (with recommended increments of 100 µm). Fibers are typically observed in sizes >500 µm. The typical size range of particles used in

threshold studies incorporates a variety of particle types and densities that are typically found in the manufacturing environment.

Threshold studies are conducted to determine the sensitivity of manual inspection methods, using a range of particle sizes, in a blinded study that yields the particle-size detection capabilities of a defined group or of an individual inspector. The threshold studies indicate that the method of inspection is valid and appropriate. For example, for clear solutions in 10-mL tubing glass vials, past thresholds studies indicate that particles within the range of 150–250 µm (500–2000 µm for fibers) can be detected with a POD of 70% or greater. Results can differ due to differences in product formulation as well as container type and size. Threshold studies are also useful as an assessment tool when evaluating or qualifying visual inspection staff on a specific method with fixed testing parameters. Detection threshold studies are typically the first step in evaluating the performance of any new inspection method.

Depending on product and/or presentation, rejects in the test set should represent all defects anticipated for a given container type or product family. For particles, use a bracketed range of types (densities) and sizes from near the lower limit of the visible range (100 µm) to the largest routinely observed in the pool of rejects. For an individual manual test set, it is important that all containers and closures are of the same type, and the samples are blinded. UV ink (invisible to the inspectors) may be used to mark all containers. Alternatively, bar codes or other coded labels may be used. Manual test sets can be used initially to qualify, or periodically to re-qualify, human inspectors. These test sets may also be used for direct comparison to semi-automated or automated inspection methods. If significantly different formulations (e.g., clear solution, suspension, lyophilized) or packages (e.g., clear vials, amber vials, ampoules, syringes) are produced at the same facility, separate test sets should be prepared to represent each unique combination. A bracketing approach may be used with regard to different container sizes.

7.7 Training and Qualification of Human Inspectors

Before training, potential inspectors should be tested for visual acuity (62) and color perception. Near-vision performance should be the equivalent of 20/20 with no impairment of color vision. Both the Snellen and Jaeger charts are useful for verifying visual acuity; they test far and near vision, respectively. Training should include a phased approach with a specified number of training hours expected for each segment. Initially, train the potential inspectors with defect photographs or a video library and clear written descriptions. Utilize subject matter experts to mentor and provide hands-on training with defect standards for the specified method. Reinforce mental or silent counting and follow the paced sequence to achieve consistent inspection timing. Stress the importance of strict adherence to the inspection process (procedure, sequence, and timing). Inspector fatigue may be addressed in the qualification process by testing under worst case conditions (e.g., at the end of a typical inspection shift). Train all inspectors (QC, QA, and production) with common procedures used for 100% inspections and AQL inspections. All inspection practices should be standardized and consistently executed across all inspection groups.

Qualification should be performed for each product type and package that the inspector will encounter. A bracketed or matrix approach can be used to simplify qualification of products with similar physical or visual characteristics such as container type and size, formulation type, product viscosity, color, and others. It is common to initially train and qualify personnel on clear solutions in clear containers (if produced at the facility) and then expand their expertise to inspection of more difficult formulations or presentations.

7.8 Inspector Qualification Requirements

The qualification of all inspection personnel utilizes a manual test set to be inspected under normal operating conditions and inspection critical parameters, including inspection timing and sequence, physical environment, and inspection duration. Three successful inspections of the test set are recommended to demonstrate consistent performance for initial qualification of new inspectors. Acceptance criteria for each defect class should be based on the POD (or RZE) observed during test set qualification. A limit is also needed for false rejection, with a recommended target of <5% falsely rejected good units.

7.9 Requalification

Inspectors should be requalified at least annually. Requalification includes a test of visual acuity and testing with at least one product/test set configuration. A single successful inspection of the test set is sufficient for requalification. Requalification may also be necessary in the event that poor performance is observed during routine inspection or if the inspector has been away from the inspection operation for an extended period of time (e.g., 3 months).

If an inspector fails the requalification test, a retraining process should be initiated to identify the root cause and allow the inspector to receive additional instruction. After this process has been completed, the inspector may attempt to meet the acceptance criteria one additional time. If the inspector fails, he or she may attempt to qualify again after a specified time period.

8. PRODUCTS IN DISTRIBUTION

Chapter *⟨790⟩* states, “If it becomes necessary to evaluate product that has been shipped to customers (e.g., because of a complaint or regulatory concern), sample and inspect 20 units. If no particles are observed in the sample, the batch is considered essentially free of visible particulates. If available, additional units may be inspected to gain further information on the risk of particulates in the batch.”

For products in distribution, questions regarding batch quality will occasionally arise from customer complaints, observations in the field, customer use questions and from the use of non-standard (sensitive) conditions of inspection. As discussed in this chapter, the detection process is probabilistic and the likelihood of detection is a cumulative function of the particle's visible attributes, drug product and container characteristics, and the inspection method used. In an appropriately qualified manufacturing process, the batch is presumed to have been prepared according to robust processes and all containers with package defects and visible particles (non-conforming units) removed prior to labeling. In that regard, the evaluation outlined in general chapter *Visible Particulates in Injections ⟨790⟩, Introduction, Sampling at Batch Release (After 100% Manufacturing Inspection), Product in Distribution* is only permissible if both Sampling at Batch Release and a 100% Manufacturing Inspection have been successfully completed.

The particle detection threshold should be determined for a specific inspection method and product/package combination incorporating a variety of particle types and densities that are typically found in the manufacturing environment. For example, the detection threshold for routine, reliable detection (≥70% probability) of a single spherical particle in a clear solution contained in a 10-mL vial utilizing diffuse illumination between 2,000 and 3,000 lux is often

near 150 µm in diameter (4). Units returned from distribution may be false positive, may contain particles larger than the acceptance threshold that were missed, may contain particle(s) in the "grey zone", e.g., less than the detection threshold, or may have suffered a physicochemical change that resulted in a visible change. Ideally there were no visible particles in the containers released to market; however, there is always a low probability that this may occur.

Upon receipt, suspect containers should be subjected to the same inspection conditions and methodology used in the release inspection. Particle(s) verified in the returned or re-evaluated supply must be carefully characterized by an analytical forensic process to determine their source and likely cause. Single particles of typical product-contact materials are unlikely to present a concern. Multiple particles, large particle sizes, and any particles indicative of physical or chemical change are significant events and should be subject to further investigation. Rare instances of particulate material falling into the "grey zone" should be expected given the probabilistic nature of the inspection process and should not routinely trigger further evaluation of retention samples. While *⟨790⟩* provides that zero particles found in the sampling and inspection of 20 units signifies that the batch is essentially free of visible particulates, if multiple suspect containers from the same batch are detected, additional units should be inspected and an appropriate rationale provided to support the batch's conformance to the registered specifications. Overall batch quality using internal systems to control particulate matter and the means to investigate these occurrences is key to the life cycle approach for modern pharmaceutical production. Evaluation of retention and stability samples provides insight to batch quality, as do the field-use effects for any medication. While the presence of particles or product or container defects discovered in retained or returned product do not necessarily incriminate the quality of the batch, careful investigation should be conducted to exclude systemic risks.

9. CONCLUSIONS AND RECOMMENDATIONS

Visual inspection for particles and other visible defects continues to be an important part of the manufacturing process for injections. Chapter *⟨790⟩* provides a useful reference method and acceptance criteria for visible particulates in injections. Successful execution of visual inspection requires an understanding of the inspection process and careful control of inspection conditions. Inspectors must be trained to ensure consistent, high-quality performance. Alternative inspection methods, either semi-automated or fully automated, may be used in place of manual inspection methods. Where machine methods are used, the equipment must be validated to demonstrate equivalent or better performance when compared to manual inspection. The use of test sets that contain standard defects is an important element in inspector training and qualification as well as machine validation. Good product development will lead to a stable product with a lower risk of particle formation. Identification of the type or types of particles found during product development and routine manufacturing is an important aid in source identification and reduction. Inspection results should be trended to further aid in continuous process improvement with the ultimate goal of defect prevention.

REFERENCES

1. Parenteral Drug Association. Technical Report No. 43. Identification and classification of nonconformities in molded and tubular glass containers for pharmaceutical manufacturing. 2013.

2. Cherris RT. Visual inspection life cycle of particulate and container–closure defect control. PDA Visual Inspection Forum, 2011. Bethesda, MD.
3. Delly JG. Diffraction lines: the eyes have it. Microscope. 1989;37:195–211.
4. Shabushnig JG, Melchore JA, Geiger M, Chrai S, Gerger ME. A proposed working standard for validation of particulate inspection in sterile solutions. PDA Annual Meeting. Philadelphia, PA: 1995.
5. Borchert SJ, Abe A, Aldrich DS, Fox LE, Freeman J, White RD. Particulate matter in parenteral products: a review. J Parenter Sci Technol.1986;40;212.
6. Watson R, Straub J. Manual inspection capability to detect particulate in parenterals. PDA Visual Inspection Forum, 2013. Bethesda, MD.
7. Thomas WH, Lee YK. Particles in intravenous solutions. New Zealand Med J 1974;80:170.
8. Turco S, Davis NM. Clinical significance of particulate matter: a review of the literature. Hosp Pharm.1973;8:137.
9. Groves MJ, deMalka SR. The relevance of pharmacopeial particulate matter tests. Drug Dev Comm.1976;2:285.
10. Groves MJ. Parenteral products: the preparation and quality control of products for injection. London: William Heinemann Medical Books, 1973.
11. Groves MJ. Particulate matter: sources and resources for heathcare manufacturers. Buffalo Grove, IL: Interpharm Press, 1993.
12. Langille SE. Particulate matter in injectable drug products. PDA J Pharm Sci Tech. 2013;67(3):186–200.
13. Bukofzer S, Ayres J, Chavez A, Devera M, Miller J, Ross D, et al. Industry perspective on the medical risk of visible particles in injectable drug products. PDA J Parenter Sci Technol. 2015;69;123–139.
14. 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.
15. Newton DW, Driscoll DF. Calcium and phosphate compatibility: revisited again. Am J Heath-Syst Pharm. 2008;65:73–80.
16. Garvin JM, Gunner BW. Intravenous fluids: a solution containing such particles must not be used. Med J Austr. 1963;2:140.
17. Garvin JM, Gunner BW. The harmful effects of particles in intravenous fluids. Med J Austr. 1964;2:1.
18. Burton JF, Zawadzki ES, Wetherell HR, Moy TW. Mainliners and blue velvet. J Forensic Sci. 1965;10:466.
19. Richman S, Harris RD. Acute pulmonary edema associated with librium abuse. Radiology. 1972;103:57.
20. Douglas FG. Foreign particle embolism in drug addicts: respiratory pathophysiology. Ann Intern Med. 1971;75:865.
21. Jones BS, Brancaccio FA, Rodriguez GA. Dyspnea and bilateral interstitial pulmonary infiltrates in an intravenous drug user. BUMC Proceedings. 2002;15:430–432.
22. Brewer JH, Dunning JF. An in vitro and in vivo study of glass particles in ampoules. J Amer Pharm Assoc. 1947;36:289–293.
23. Schoenberg MD, Gillman PD, Mumaw V, Moore RD. Proliferation of the reticuloendothelial system and phagocytosis. Exp Mol Pathol. 1963;2:126.

24. Hozumi K, Kitamura K, Kitade T, Iwagami S. Localization of glass particles in animal organs derived from cutting of glass ampoules before intravenous injection. Microchem. 1983;28:215.
25. Brekkan A, Lexow PE, Woxholt G. Glass fragments and other particles contaminating contrast media. Acta Radiol.1975;16:600.
26. Liu JF, Su ZK, Ding WX. Quantitation of particulate microemboli during cardiopulmonary bypass: experimental and clinical studies. Ann Thorac Surg. 1992;54(6):1196–1202.
27. Walpot H, Franke WP, Burchard WG, Agternkamp C, Muller FG, Mittermayer C, et al. Particulate contamination of infusion solutions and drug additives in the framework of long-term intensive therapy. 2. An animal model. Anaesthesist [in German]. 1989;38(11):617–621.
28. Jones ML, Warren JS. Monocyte chemoattractant protein 1 in a rat model of pulmonary granulomatosis. Lab Invest. 1992;66(4):498–503.
29. Bautista AP, Schuller A, Spolarics Z, Spitzer JJ. In vivo latex phagocytosis primes the Kupffer cells and hepatic neutrophils to generate superoxide anion. J Leukocyte Biol. 1992;51(1):39–45.
30. Gentile F, Curcio A, Indolfi C, Ferrari M, Decuzzi P. The margination propensity of spherical particles for vascular targeting in the microcirculation. J Nanobiotech. 2008;6:9.
31. Repa I, Moradian GP, Dehner LP, Tadavarthy SM, Hunter DW, Castaneda-Zuniga WR, et al. Mortalities associated with use of a commercial suspension of polyvinyl alcohol. Radiology. 1989;170:395–399.
32. Brown KT. Fatal pulmonary complications after arterial embolization with 40–120 µm tris-acryl gelatin microspheres. J Vascu Intervent Radiol. 2004;15(2):197–200.
33. Siskin GP, Englander M, Strainken BF, Ahn J, Dowling K, Dolen EG. Embolic agents used for uterine fibroid embolization. Am J of Roentgen. 2000;175(3):767–773.
34. Wijeyaratne SM, Ubayasiri RA, Weerasinghe C. Fatal pulmonary embolism of polyvinyl alcohol particles following therapeutic embolisation of a peripheral arteriovenous malformation. BMJ Case Reports, 2009.
35. Reedy JS, Kuhlman JE, Voytovich M. Microvascular pulmonary emboli secondary to precipitated crystals in a patient receiving total parenteral nutrition. Chest. 1999;115:892–895.
36. Injectable drug delivery: probing the route of growth. Datamonitor. London. January 2004.
37. Madsen RE, Cherris RT, Shabushnig JG, Hunt DG. Visible particulates in injections—a history and a proposal to revise *USP general chapter Injections ⟨1⟩.* Pharma Forum. 2009;35(5):1383–1387.
38. FDA. Sterile drug process inspections. Compliance Program Guidance Manual, Program 7356.002A. 2012. http://www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/ucm125409.pdf
39. ICH. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Q10 Pharmaceutical Quality System (PQS).

2008. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Presentation/Q10_General_Presentation.pdf
40. ANSI/ASQ. Z1.4 sampling procedures and tables for inspection of attributes. Milwaukee, WI: American Society for Quality; 2013.
41. International Organization for Standardization. Sampling procedures for inspection by attributes— Part 1: sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection. Geneva, Switzerland: ISO; 1999.
42. Japanese Industrial Standard. JIS Z 9015–1 Sampling procedures for inspection by attributes—Part 1: sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection. Tokyo: Japanese Standards Association; 2006.
43. Shabushnig JG, Leversee RL. A survey of industry practice for the visual inspection of injectable products (preliminary report). PDA Visual Inspection Forum. Berlin: 2008.
44. Code of Federal Regulations Title 21 Food and Drugs, 21 CFR 210.3 Definitions (2014).
45. Code of Federal Regulations Title 21 Food and Drugs, 21 CFR 211.115 Reprocessing (2014).
46. FDA. Advisory to Drug Manufacturers: formation of glass lamellae in certain injectable drugs. 2011. http://www.fda.gov/drugs/drugsafety/ucm248490.htm
47. ICH. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Q8 Pharmaceutical Development. 2008. http://www.ich.org/fileadmin/Public_Web_Site/Training/ICH_Endorsed_Training_Events/ASEAN_training_on_Q8_Q9_Q10_Guidelines/Q8_Pharma_development_JL.Robert.pdf
48. Chang BS, Hershenson S. Practical approaches to protein formulation development. In: Carpenter JF, Manning MC, eds. Rational design of stable protein formulations-theory and practice. New York: Kluwer Academic Press/Plenum; 2002:1–25.
49. Barber TA. Pharmaceutical particulate matter: analysis and control. Buffalo Grove, IL: Interpharm Press; 1993:243–246.
50. Haleblian JK. Characterization of habits and crystalline modification of solids and their pharmaceutical implications. J Pharm Sci.1975;65(8):1269–1286.
51. Jenke D. An extractables/leachables strategy facilitated by collaboration between drug product vendors and plastic material/system suppliers. Pharm Sci Tech. 1986;61(1):17–33.
52. Dimbleby V. Glass for pharmaceutical purposes. J Pharm Pharmacol. 1953;5:969.
53. Knapp JZ, Kushner HR. Generalized methodology for evaluation of parenteral inspection procedures. J Parenter Sci Technol.1980;34(1):14–61.
54. Knapp JZ, Kushner HR. Implementation and automation of a particle detection system for parenteral products. J Parenter Sci Technol. 1980;34(5):369–393.
55. European Directorate for the Quality of Medicines & Healthcare. European Pharmacopoeia 8.2 / Ph. Eur. Chapter 2.9.20 Particulate Contamination: Visible Particles. Strasbourg, France: EDQM; 2014.
56. Japanese Pharmacopoeia. JP 16. 6.06 Foreign Insoluble Matter Test, Tokyo, Japan, 2014.
57. Wolfe JM, Horowitz TS, Van Wert MJ, Kenner NM, Place SS, Kibbi N. Low target prevalence is a stubborn source of errors in visual search tasks. J Exper Psych. 2007;136(4):623–638.

58. Rich AN, Kunar MA, Van Wert MJ, Hidalgo-Sotelo B, Horowitz TS, Wolfe JM. Why do we miss rare targets? Exploring the boundaries of the low prevalence effect. J Vision. 2008;8(15):1–17.
59. Parenteral Drug Association. Technical Report No. 27. Pharmaceutical Packaging Integrity. 1998. https://store.pda.org/ProductCatalog/Product.aspx?ID=1185
60. Prinz H. Particle detection in freeze dried and suspension products: new technology. PDA Visual Inspection Forum. Bethesda, MD: 2011.
61. Melchore JA, Berdovich D. Considerations for design and use of container challenge sets for qualification and validation of visible particulate inspection. PDA J Pharm Sci Technol. 2012;66(3):273–284.
62. Houf JW. Understanding near vision eye tests. The NDT Technician. 2009;8(4):1.▲