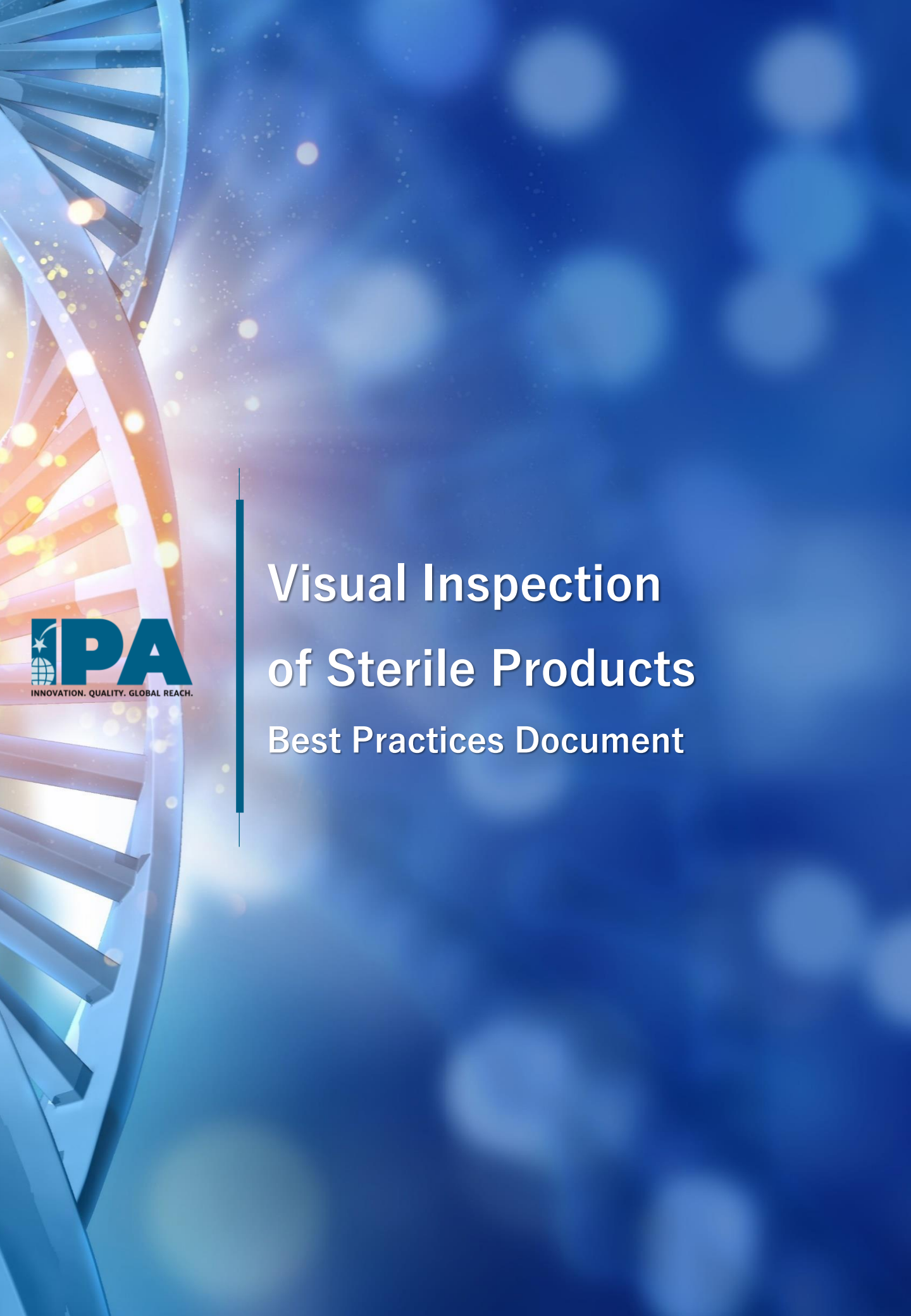

Visual Inspection of Sterile Products

Best Practices Document

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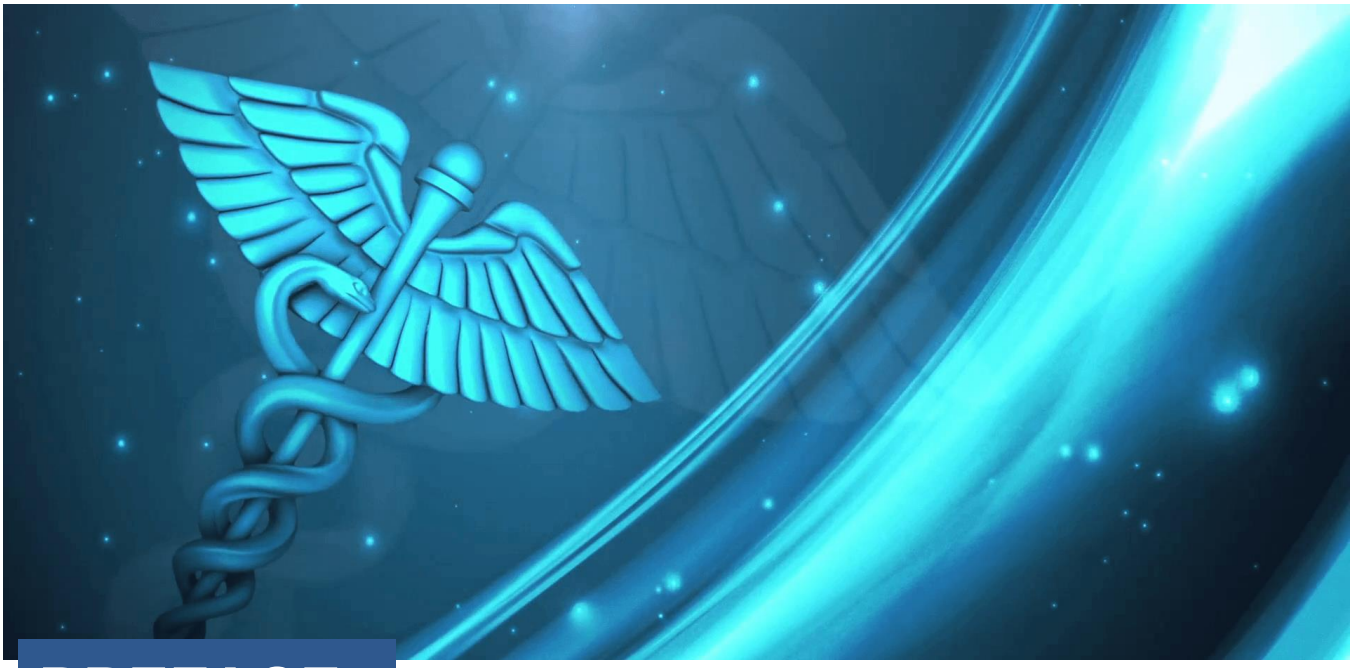


PREFACE

The IPA launched its Quality Forum (QF) in April 2015 to help Indian pharmaceutical manufacturers to achieve parity with global benchmarks in quality. The QF made for commitment to a multi-air journey to address key issues facing the industries and develop best practices. McKinsey & Company joined this journey as a knowledge partner.

In 2020-21, the QF focused on one of the key priority areas: Visual Inspection of Injections for Visible Particles. It took upon itself the challenge of establishing robust and seamless visual inspection and process, and release a comprehensive set of guidelines in 2021.

The six participating companies in the QF nominated one senior manager each to study the best practice and frame the guidelines. They are: Mr. Manikandan Ganesan (Cipla), Mr. Venugopal Gurram (Dr. Reddy's Laboratories), Mr. Abid Hashmi (Cipla), Mr. Prabu Natarajan (Lupin), Mr. Bhavesh Shah (Zydus Cadila) and Mr. Roshan Tathed (IPA). This group is led by Mr. Mustak Sherasia (Sun Pharma) and Ms. Ranjana Pathak (Cipla), and Dr. Rajiv Desai (Lupin) was nominated as Mentor.

The IPA wishes to acknowledge the concerned efforts made by the team over the last twelve months. They shared current practices, benchmarked these against existing regulatory guidelines from the USFDA and regulatory agencies such as UK MHRA, WHO, etc., developed a robust draft document and had it vetted by a leading subject matter expert. The IPA acknowledges their hard work and commitment to Quality.

The IPA also wishes to acknowledge the CEOs of six member companies who have committed their personal time, human resources and funding for this initiative.

This document is being released at the 6th India Pharmaceutical Forum, to be held by the IPA in Feb 2021 on a virtual platform. This will be hosted on the IPA website (www.ipa-india.org) in order to make it accessible to all manufacturers in India and abroad.

2 Introduction

2.1 Purpose and Scope

- This Best Practices document highlights, and in some instances clarifies, the inspection of injections for visible particles. Particulate matter is defined 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 document are also applicable to the detection of other visible defects that are not the subject of this document, but critical to a qualified and comprehensive inspection process.
- This general descriptions provided herein are applicable for the visual inspection activities carried out for different sterile dosage forms, i.e., injectable, ophthalmic products, lyophilized products, suspensions, and media fill containers.

2.2 Background

2.2.1 Inspection Process Capability

- The desire to detect defects, despite their very low frequency and the randomness of their occurrence, has resulted in the longstanding 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 capabilities, and the probabilistic nature of the inspection process by manual and automatic machines
- Since the detection process is probabilistic, the likelihood of detection is a cumulative function of visible attributes such as particle quantity, size, shape, color, density, and reflectivity.

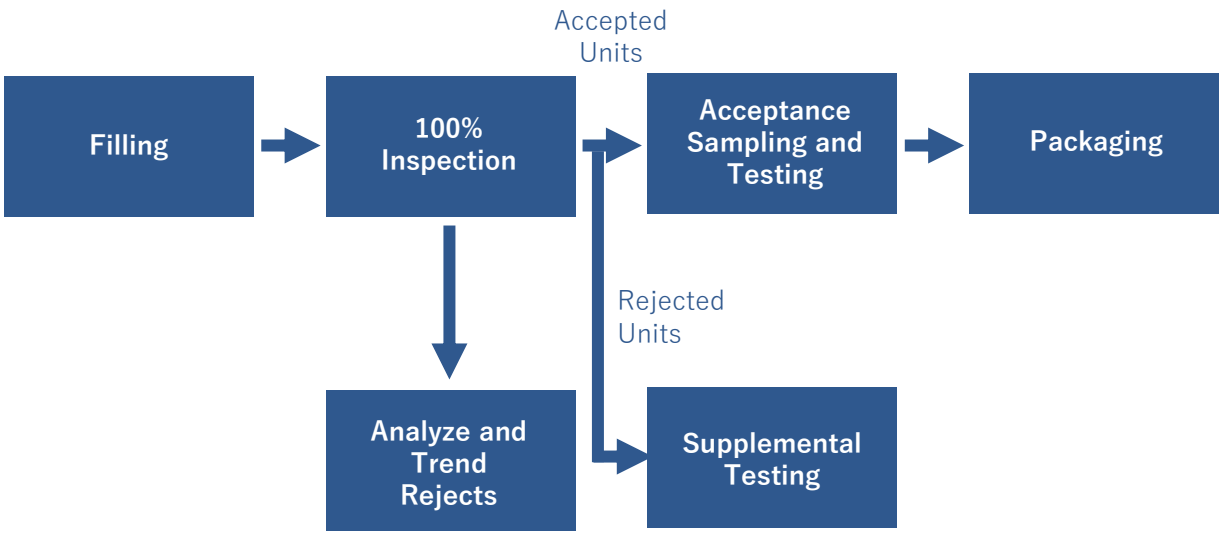
2.2.2 Patient Risk

- The clinical implications of 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.
- The clinical risk to human patients posed by a small numbers of particles is difficult to infer from a consideration of the factors mentioned above, due to the extreme number [RS1] of insoluble particles and the uncontrolled conditions in which they were administered.
- 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 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.

3 Inspection Process Flow :

3.1 100% Inspection:

- Each unit (container closure and its content) of injectable product should be inspected as part of the routine manufacturing process. This inspection should take place at a point when and where defects are most easily detected. Each unit may be examined manually with the unaided eye or semi-automated inspection or light obscuration (LO) or automated inspection.
- Manual and semi-automated inspection should only be performed by trained and 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 at-line or 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.



- Inspection may be accomplished in a single operation or in multiple steps using a combination of technologies.
- 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).
- 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. 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.
- 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 AQL Sampling and Testing

- After 100% inspection, a statistically valid sample is taken from the units accepted by the inspection process. These sampled units should be manually inspected under controlled conditions by trained inspectors. The sample should be a representative sample (represents the whole lot).
- 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, that 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.

Table 1
Typical AQL AccValues for Visual Inspection Processes

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

- When selecting a sampling plan for AQL testing after 100% inspection using ANSI/ASQ Z1.4, ISO 2859, or JIS Z9015, it is important to choose the sample size which satisfy the AQL value for the most critical category (e.g., critical) of defects being evaluated. The accept numbers for this sample size for the AQL values should be 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.
- 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 forensic classification/identification of the particle, and 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 that is better suited to detection of a specific defect may also be chosen for reinspection. After reinspection (performing a second 100% inspection of the batch), a new AQL sample of the accepted units should be taken and compared against the established acceptance criteria.

3.3 Remediation and Alternative Practices

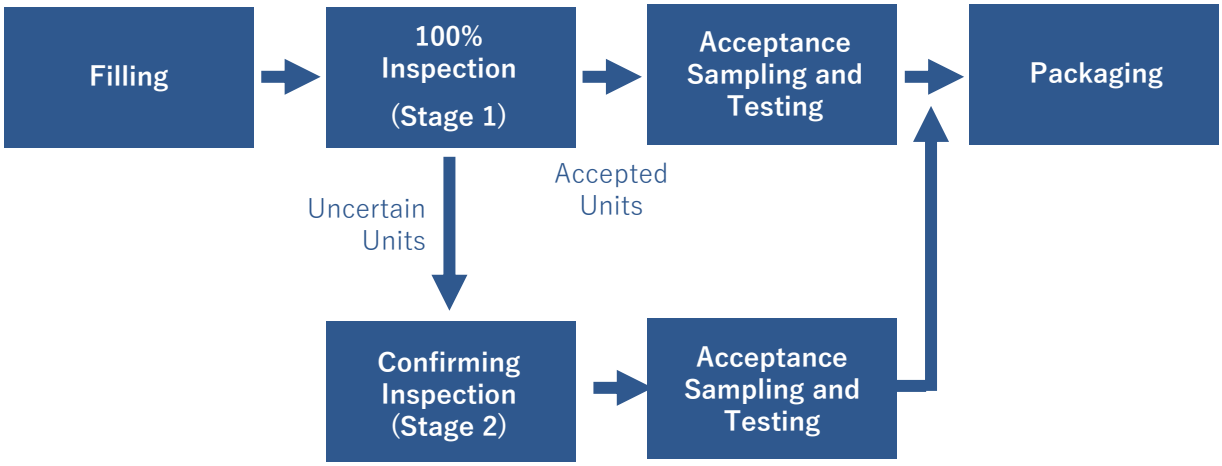
3.3.1 REINSPECTION

- Reinspection (repeating the 100% inspection followed by acceptance sampling inspection) 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 procedure that has been approved by the Quality department and addresses key parameters such as the inspection conditions (e.g., same as primary inspection or modified to enhance detection of a specific type of defect), 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 and with repeated reason, consideration should be given to check appropriateness of CAPA taken and improving the sensitivity of the primary inspection process or of the manufacturing controls as determined by root cause analysis

3.3.1 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.
- Inspection conditions may be adjusted to provide greater sensitivity in this second inspection step (e.g., additional inspection time) so as 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.
- 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.

Figure 2: Two-stage Inspection Process Flowchart



- •If a two-stage inspection strategy is used, it must be validated as intended for use. Defective containers with less than a 100% PoD will have the PoD reduced further with each stage of inspection, thus the PoD should be determined after inspection through both stages to ensure that acceptable sensitivity is maintained.

4 INSPECTION LIFECYCLE

4.1 Extrinsic, Intrinsic, or Inherent Particles

- **Extrinsic Particles:** Foreign particles 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. Inclusion of 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 contamination from the same source. These particles may carry an increased risk of microbiological or extractable contamination, because not much is known about their path prior to deposition in the product container or their interaction with the product.

- **Intrinsic Particles:** These are particles within the process, or "inherent", which are known to be or intended to be associated with specific product formulations. Any process-related intrinsic particles should have controls established based on the use of a lifecycle approach such as Defect Prevention. Another group of particles considered intrinsic is interrelated with the stability of the product. Such 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. Particulate formation related with product formulation 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.

4.2 Control and 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.

4.2.1 Robust Design during Development

- To anticipate potential sources of instability that yield intrinsic particles, the product design should be evaluated from many perspectives, beginning with a literature review of similar formulae/packages. Points to consider include the reported sensitivities of the active ingredient, 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 as discussed in Evaluation of the Inner Surface Durability of Glass Containers 〈1660〉 and by the FDA (45). 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 include the product concentration, solution pH, critical micelle concentration, oligomerization content/potential, package effects (large surface area, product volume, headspace, light/oxygen transmission), and compatibility of the formulation with the package. Furthermore, shock/vibration sensitivity at the air/liquid interface can be a significant contributor to particle formation that requires investigation during product development. 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, it is necessary to 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 document, 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 a period of several months. Particles will be detected, and the investigation of type is essential in order to differentiate additive types from instability or package interaction. Pursuit of extrinsic particles at this stage of development is generally not significant, as the particles do not reflect on the formulation or manufacturing process that is under development, but rather the manner in which they were filled.

- The second, more refined level of stability study involves conducting visual inspections of the injection in defined, International Council for Harmonization (ICH)-relevant trials (46). 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 for changes due to instability. It is important to be able to analyze the particulate matter or condition (color, haze) in order to identify the cause of truly stability-indicating events. A typical sample size is 80–100 units. This should be sufficient for the trial of the package and formulation interaction. 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.

4.2.2 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. The threshold levels for the formation of visible change for certain substances may be only 10–100 ppm (0.001%–0.01%) based on the ability to detect a single 100-μm particle or many sub-10 particles giving a hazy or cloudy appearance. However, if all of this insoluble material were contained in a single visible particle, it would likely be cause of rejection of the container.

4.2.3 Formulation Components

- The active ingredient may also contribute to the presence of stability-indicating intrinsic particles. 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.

4.2.4 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 the materials that could have contributed, and leachables represent the practical contribution upon contact between packaging components and drug formulation. These substances can also contribute to the formation of sub-visible 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. 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 stopper or plunger insertion and its movement within the syringe barrel. 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

4.3.1 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 LO and/or membrane microscopic particle-counting method scan provide a means to demonstrate reduction of both subvisible and visible particles during washing cycle development and validation. The membrane filtration microscopic method is superior to LO methods for capturing and characterizing larger foreign particles in the visible range (>100 μm) during validation or monitoring activities. 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. It is very important to review the maintenance procedures of the wash-water recirculating filter to ensure that particle overloading or breakthrough is being prevented.
- Glass breakage that occurs during the component washing process could affect surrounding containers where introduction of glass particle may not be ruled out. 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. It is recommended to perform recording and trending of glass breakage incidents in order to evaluate the consistency of container washing process.

4.3.2 Elastomeric Closures

- Each step of the elastomeric-component washing and rinsing process should be evaluated for particle-reduction opportunities. Appropriate statistical sampling plans should be utilized to collect meaningful test units. LO or other automated particle counting and membrane microscopic particle-counting methods may be used to demonstrate reduction of both sub-visible and visible particles during washing validation. The membrane filtration microscopic method is superior to LO methods for capturing and characterizing larger foreign particles in the visible range (>100 μm) during validation or monitoring activities. 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.

- **Ready to Sterilize and Ready to Use components** : Periodic assessment of component cleanliness and washing capabilities of the supplier should be included as part of the supplier qualification program when using purchased, ready-to sterilize, or ready-to-use components.

- **Silicon Oil Level** : It is recommended that any current siliconization process used, whether in-house or by the supplier, should be evaluated in order to minimize excess silicone levels while maintaining machinability of the stoppers. LO 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.

4.3.3 Glass Handlings for Depyrogenation Process

- 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 with increased risk of subsequent fracture. The use of polymeric facing on guides can help in reducing such damage.

4.3.4 Equipment Preparation for Sterilization Process

- 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, low-shedding, noncellulose (synthetic) wrapping materials should be utilized. 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. Final wrapping can be performed in a grade A environment.

- Personnel are a concern for introduction of extrinsic particle types such as eyebrows, eyelashes, facial hair, and skin cells. The equipment preparation staff should be adequately gowned with hair covers, facial hair covers, and goggles to prevent contaminating cleaned process equipment.

- During validation and monitoring activities of clean- and/or steam-in-place (CIP-SIP) systems (vessels, filters, tubing, and other product contact equipment), foreign particle burden should be evaluated after cleaning.

4.3.5 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 be removed from the affected portion of the line. It should be noted 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 (spallation). Overheated silicon tubing may get hardened and can generate 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. Usage of oRABS/Isolator would be a better practice. 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 of Visual Inspection process

- Data obtained from the in-process 100% inspection followed by AQL inspection are used for batch release. A continuous process verification program with statistical evaluation against pre-established alert and action limit of each batch prior to release of the batches is a very helpful tool. Both 100% and AQL inspection data should also be analyzed for adverse trends on a periodic basis, typically at least annually. Data from the 100% inspection provides the best source of typical defect types and rates during normal production. 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 and/or action levels may be established and/or adjusted 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. A minimum of data for 20 lots is usually sufficient to establish the alert and action limit. 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 Visual Inspection Results

5.1 Defect Classification

- Defects are commonly grouped into classifications based on patient and compliance risks. The most common system uses three groups: critical, major, and minor.

Critical Defects

- 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

- 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

- Minor defects do not impact product performance or compliance; they are often cosmetic in nature, affecting only product appearance or pharmaceutical elegance.

5.2 Unique Products and Containers Considerations

5.2.1 Lyophilized Product

- Lyophilized products receive 100% inspection after the freeze-drying step is 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 representative sample of the lot is to be selected and reconstituted and inspected for visible particles in addition to 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. Filtered WFI or Diluent (which is to be used for reconstitution) should be filtered before use by using a 0.2 micron filter. 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.

- 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%). Sample sizes larger than 20, as found in these sampling plans, may be appropriate for larger batch sizes when additional sensitivity is desired. Alternative plans are acceptable, but care should be taken to examine the UQL of such plans in order 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. The size of the additional sample should be based on the total sample size (initial plus additional sample) required to have an accept number greater than 0 for a sampling plan with an AQL of 0.65% or less. This will be based on the batch size. The results from the samples must be combined, rather than resampling and basing the accept decision on the results of the second sample only.

- Alternatives to reconstitution can be considered, such as collection of lyophilized samples from the filling line after stopper insertion. Such samples represent the majority of particle exposure risk. These risks should be assessed and documented to justify this approach.

- Filling line performance can be evaluated by performing water run/liquid products filled in same filling line used for lyophilized product.

5.2.2 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.

5.2.3 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.

5.2.4 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 transferred to clear, clean containers. The membrane filtration microscopic method is also suitable for capturing and characterizing larger foreign particles in the visible range (>100 μm).

5.2.5 Translucent Plastic Containers

- Translucent plastic 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.

5.2.6 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. PVC 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.

5.2.7 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.

5.3 Alternate Inspection Strategies for Supplemental Testing

5.3.1 Transfer

- When the container limits thorough inspection, transfer to a clear and readily inspectable container is recommended. Using verified clean and verified clear containers, the sample is opened and drained to the receiving container, plugged, and then visually inspected.

5.3.2 Filtration

- Membrane filtration methods, such as in Particulate Matter in Injections, Method 2 Microscopic Particle Count Test, collect all solid particles from the fill onto a membrane. Samples may be individual or pooled for analysis. This method will reveal all solid particles (visible and subvisible), which may be sized microscopically, and permits qualitative categorization of these retained solids.

5.3.3 Clarification

- In the case of suspensions, there is a wide range of active ingredient particle sizes, from nano–sized ($<1\,\mu m$) to tens of micrometers. In all cases, the solids may be clarified and/or dissolved in the original container with an appropriate filtered solvent to allow subsequent visual inspection. Solvent compatibility with the formula and package must be demonstrated.

5.3.4 Sieving

- If the solid particle suspension is small enough to allow selective sieving, this may be used as an alternative to membrane filtration. The very small solids pass through the sieve and larger (>100 μm) particles are retained, counted, and categorized.

6 Inspection Methods and Technologies

6.1 Manual Visual Inspection (MVI)

- Manual visual inspection (MVI) is the reference inspection method described in all of the major pharmacopoeias. 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.

6.1.1 Critical Process Parameters in MVI

- **Light intensity** : Increasing the intensity of the light that illuminates the container being inspected will improve inspection performance. Light levels NLT of 2,000 – 3,750 lux at the point of inspection is recommended for routine inspection of clear glass containers. Increased light levels are recommended for translucent plastic containers or those made from amber glass. Under these circumstances, light levels as high as 10,000 lux may prove beneficial. Care should be taken to avoid glare and direct viewing of the light source at these high intensities, as this may result in eye strain and fatigue.

- 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. 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 daily to ensure continued compliance within the specified range.
- 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. Matte/nonglossy backgrounds are recommended in order to avoid interference from reflection. The use of white/black backgrounds provides good contrast for a wide range of particulate and container defects, which can be light or dark in appearance.

- **Inspection rate** : Ten (10) second per container (5 second each against both black and white backgrounds) time must be provided to allow for thorough inspection of each container. It is recommended that auto time beacon be used to provide consistency.

- Larger or more complex containers require additional time for inspecting all attributes. Increased time may facilitate detection of defects near the threshold of detection.

- Time spent per container may be controlled through the use of a pacing device such as a light or tone. 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** : Good techniques for manual inspection include a careful swirl or inversion of the liquid product within the container. This displaces 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. Holding many containers by hand at once should be avoided. Container motion or rotation is also helpful for identifying small container defects such as cracks or chips. Following table provide guidance for recommended quantity to be inspected at a time

Container Size	Containers to be checked at a time
1-2 ml	Not More Than 6
3-5 ml	Not More Than 6
06-15 ml	Not More Than 5
16-25 ml	Not More Than 4
26-30 ml	Not More Than 3
31-50 ml	Not More Than 2
51-100 ml and more	Not More Than 1

- **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 the use of magnification. 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.

6.1.2 Inspector Fatigue and Ergonomic Considerations

- Inspecting for extended periods of time can cause inspector fatigue and a decrease in inspection performance. 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., 10 min/hour) 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.

- Temperature and humidity should be controlled in inspection room. Reduced ambient lighting is recommended in order 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.
- These systems offer a means of controlling 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.

6.2.1 Basic Principle

- As mentioned earlier, SAVI combines automated handling of the containers to be inspected with human vision and judgment to make the decision to accept or reject the container.

- As per the Tyndall principle, the contrast of foreign particle is intensively enhanced under the strong light beam and the container can be inspected very quickly.

6.2.2 Equipment Design

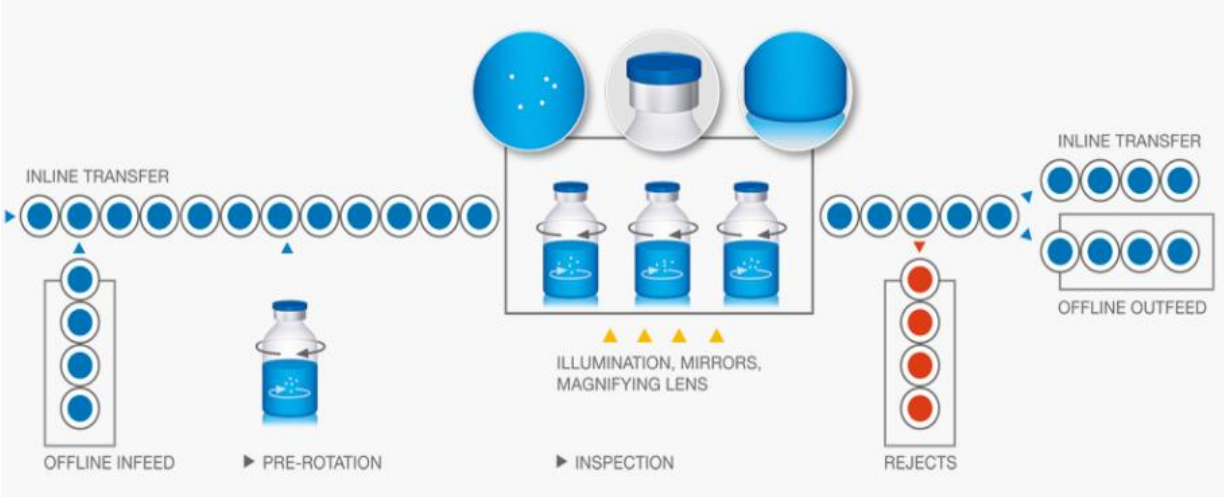
A semi-automated visual inspection system comprises:

a) Infeed conveyors with rollers to transport the containers in front of the inspector inside an inspection booth or station.
Inspection booths equipped with additional lighting system, with or without magnification, which enhance the appearance of some defects such as cracks and small particles. High-speed spin stations or rollers are fitted in the machine to set particles in motion by rotating the containers in front of inspectors as they pass through the inspection zone. In addition, mirrors may also be used to provide a clear view of the top and bottom of each container.

b) Rejection system equipped with a remote rejection arrangement that can be triggered by the inspector, or rejected units may be removed from the rollers by hand.

c) Outfeed conveyors to transport the containers to collection of inspected units for further processing.

IMAGE OF A TYPICAL SEMI-AUTOMATIC INSPECTION MACHINE



SCHEMATIC REPRESENTATION OF SEMI-AUTOMATED INSPECTION PROCESS

6.2.3 Critical Process Parameters for Semi-automated Visual Inspection System

Following are the critical process parameters to be taken care during qualification and operation:

a) **Light intensity** must be controlled as with manual visual inspection to allow for detection of particulate suspended in liquid as well as other defects like cracks, abnormal sealing, etc.

b) **Rate of inspection** is controlled by the speed of the infeed conveyor/rollers to produce an acceptable detection rate for defects of interest.

c) **Spin speed** for the liquid products and rotation rate of containers to ensure full rotation of vials in the inspection zone; this allows examination of all surfaces. 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

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. Multiple cameras are used to image various regions on the container in great detail.

- A defect found by any camera is tracked through the machine to allow accurate ejection by the rejection system. These machines also offer detailed reporting of defects observed in a specific production lot.

- 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. Significant effort is required to program these systems and to test their performance against a range of known defects, as well as acceptable containers.

6.3.1 Basic Principle

- As mentioned earlier, an Automated Visual Inspection (AVI) machine acquires a sequences of images of product appearance by electronic sensing, processes them according to parameter setting of recipe (pre-programmed acceptance criteria), and provides inspected results as ‘accepted’ or ‘rejected’ automatically.

6.3.2 Equipment Design

An automated inspection system comprises:

a) Vision system with multiple cameras in order to image various regions on the container in great detail. Cameras are connected to processing boards of the machine which track defect detection and allow accurate ejection by the rejection system.

b) Illumination system by which lighting from bottom, sides, and polarized lighting is provided, depending on the type of defect to be detected. Each camera is coupled with unique lighting which highlights specific defects in the region of interest.

c) Spinning system for rotation of container/the liquid with a view to “move” possible objects inside the liquid before inspection.

6.3.3 Automated inspection Process Type:

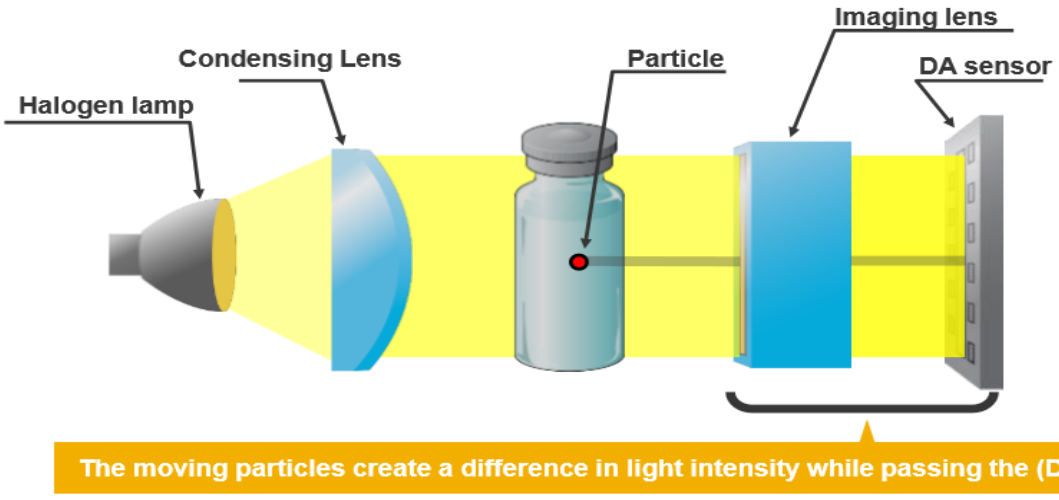
6.3.3.1 Light Obscuration Methods (static division detection)

Light obscuration method comprise of following steps:

- Spinning: the container is spun, which pushes the contents up to wall of the container, lowering the meniscus of solution inside.

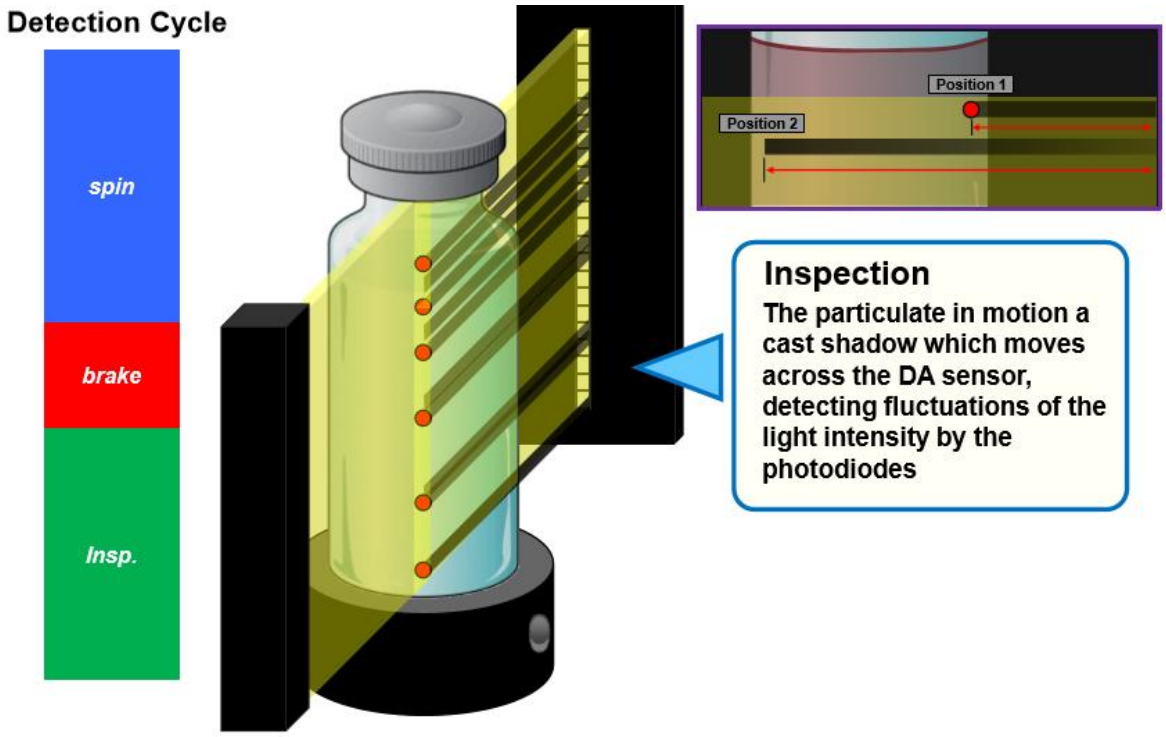
- Break on: the container is brought to an abrupt halt, forcing the particulate matter into motion.

- Inspection: the particulate in motion casts shadows which move across the Diode Array (DA) sensor which detects the fluctuation of light intensity which then is converted to an electric current signal.



The shadow created by particle causes the difference in light intensity reaching to Diode Array (DA) sensor, which is converted to an electric current signal.

SCHEMATIC REPRESENTATION OF LIGHT OBSCURATION PRINCIPLE IN AUTOMATED INSPECTION PROCESS



DIAGRAMMATIC REPRESENTATION OF DETECTION CYCLE OF LIGHT OBSCURATION PRINCIPLE IN AUTOMATED INSPECTION PROCESS

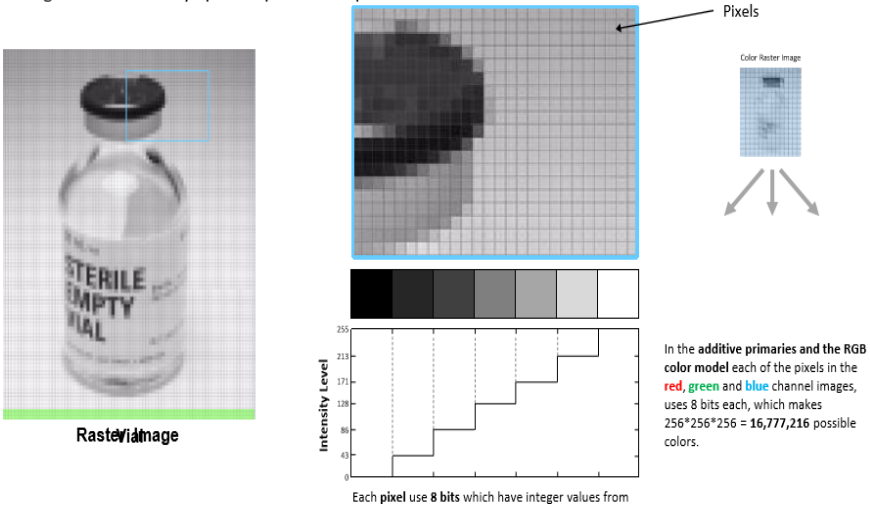
6.3.3.2 Imaging Methods (camera inspection detection)

Imaging methods comprises the following steps:

- Image capture: high-resolution digital images of containers under inspection are acquired by the digital cameras.

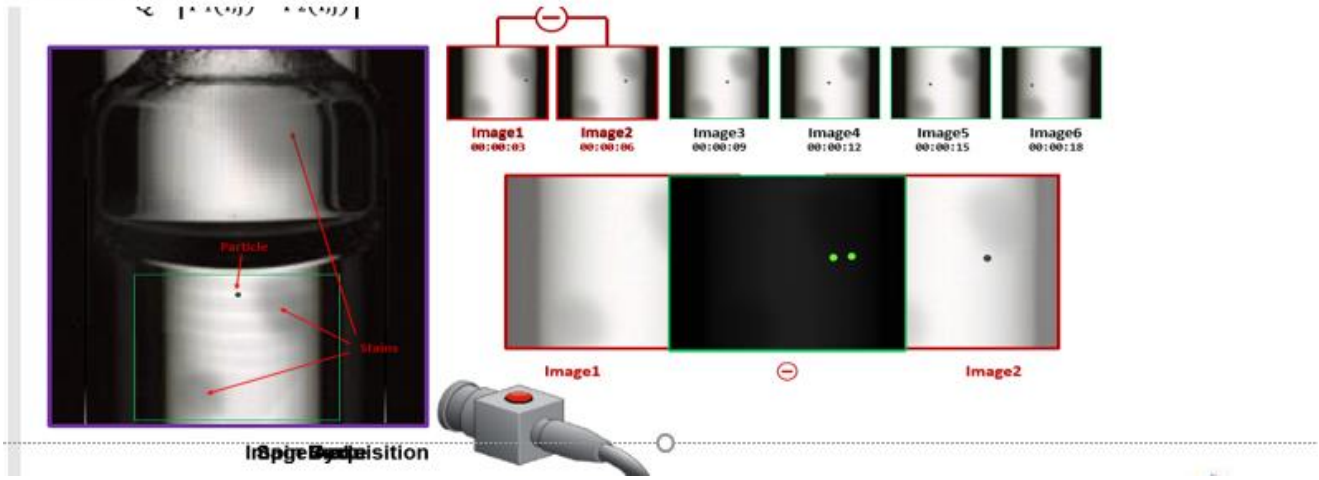
- Image processing: the acquired digital images are processed by high-speed processors by dividing into inspection windows, and a collection of tools such as image subtraction, pixel counting, intensity analysis, and others are used to assess the images against programmed quality attributes.

The digital raster images acquired by the digital camera have a finite set of pixels which are the smallest individual element in an image, holding quantized values that represent the brightness of a given color at any specific point. The pixels contain fixed number of rows and columns.



DIAGRAMMATIC REPRESENTATION OF DETECTION CYCLE OF IMAGE METHOD PRINCIPLE IN AUTOMATED INSPECTION PROCESS

Aim at identifying points in a digital image at which the image brightness changes sharply or, more formally, has discontinuities. The result of the difference of the intensities of pixels from the same location in two images. Represent a movement or a difference between the images. And the rejects are based on a pixel count (contrast).



6.3.4 Light Obscuration Methods

- LO methods are optimized for sensitivity to moving particles, and can thus be made less sensitive to minor container imperfections. These methods can be used with both tubing and molded containers. Results are generally robust in detecting single particles that are 100 μm in diameter and larger, though detection of smaller particles at or below the visible threshold is improved when multiple particles are present.

- 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 being achieved in small-diameter containers.

6.3.5 Imaging Methods

- Imaging systems can detect particles and fill level, as well as other container and closure attributes. Inspection in this manner can provide comprehensive inspection of 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. 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. X-ray imaging has also been explored as a means of detecting particles within freeze-dried cakes, powders, or suspensions.

7 Qualification and Validation of Inspection Processes

7.1 Qualification and Validation of Manual Visual Inspection

Selection and training of Visual Inspectors

- A potential Visual Inspector should be tested for vision acuity and color perception by a certified medical practitioner. Near vision should be equivalent to 20/20 or corrected with no impairment of color vision. Medical test reports should be reviewed by Production Quality Assurance.

- Training should be on the basis of a phased approach. Initially, injection manufacturing process should be explained, together with the importance of visual inspection activity for injection product and a tour of inspection facility/room to understand the inspection activity sequence should be explained. Further, the library of actual sample containers should be demonstrated and explained, combined with digital/album pictures of representative container defects for respective format of dosage form. It is also important to impart training on inspection procedure at site combined with demo on inspection process by person qualified in visual inspection activity.

Qualification of Visual Inspector:

- The qualification of all visual inspectors shall be performed under normal operating conditions. Qualification shall be performed with Kit and actual product batches.

- Initially, a trained visual inspector should allow inspection of qualification kit. Selection of container type and size will be determined by the inspector in inspection process. The trained inspector should document the code/number of each unit in the kit with details like types of rejection or good unit. The qualified inspector should check number details of rejected and good units and quantity segregated by the trainee visual inspector, by comparing the container numbers with 'Master List for Qualification Kit'. The trainee visual inspector must identify and record all number of rejects and good units from the provided qualification kit. A maximum of three attempts to pass the test should be given to the trainee.

- Further, the trainee should be allowed to inspect three consecutive product batches. Good and rejected units inspected from product batches by the trainee inspector shall be re-inspected by the qualified inspector. Inspected units should comply with the categorizations of good and defective types.

- Maximum three attempts shall be given to trainee for qualification with kit and product batches. Qualification activity should cover regular practices and conditions like inspection rate, break time, etc. Qualification activity shall be performed at the end of shift to evaluate fatigue.
- Candidate should be awarded with certification of Qualified Inspector. A list of qualified Visual Inspectors should be prepared and updated. This list shall be reviewed periodically to ensure compliance.

7.1.1 Distance criteria

- Distance of object from the eyes of the inspector should be between 200 mm to 400 mm.

- Distance of the object from the background of the inspection booth should be between 200 mm to 300 mm.

7.1.2 Holding of containers against the white and black background

- The inspector should take the container to be checked in one hand, and hold it in front of a white background. The container should be inspected with a very steady hand, without any jerky movement. The hand movement and the inspection should cover from the upper side through to the bottom, looking for black fibers, settling black particles, glass particles and any other particles. This should be continued for a minimum of 5 seconds; more time should be allowed, if required, for complete and thorough inspection of the container. The same procedure should be followed for inspection against black background.

7.1.3 Total time for visual inspection

- Visual inspector should inspect the challenge kit, or similar container size or type of product, seven times within a working shift including breaks. Breaks include eye rest of ten minutes after every one hour of inspection, lunch break, etc. The inspection should continue until the seventh inspection run. The first hour (Initial), fourth hour (Middle), and seventh hour (End, intended to simulate fatigue of the inspector/operator) of visual inspector qualification/requalification should be performed with the visual inspector qualification/re-qualification challenge kit. The second, third, fifth and sixth hours of inspection should include other products of similar dosage form and similar container or the same visual inspector qualification/requalification challenge kit. An inspector should not conduct more than seven inspections in one working shift in a day.

- The inspector should not exceed one hour during qualification for each qualification/ re-qualification run (Initial, Middle and End) accordingly provide standard containers kit which contains number equivalent to one-hour inspection theoretically.

7.1.4 Light lux requirements

- Light lux at the viewing point should be between 2,000 and 3,750 Lux for clear glass containers.

- Light lux at the viewing point should be between 8,000 and 10,000 Lux for amber color vial/ampoule and plastic bottle product.

- Light lux at the viewing point shall be between 4,000 and 6,000 Lux for large volume containers including infusion bags.

7.1.5 Bracketing approach

- Minimum and maximum container sizes should be taken for initial qualification of the visual inspector. For example, two runs with maximum container size and one run with minimum container size, and vice versa, should be taken.
- For requalification or next requalification of same container closure, alternatively, minimum and maximum container size should be considered for requalification of the same visual inspector.

7.1.6 Environment control

- Temperature should be NMT 25° C in the visual inspection area, and the visual inspection challenge kit should be stored as per respective product storage condition. For sex hormone product, temperature of visual inspection area needs to be within 20° C to 25° C and the same is to be maintained for storage of visual inspection challenge kit.

7.1.7 Initial qualification

The training and qualification of personnel for visual inspection should be done on following phases.

Phase I

- Work experience (total work experience/visual inspection work experience)
- Eye sight testing
- Training (cGMP, general SOPs and job specific SOPs)

Phase II

- Demonstration of visual inspection library
- Demonstration of the album for the defective containers not available in visual rejection library
- Demonstration of visual inspection process by the qualified visual inspectors
- On-the-job training by exposing the visual inspector, who is to be qualified, with routine visual inspection (for new joiners)
- Eye check-up certification of the inspector to be ensured prior to start of the phase I activity

Phase III

- Final qualification by giving a set of characterized containers having both good as well as defective containers

7.1.8 Requalification

- Requalification is recommended annually; an approach similar to first qualification should be applied during requalification.

7.2 Qualification of Manual Visual Inspection Booth (MVI)

7.2.1 Verification of individual components

- Light ON/OFF switch shall be available.
- Beacon (indicator) with push button shall be available for individual booth.
- Control panel with PLC and selector switch shall be available.

7.2.2 Verification of level with different lights under visual inspection booth at working height

- The single lights should be switched ON.
- The lighting lux below the visual inspection booth should be measured and recorded with calibrated Lux meter.
- Attach the location drawing with rational.
- The same activity should be repeated with two and three lights.
- The same test should be performed for each visual inspection booth.

Acceptance criteria

- Single light: 2,000 – 3,750 Lux
- Double lights: 4,000 – 6,000 Lux
- Three lights: 8,000 – 10,000 Lux

7.3 Preparation of Visual Inspection Challenge Kit

7.3.1 Preparation of Containers for Qualification Kit

- Containers for Visual Inspection Qualification kit should be created under controlled environments, such as in Production area, using a vehicle such as water for injection. Such containers shall be equivalent to naturally occurring defects. It can also be prepared by selecting naturally occurring particulates and physical or cosmetic production rejects removed from product lots. If in-house expertise or manpower is not available, a certified laboratory should be used to provide qualification kit. A certified laboratory will provide a certificate of analysis, expiration date and will guarantee the contents of each container.

- Containers in qualification kit must be absolutely free of visible particles or have one and only one particulate per container. The rationale for having only one defect per container is that it provides with absolute certainty the reason for container rejection. The practice of using multiple particles should be discouraged, since it is not possible to know which defect led to container rejection. Also, having more than one defect adds a multiplying effect for detection.

- Visual Inspection Kit is prepared for the qualification of the Visual Inspector.

- It is recommended that good samples and rejections are collected from the routine batch or water trial.

- Expiry date of the challenge kit should be defined based on shelf life of the product and these should be replaced as appropriate.

- The number of containers taken for testing must equal the maximum number of containers which can be inspected in one hour. If an average time of fifteen seconds per container is taken for complete inspection, then a total of 240 containers have to be taken for the challenge kit. The serial number of the container is to be marked by using invisible UV pen/marker on a sticker.

- A minimum of one rejection for each category available should be added during the qualification.

- Defects should be distributed in the kit for total rejection, ranging from 5% to 15%, including critical, major and minor defects.

- The typical size range of particles, used in visual inspection kit preparation, incorporates a variety of particle types and densities that are typically found in the manufacturing environment.

- Particle detection is reproducible in detecting particles within the range of 150 – 250 µm (500 – 2,000 µm for fibers). Detection probability at various particle types and sizes is 100 µm to 250 µm (500 – 2,000 µm for fibers). Hence, the size of particles used for preparation of standard rejected containers should be between 100 µm to 250 µm (500 – 2,000 µm for fibers).

- Determination of particle size (using microscopic technique) can be performed by the firm; ready-to-use defects can also be prepared by external qualified vendors.

- Only one particle per container should be used for preparation of standard rejection. These containers must be prepared with actual product primary packaging material having same container and closure.

7.3.2 Construction and Qualification of Kit

- Once a well-defined container with defects is prepared, it is assigned a detection frequency or probability of detection by conducting a documented, manual human inspection qualification that is accomplished by repeated manual inspections. This repeated inspection is the basis for qualifying the containers for defect type.

- Knapp's methodology is based on developing the statistical rejection probability for each individual container. The Knapp methodology recognizes that detection of particles is probabilistic, and repeated inspections with strict controls on lighting and inspection conditions generates statistical confidence to assign a reject probability to each container. The population is divided into three categories according to the container's probability of rejection:

CATEGORY OF REJECTION

Category	Probability of Rejection (Single Inspection)		
Accept Zone	0.00	-	0.30
Grey Zone	0.31	-	0.69
Reject Zone	0.70	-	1.00

- Construction of the qualification kit should be done by assembling containers whose probability of rejection is 0.7 or higher for particulate matter defect and container-closure defects. Qualification kit shall include good containers (defect-free) to obtain the population of units. The constructed kit is to be used to specifically challenge the particle detection technique of the human inspector in manual inspection qualification or for comparison during automated equipment qualification.

- Depending on product and presentation, rejects in the test should represent all defects observed for the given container type or product batches at site. Each kit shall have same containers and closures of same type and coded/numbered for identification. If significantly different formulations (e.g., clear solutions, suspension, lyophilized) or formats (e.g., clear vials, amber vials, ampoules, syringes, cartridges) are produced at same site, separate kits should be prepared to represent each unique combination. To avoid the possibility of skewing the results by prediction, each container type and format size should have a minimum of two kits and should be rotated for each qualification. Other alternative approaches, like using same kit with change in sequence numbering of containers in kit, can also be adopted.

7.3.3 Maintenance of Qualification Kit

- It is recommended to establish procedures for maintenance, issuance, retrieval and periodic replacement of the visual inspection kit.

- A master list of the qualification kit with details of defective/good container and respective allotted numbers should be prepared and approved by Quality department at site. The constructed kit should be used initially to qualify the human inspector, and, thereafter, periodically for requalification. These kits may also be used for direct comparison to semi-automated or automated injection methods.

- The qualification kit should be stored under controlled secured conditions and clearly labeled with the kit identification and construction information. In the event of any container in qualified kit being impaired with defect of container-closure or content, it shall be replaced with pre-qualified back-up containers. If there is gross physical damages as well as changes in content of containers in kit, the kit shall be discarded. A documented procedure shall be followed for the disposal of such kit and shall be pre-approved by Quality unit at site.

8 Qualification of Automated Visual Inspection (AVI)

General instruction

- AVI combines automated material handling of the containers with electronic sensing of product appearance.

- Containers that do not meet preprogramed acceptance criteria are automatically rejected by the machine.

- 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 thus making 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.

- AVI offers advantages in the areas of throughout and consistency, compared with manual visual inspection.

8.1 Procedure for Knapp Kit Preparation and Qualification:

- The Knapp Kit should be prepared with real product particulate defects.

- The Knapp Kit contains containers with particulate defects and good containers (for particulate defects, containers should be prepared with real product defects or particle defects prepared with same kind sources observed during routine production).

- Size of particles used for preparation of rejected containers should be between 50µm to 2000µm. The reason is that the visible range starts from 50 µm, and depending on the probabilistic nature of dynamic particle sizes and variability in detect ability, a narrow range is provided to challenge the inspectors and Automatic Inspection machine).

- Out of a total of 80 containers with particulate defects, 50% should be >500 µm, and the remaining 50% should be <500 µm. In case of fibers, 50% shall be >1,000 µm, and the remaining 50% shall be <1,000 µm.

- After preparation of all type of defects, each container of the Knapp Kits shall be numbered with fluorescent marker.

- It is extremely important that the resource dedicated to inspect each container is the same as the one used during the standard inspection process.

- The manual inspection process is performed by qualified visual inspectors by using inspection hoods.

- Lux level for the visual inspection hood shall meet the acceptance criteria, i.e., NLT 2,000 to NMT 3,750 Lux for clear container type, and NLT 8,000 to NMT 10,000 Lux for amber, suspensions, and opaque containers.

- A run of fifty inspections shall be performed by using five qualified inspectors, i.e., each qualified inspector should inspect the same kit 10 times in order to identify all the types of particulate defects. Calculations should be done for the overall rejection probability (POD) of each defect container, and each container should be categorized as a reject zone (manual rejection zone efficiency, mRZE) 70 to 100%, gray zone (manual gray zone efficiency, mGZE) 30 to 69% and accept zone (manual acceptance zone efficiency, mAZE) 0 to 29%.

- The zone efficiency should be calculated as follows:

$$\text{Overall POD of each container} = \frac{\text{Overall times detection of each container}}{50} \times 100$$

$$\text{mRZE} = \frac{\text{Addition of Overall times detected of each containers within POD range (70\% to 100\%)}}{\text{Total number of containers with in overall POD range (70\% to 100\%) X 50}} \times 100$$

$$\text{mGZE} = \frac{\text{Addition of Overall times detected of each containers within POD range (30\% to 69\%)}}{\text{Total number of containers with in overall POD range (30\% to 69\%) X 50}} \times 100$$

$$\text{mAZE} = \frac{\text{Addition of Overall times detected of each containers within POD range (0\% to 29\%)}}{\text{Total number of containers with in overall POD range (0\% to 29\%) X 50}} \times 100$$

- Factor Quality value is provided to each container (FQA) as per the formula below:

FQ (Container NR.XXX) = (n/N)*10

n= No. of times the container has been rejected.
N= Total No. of inspections.
Note: Final FQA values should be updated as per the table below.

TABLE 1

Sl. No.	Actual Value	Rounded Value
1.	0.0 to 0.4	0
2.	0.5 to 1.4	1
3.	1.5 to 2.4	2
4.	2.5 to 3.4	3
5.	3.5 to 4.4	4
6.	4.5 to 5.4	5
7.	5.5 to 6.4	6
8.	6.5 to 7.4	7
9.	7.5 to 8.4	8
10.	8.5 to 9.4	9
11.	9.5 to 10	10

- Cosmetic defects shall be prepared as per defined procedure and shall be challenged in automatic machine.

8.2 Procedure for Qualification of Automatic Machine:

- Each container of the Knapp Kit shall be subjected to automatic inspection for 10 iterations.
- FQ value for each container is calculated by machine (FQB) as follows:
- Qualification Criteria for automatic Inspection system:
- Automatic Inspection FQB should be equal or greater than manual inspection FQA.
  (Refer Annexure 1 for the process of Automatic and Semi-Automatic Visual Inspections).

8.3 Performance Run

- The product is subjected to automatic inspection three times and the same shall be inspected manually by qualified inspectors.
- Accept criteria: AVI should not miss any defect and should not exceed false rejection with a limit of 2.5 %.

9 Visual Inspection of Media fill Containers

- Media fill inspection process is performed by the Qualified Inspector by manual inspection process, similar to that applied for product; however, the main focus during this inspection is to identify containers with obvious closure integrity and turbid containers.

- Media fill visual inspection kit and media fill library should be prepared with good containers as well as physical rejections of all container types. These should be preserved from previously executed media fill studies, and should be utilized for the preparation of media fill visual inspection kit and media fill library.

- The recommended expiry periods for good containers should be defined based on risk assessment and internal evaluation. It is recommended that turbid/contaminant unit be freshly prepared during qualification time.

- Qualification should be carried out with a quantity of physical rejection, containers inoculated with microorganisms, containers filled with McFarland standard and/or good containers. In addition, each kit may vary on the type of test units (McFarland standard, bacterial culture and yeast culture) during the qualification.

- It is recommended to utilize Colour Indicating media Powder for Media fills to easily defects contaminant by change in colour medium.

10 Inspection of Retain/Control Samples

- The control sample should be inspected as per predefined frequency (annual inspection is recommended).
- The control sample inspection should be performed by qualified inspectors.
- The procedure and criteria applied for inspection of control is the same as defined in manual inspection process.
- Destructive testing can be performed in unique dose consideration like lyophilized products, powder and suspension products.
- Adequate reconciliation and documentation is required for inspection of control samples.

11 Investigation Considerations for Visible particles

Evaluation of following parameters is recommended to considered for Investigation of higher Visual inspection rejection :

- Personnel training and qualification
- Inspection booth/machine qualification/performance
- Inspection process
- Rejection pattern, e.g., entire lot or portion of lot
- Type of defects
- Type of dosage form
- Raw materials assessment
- Packing material assessment
- Manufacturing process assessment (compounding to final stage of process)
- Products rejection trends
- Filling line rejection trends
- Breakdown history of filling line
- Preventive maintenance of filling line
- Environment controls
- Supplement testing
- Over all rejection trends
- Identification of defects (morphology, IR, SEM, X-Ray analysis and elemental analysis)
- Source of defects
- Vendor assessment
- Risk assessment for visual defects
- HHE evaluation for visual defects
- Root cause analysis
- Corrective actions
- Preventive actions

12 Annexures

- **Annexure 1: Manual Inspection Schematic Diagram**
- **Annexure 2: Manual Inspection Qualification Flow**
- **Annexure 3: Construction of Qualification Kit**
- **Annexure 4: Semiautomatic and Automatic Inspection Qualification**
- **Annexure 5: Automatic Inspection Validation**

Annexure 1

Manual Inspection Schematic Diagram

DIAGRAMMATIC PRESENTATION OF MANUAL VISUAL INSPECTION PROCEDURE

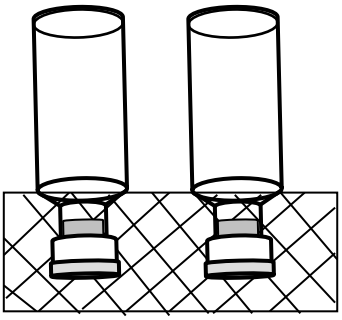
VIAL (CLEAR SOLUTIONS)

White

Left Hand

Black

Right Hand

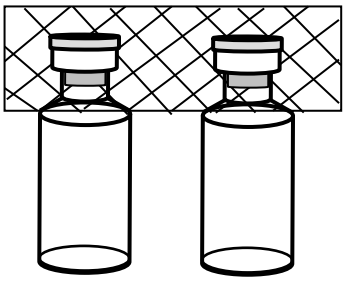


Step 1:
Hold vials by the base against white background to check for seal quality and presence of bung. Flick/tap vials to displace any glass or particle that may have adhered to the bung.

Step 2:
Hold the top of the vial invert and inspect against black background.

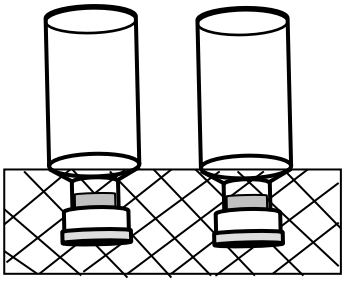
White

Right Hand



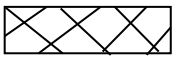
Black

Right Hand



Step 3:
Holding the top turn the vials and inspect against white background.

Step 4:
Invert and inspect against black background holding the top of the vial.

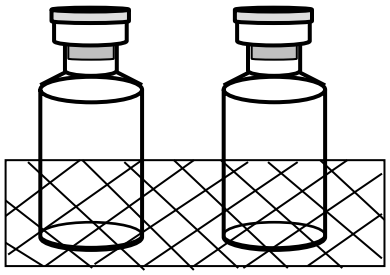


Hand Position

VIAL (SUSPENSION)

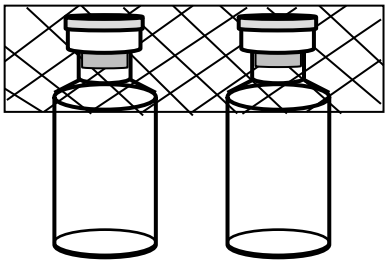
White

Left Hand



Black

Right Hand



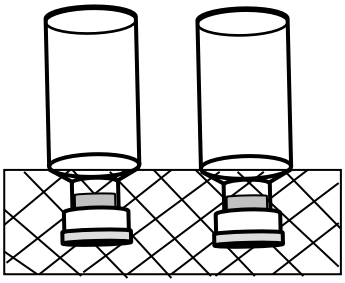
Step 1:
Hold vials by the base against white background to check for seal quality and presence of bung.

Step 2:
Hold the top of the vial and inspect the sediment against black background.

White

Black

Right Hand

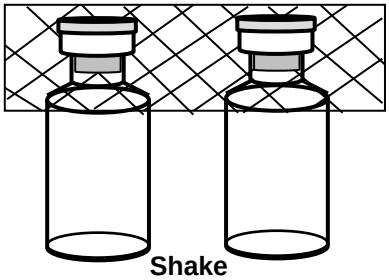


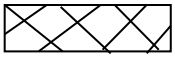
Step 3:
Invert the vials holding the tops and inspect the clear liquid before the sediment falls against black background.

White

Black

Right Hand





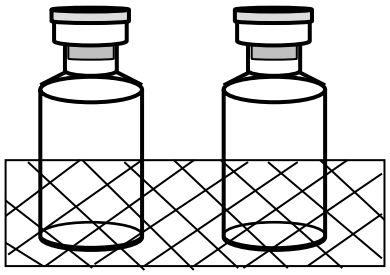
Hand Position

Step 4:
Rotate and shake the contents to check for clumping or flocculation against black background.

VIAL (FREEZE DRIED)

White

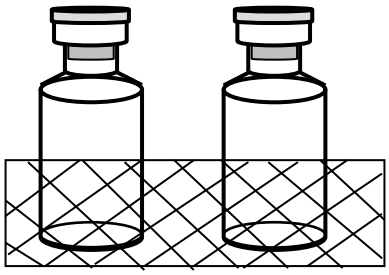
Right Hand



Step 1:
Hold vials by the base against white background to check for seal quality and presence of bung.

Black

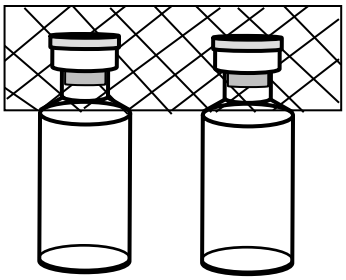
Right Hand



Step 2:
Hold vials by the base against black ground background.

White

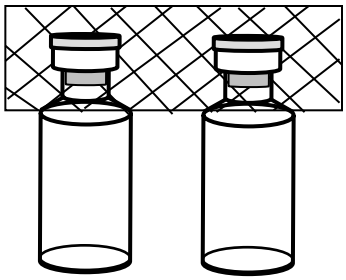
Right Hand



Step 3:
Hold the top of the vial and inspect against white background.

Black

Right Hand

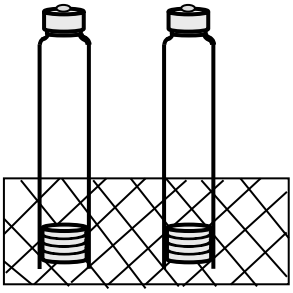


Step 4:
Hold the top of the vial and inspect against black background.

CARTRIDGE (CLEAR SOLUTIONS)

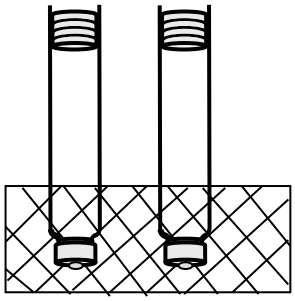
White

Left Hand



Black

Right Hand

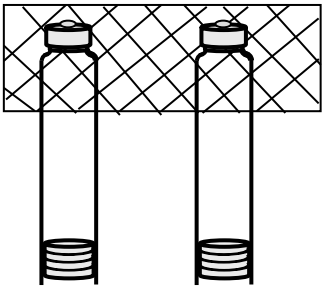


Step 1:
Hold cartridges by the base against white background. Check the seal quality.

Step 2:
Invert against black background, rotate and inspect the plunger.

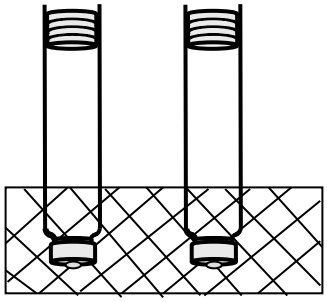
White

Right Hand



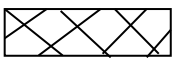
Black

Right Hand



Step 3:
Invert against white background and inspect the solution.

Step 4:
Invert against black background and inspect the solution. Rotate and check the quality of the combi seal.

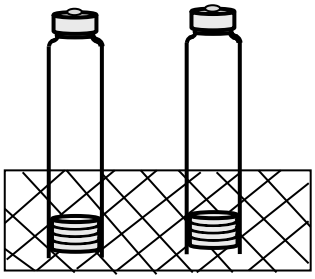


Hand Position

CARTRIDGE (SUSPENSION)

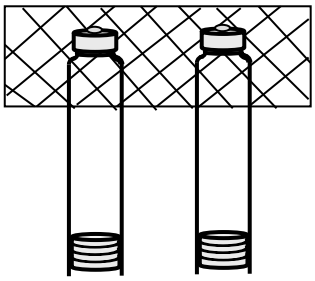
White

Left Hand



Black

Right Hand

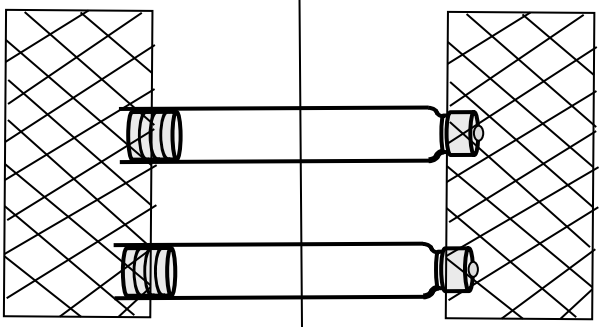


Step 1:
Hold cartridges by the base against white background. Check the seal quality.

Step 2:
Hold the top of the cartridge against black background and inspect the suspension.

White

Both Handles



Black

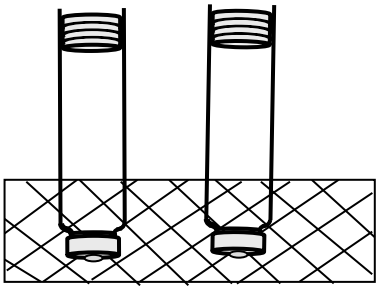
Both Handles

Step 3 & 4:
Support the bottom, tilt the cartridges from side to side and inspect for glass bead.

White

Black

Right Hand



Shake

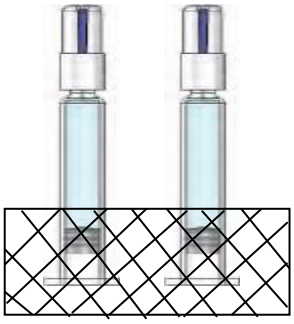
Hand Position

Step 4:
Invert against black background and rotate inspect the plunger and the quality of the combi seal. Shake the contents to check for clumping and flocculation.

PRE-FILLED SYRINGE (CLEAR SOLUTIONS)

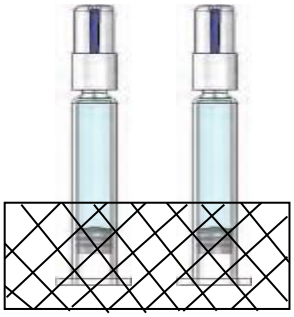
White

Right Hand



Black

Right Hand

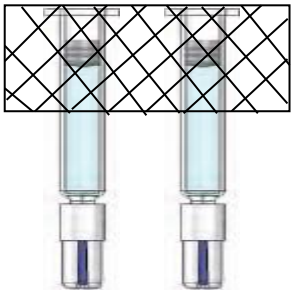


Step 1:
Hold syringes by the base against white background. Check the tip cap/lure lock.

Step 2:
Hold syringes by the base against black background. Check the tip cap/lure lock.

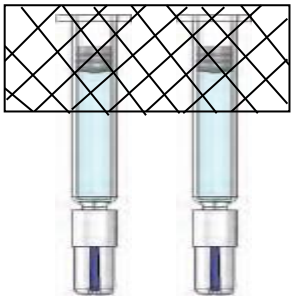
White

Right Hand



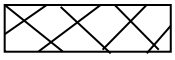
Black

Right Hand



Step 3:
Invert and hold syringes by the base against white background.

Step 4:
Invert and hold syringes by the base against black background.



Hand Position

OPHTHALMIC BOTTLES

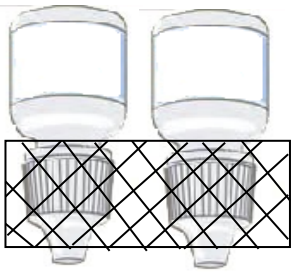
White

Right Hand

Step 1:
Hold bottles by the base against white background. Check the cap side.

Black

Right Hand



Step 2:
Hold the top of bottles invert and inspect against black background.

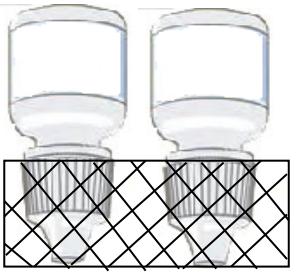
White

Right Hand

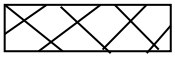
Step 3:
Hold the top turn the bottles and inspect against white background.

Black

Right Hand



Step 4:
Invert and inspect against black background by holding the top of bottles.

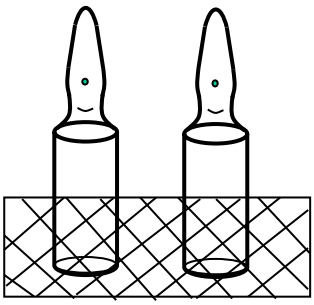


Hand Position

AMPOULES (CLEAR SOLUTIONS)

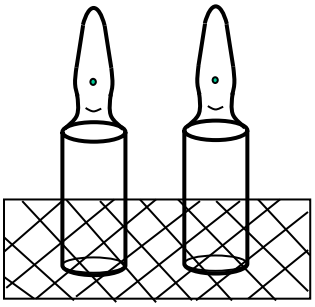
White

Left Hand



Black

Left Hand



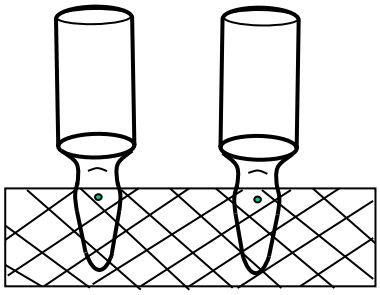
Step 1:
Hold ampoules by the base and inspect against white background.

Step 2:
Repeat against black background.

White

Black

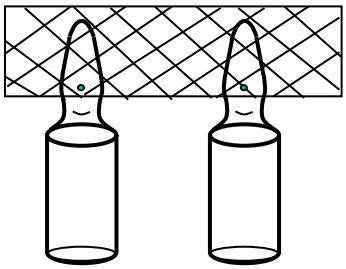
Left Hand



Step 3:
Invert holding the top, inspect against black background.

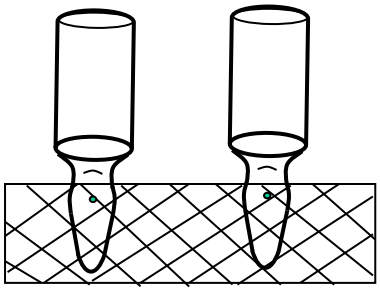
White

Right Hand



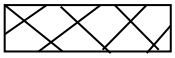
Black

Right Hand



Step 4:
Turn the ampoule and inspect against white background.

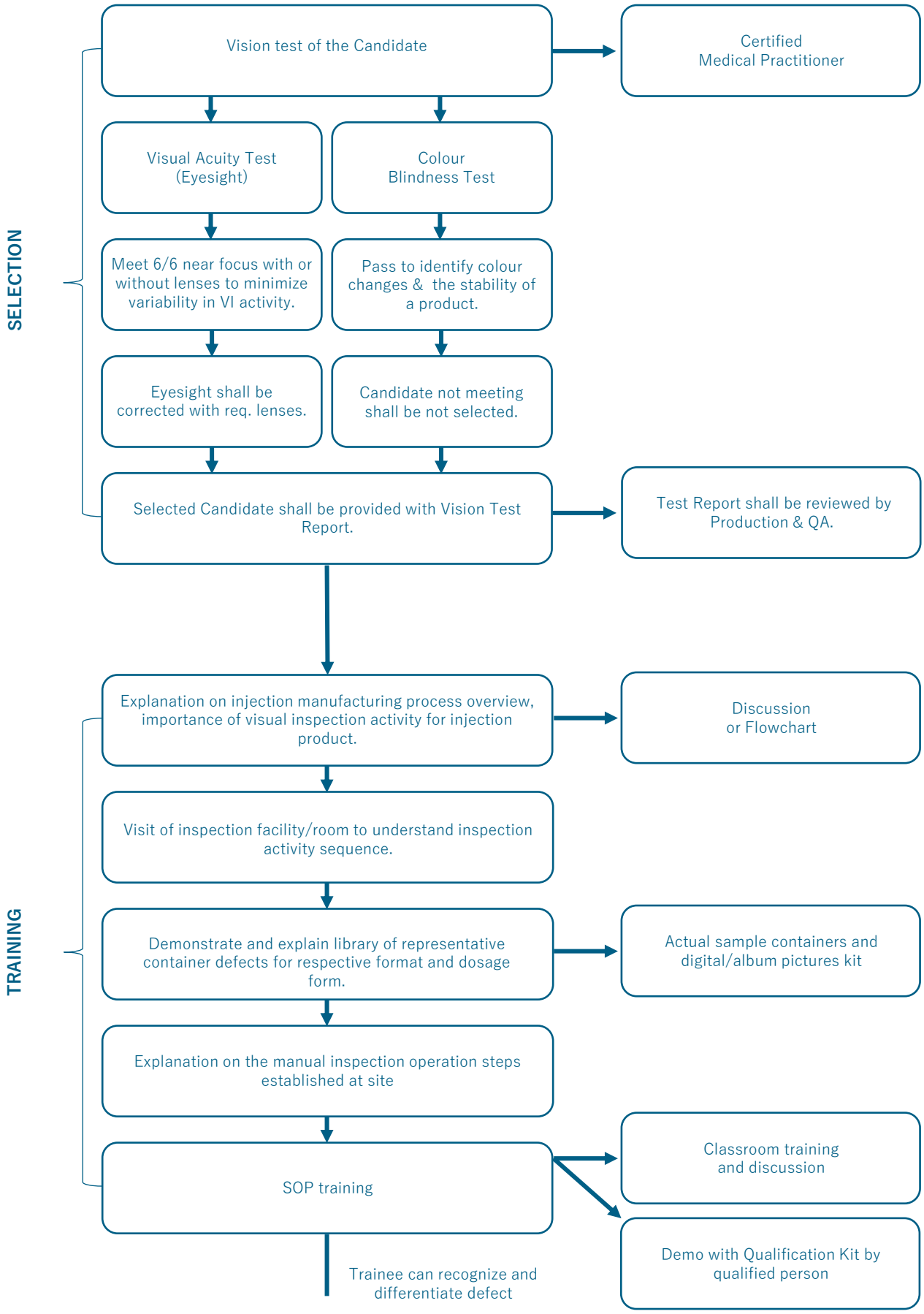
Step 5:
Rotate and shake the contents to check for clumping or flocculation against black background.

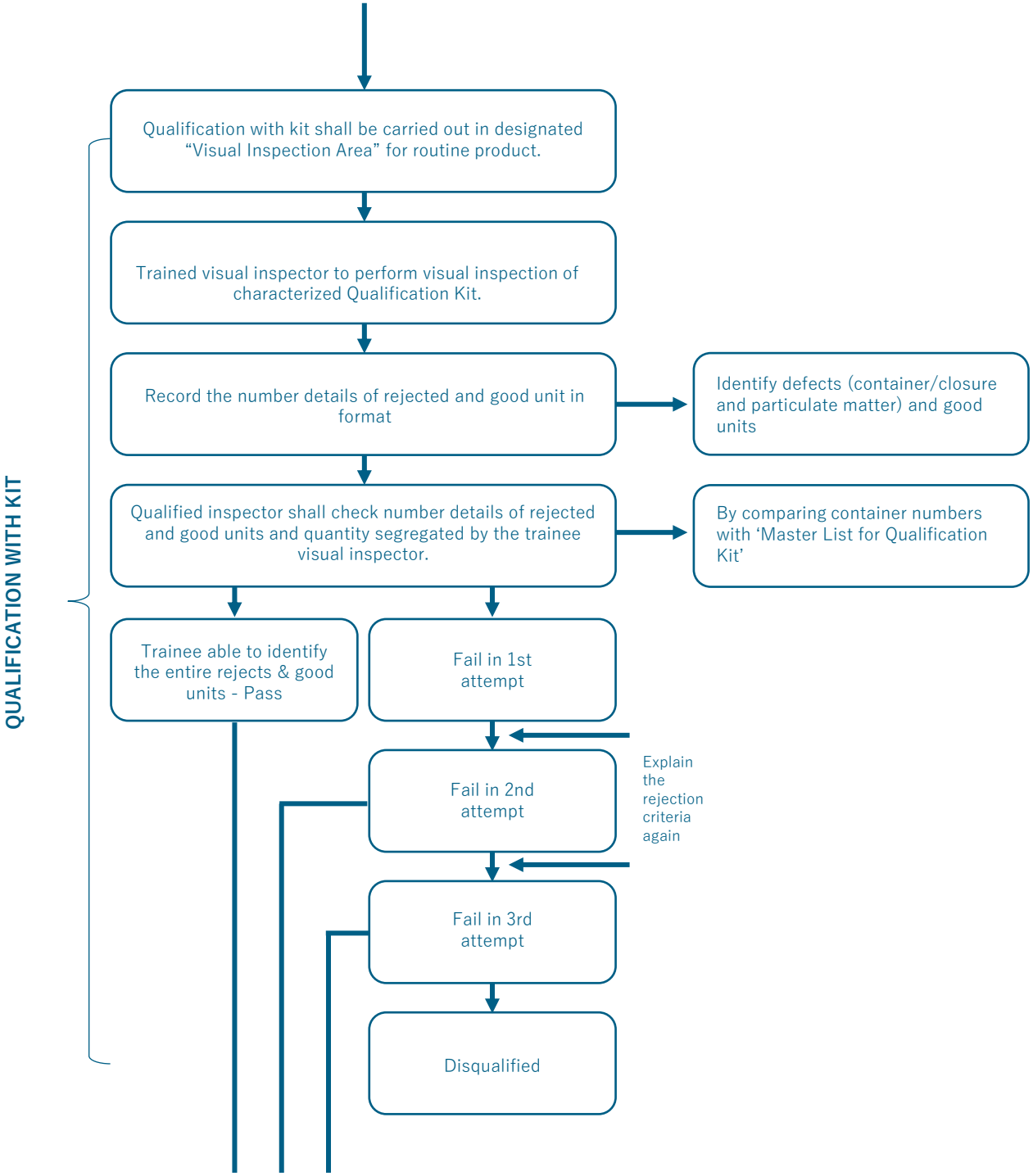


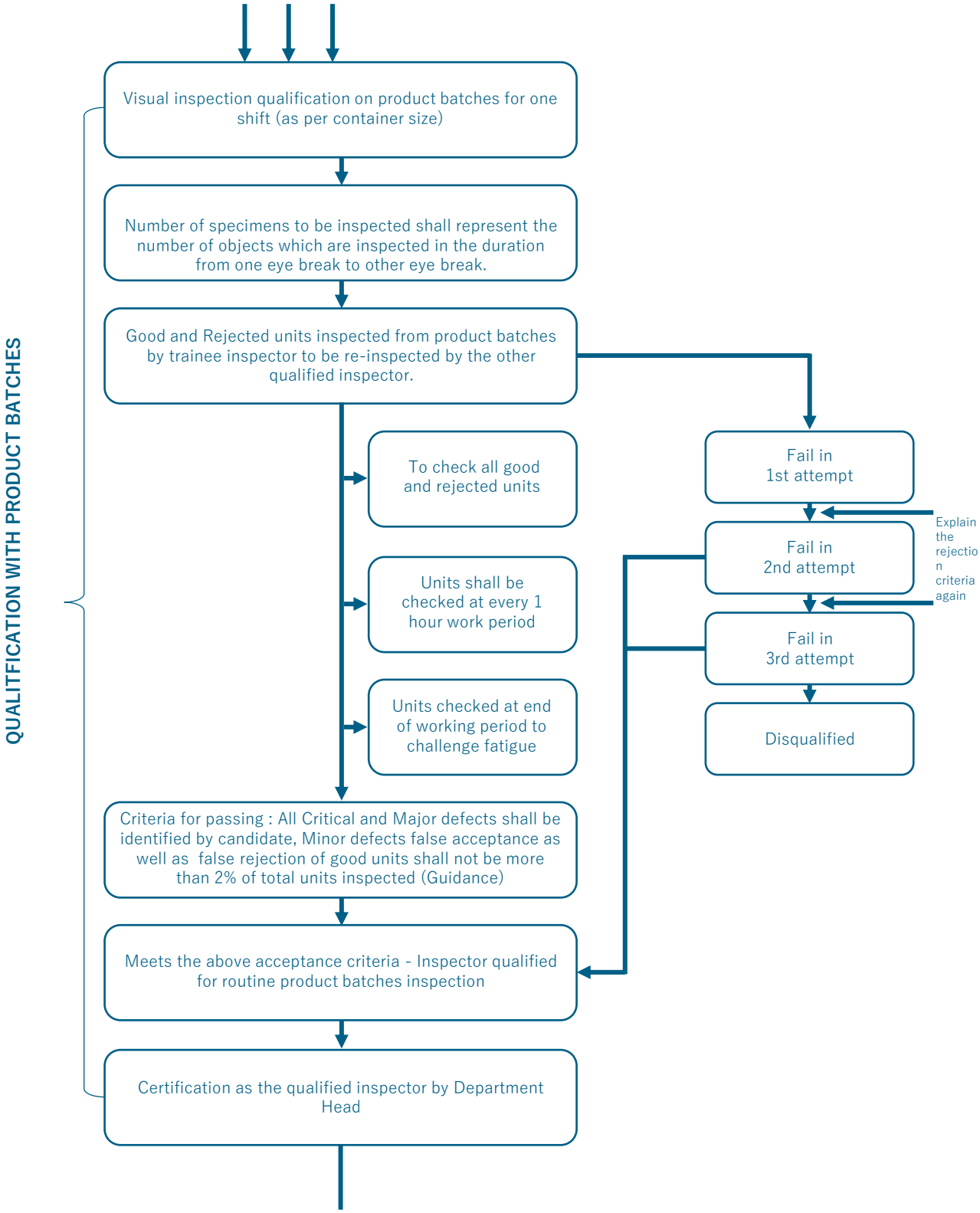
Hand Position

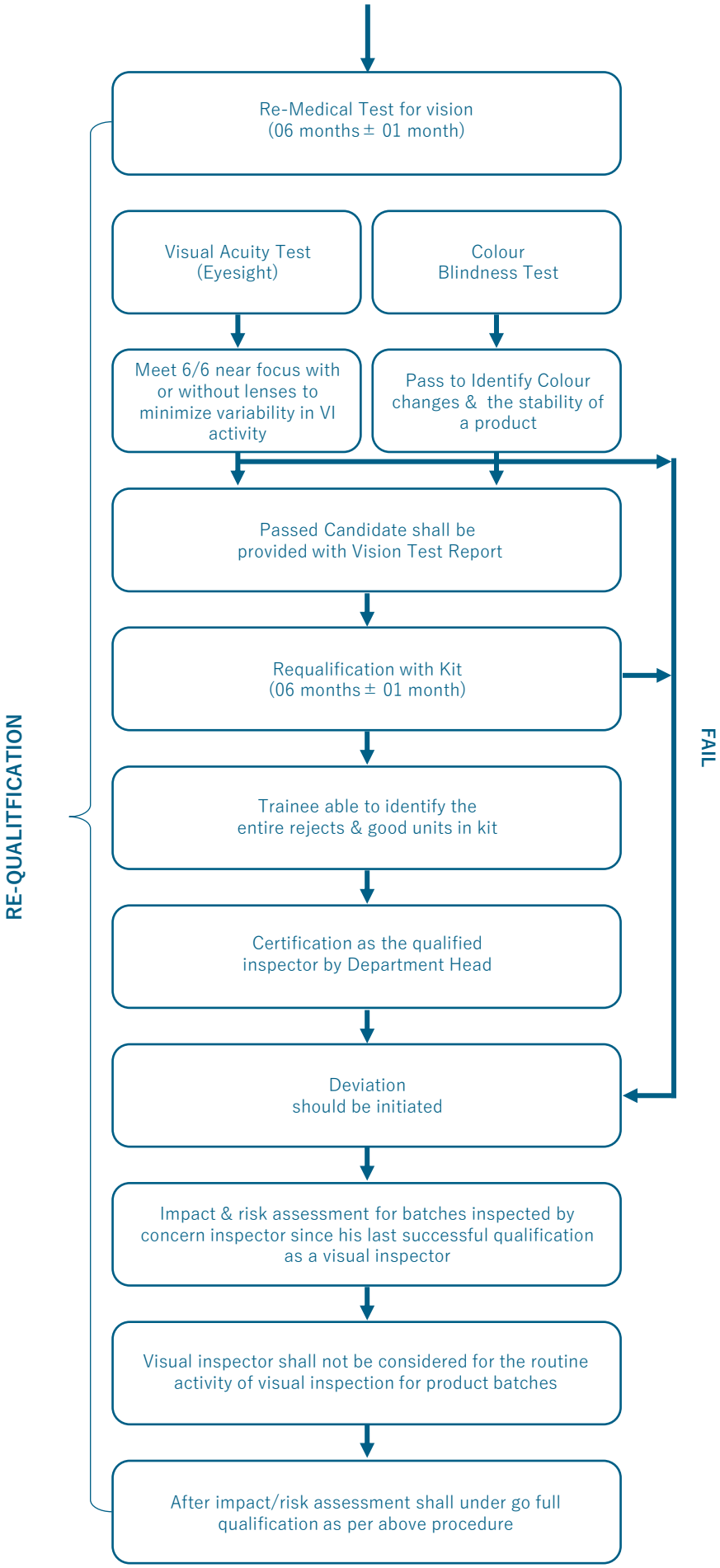
Annexure 2

Manual Inspection Qualification Flow


SELECTION
Vision test of the Candidate
Certified Medical Practitioner
Visual Acuity Test (Eyesight)
Colour Blindness Test
Meet 6/6 near focus with or without lenses to minimize variability in VI activity.
Pass to identify colour changes & the stability of a product.
Eyesight shall be corrected with req. lenses.
Candidate not meeting shall be not selected.
Selected Candidate shall be provided with Vision Test Report.
Test Report shall be reviewed by Production & QA.
TRAINING
Explanation on injection manufacturing process overview, importance of visual inspection activity for injection product.
Discussion or Flowchart
Visit of inspection facility/room to understand inspection activity sequence.
Demonstrate and explain library of representative container defects for respective format and dosage form.
Actual sample containers and digital/album pictures kit
Explanation on the manual inspection operation steps established at site
SOP training
Classroom training and discussion
Demo with Qualification Kit by qualified person
Trainee can recognize and differentiate defect

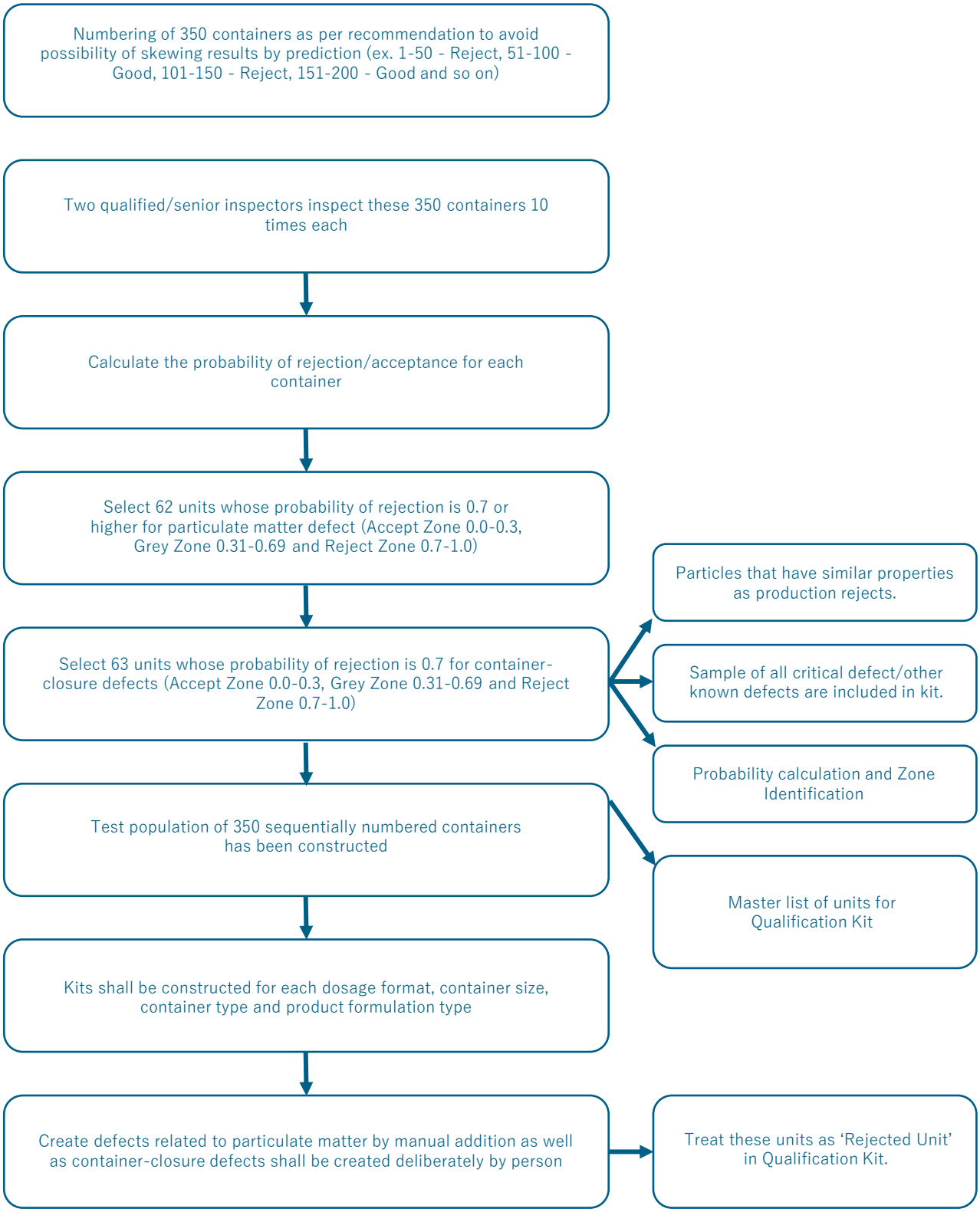

QUALIFICATION WITH KIT
Qualification with kit shall be carried out in designated "Visual Inspection Area" for routine product.
Trained visual inspector to perform visual inspection of characterized Qualification Kit.
Record the number details of rejected and good unit in format
Identify defects (container/closure and particulate matter) and good units
Qualified inspector shall check number details of rejected and good units and quantity segregated by the trainee visual inspector.
By comparing container numbers with 'Master List for Qualification Kit'
Trainee able to identify the entire rejects & good units - Pass
Fail in 1st attempt
Fail in 2nd attempt
Explain the rejection criteria again
Fail in 3rd attempt
Disqualified


QUALITFICATION WITH PRODUCT BATCHES
Visual inspection qualification on product batches for one shift (as per container size)
Number of specimens to be inspected shall represent the number of objects which are inspected in the duration from one eye break to other eye break.
Good and Rejected units inspected from product batches by trainee inspector to be re-inspected by the other qualified inspector.
To check all good and rejected units
Units shall be checked at every 1 hour work period
Units checked at end of working period to challenge fatigue
Fail in 1st attempt
Explain the rejection criteria again
Fail in 2nd attempt
Fail in 3rd attempt
Disqualified
Criteria for passing : All Critical and Major defects shall be identified by candidate, Minor defects false acceptance as well as false rejection of good units shall not be more than 2% of total units inspected (Guidance)
Meets the above acceptance criteria - Inspector qualified for routine product batches inspection
Certification as the qualified inspector by Department Head


Re-Medical Test for vision
(06 months ± 01 month)
Visual Acuity Test
(Eyesight)
Colour
Blindness Test
Meet 6/6 near focus with or without lenses to minimize variability in VI activity
Pass to Identify Colour changes & the stability of a product
Passed Candidate shall be provided with Vision Test Report
Requalification with Kit
(06 months ± 01 month)
Trainee able to identify the entire rejects & good units in kit
Certification as the qualified inspector by Department Head
Deviation
should be initiated
Impact & risk assessment for batches inspected by concern inspector since his last successful qualification as a visual inspector
Visual inspector shall not be considered for the routine activity of visual inspection for product batches
After impact/risk assessment shall under go full qualification as per above procedure
RE-QUALITFICATION
FAIL

Annexure 3

Construction of Qualification Kit


Numbering of 350 containers as per recommendation to avoid possibility of skewing results by prediction (ex. 1-50 - Reject, 51-100 - Good, 101-150 - Reject, 151-200 - Good and so on)
Two qualified/senior inspectors inspect these 350 containers 10 times each
Calculate the probability of rejection/acceptance for each container
Select 62 units whose probability of rejection is 0.7 or higher for particulate matter defect (Accept Zone 0.0-0.3, Grey Zone 0.31-0.69 and Reject Zone 0.7-1.0)
Select 63 units whose probability of rejection is 0.7 for container-closure defects (Accept Zone 0.0-0.3, Grey Zone 0.31-0.69 and Reject Zone 0.7-1.0)
Particles that have similar properties as production rejects.
Sample of all critical defect/other known defects are included in kit.
Probability calculation and Zone Identification
Test population of 350 sequentially numbered containers has been constructed
Master list of units for Qualification Kit
Kits shall be constructed for each dosage format, container size, container type and product formulation type
Create defects related to particulate matter by manual addition as well as container-closure defects shall be created deliberately by person
Treat these units as 'Rejected Unit' in Qualification Kit.

Annexure 4

Semiautomatic and Automatic Inspection Qualification

STEP 1

Particulate Inspection

STAGE 1 CONSTRUCTION OF TEST POPULATION

Collect rejected containers (includes defect types) for real time inspection (manual inspection) from production batches. (e.g. 300 nos.).

→ Various size particulate and fiber defect type. Qualification with cosmetic defects population is separate.

↓

Create defects related to particulate matter by manual addition; or get a ready made defective kit from certified party.

↓

Select randomly containers from production batches which are categorized as good units (e.g. 200 nos).

→ Total 500 nos. container population

↓

Above containers (Rejects and Good) should be numbered randomly to avoid possibility of skewing.

→ Population record shall be maintained wrt number and type (Defect or Good).

↓

Two experienced and qualified inspectors shall inspect this container population 5 times each (Total 10 inspections).

→ Time of inspection and conditions shall be same as followed in routine product inspection process.

↓

For each inspection observations wrt identification shall be documented (total 10 inspection records).

↓

STAGE 2 MANUAL INSPECTION OF TEST POPULATION

Calculate the probability of rejection/acceptance for each container from the Stage 1,

→

Category	Probability of Rejection
Accept Zone	0-0.3
Grey Zone	0.31-0.69
Reject Zone	0.7-1

Formula

Probability of Rejection =

$$\frac{\text{Number of times container has been rejected (n)}}{\text{Total Number of inspections}} \times 10$$

↓

From inspected and probability calculated units, select (between 38 &75) containers with probability above 0.7 (Reject Zone).

↓

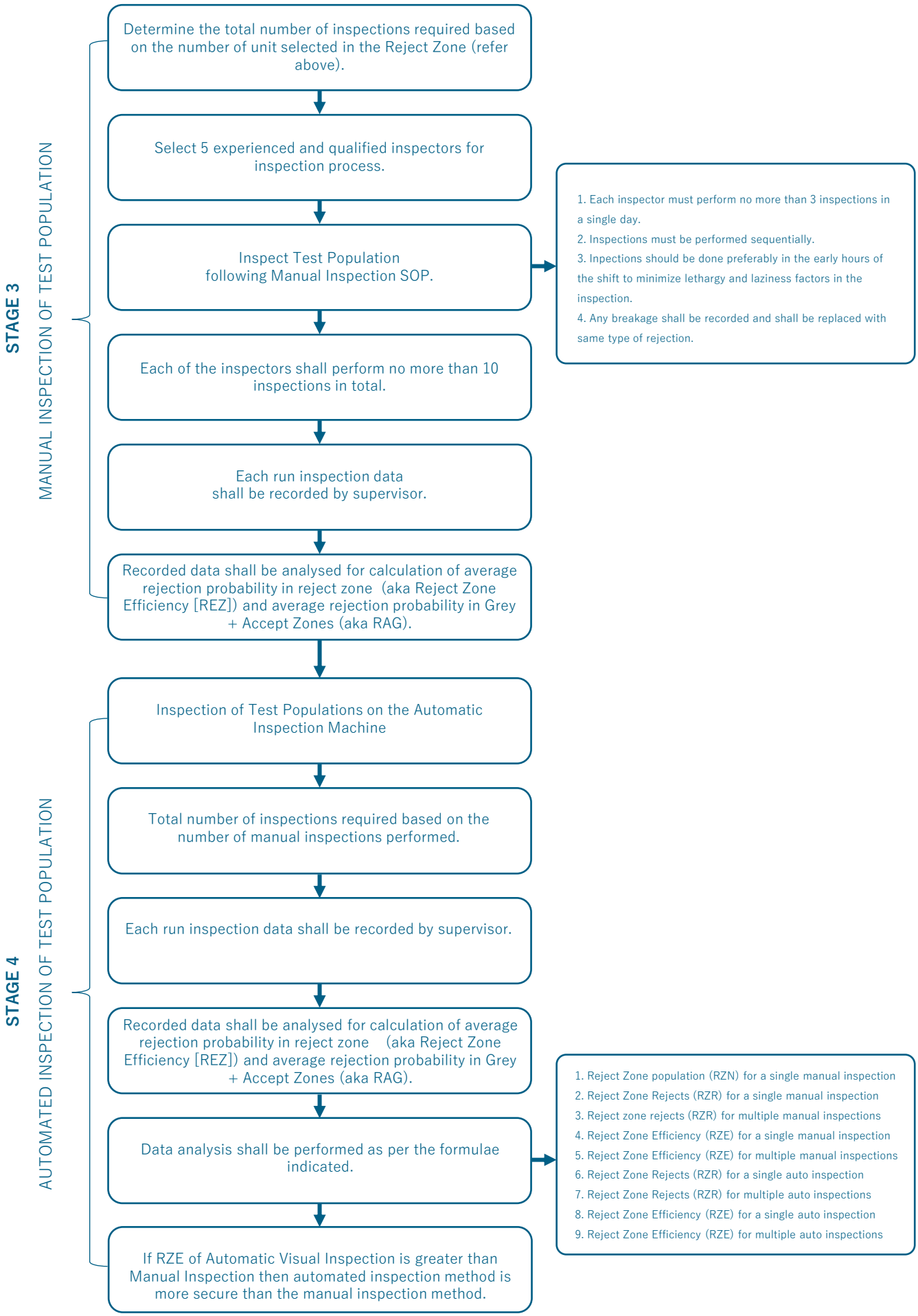
To bring up above container quantity to a total of 150 nos., add containers whose probability of rejection is 0.31 to 0.69. (Grey Zone).

↓

Number the 150 containers randomly selected from the production batch (Good units) with the numbers of the unused containers.

↓

A Test Population of 300 sequentially numbered containers has now been constructed.


STAGE 3
MANUAL INSPECTION OF TEST POPULATION
Determine the total number of inspections required based on the number of unit selected in the Reject Zone (refer above).
Select 5 experienced and qualified inspectors for inspection process.
Inspect Test Population following Manual Inspection SOP.
1. Each inspector must perform no more than 3 inspections in a single day.
2. Inspections must be performed sequentially.
3. Inpections should be done preferably in the early hours of the shift to minimize lethargy and laziness factors in the inspection.
4. Any breakage shall be recorded and shall be replaced with same type of rejection.
Each of the inspectors shall perform no more than 10 inspections in total.
Each run inspection data shall be recorded by supervisor.
Recorded data shall be analysed for calculation of average rejection probability in reject zone (aka Reject Zone Efficiency [REZ]) and average rejection probability in Grey + Accept Zones (aka RAG).
STAGE 4
AUTOMATED INSPECTION OF TEST POPULATION
Inspection of Test Populations on the Automatic Inspection Machine
Total number of inspections required based on the number of manual inspections performed.
Each run inspection data shall be recorded by supervisor.
Recorded data shall be analysed for calculation of average rejection probability in reject zone (aka Reject Zone Efficiency [REZ]) and average rejection probability in Grey + Accept Zones (aka RAG).
Data analysis shall be performed as per the formulae indicated.
1. Reject Zone population (RZN) for a single manual inspection
2. Reject Zone Rejects (RZR) for a single manual inspection
3. Reject zone rejects (RZR) for multiple manual inspections
4. Reject Zone Efficiency (RZE) for a single manual inspection
5. Reject Zone Efficiency (RZE) for multiple manual inspections
6. Reject Zone Rejects (RZR) for a single auto inspection
7. Reject Zone Rejects (RZR) for multiple auto inspections
8. Reject Zone Efficiency (RZE) for a single auto inspection
9. Reject Zone Efficiency (RZE) for multiple auto inspections
If RZE of Automatic Visual Inspection is greater than Manual Inspection then automated inspection method is more secure than the manual inspection method.

STEP 2

NON-PARTICULATE INSPECTION

Prepare containers with specified cosmetic defect and identify such containers.

Feed good and defective as mix containers on machine in-feed.

Operate the machine as per SOP and set parameters established.

Verify that each defect category is accurately detected in the rejects.

→ Machine shall identify and reject the specified defective containers and all the rejects shall be rejected to the rejection station

If rejection percentage of each type of rejects is ≥ 98%, the defect category is accurately detected, and manual re-inspection is not required at rejection station.

If the rejection percentage of each type of rejects is <98%, the defect category is inaccurately detected and manual inspection is required at rejection station.

STEP 3

PROCESS VALIDATION WITH PRODUCT BATCH

Perform inspection of the complete product batch.

All the rejects from the rejection tray should be subjected to manual inspection.

Perform manual inspection for all the good containers obtained from the machine.

→ AQL testing shall pass for the manual inspection of the total inspected good quantity of machine.

If the false rejects as observed from the rejected vials of machine is above 5% of the inspected quantity, the machine set parameters shall be fine-tuned.

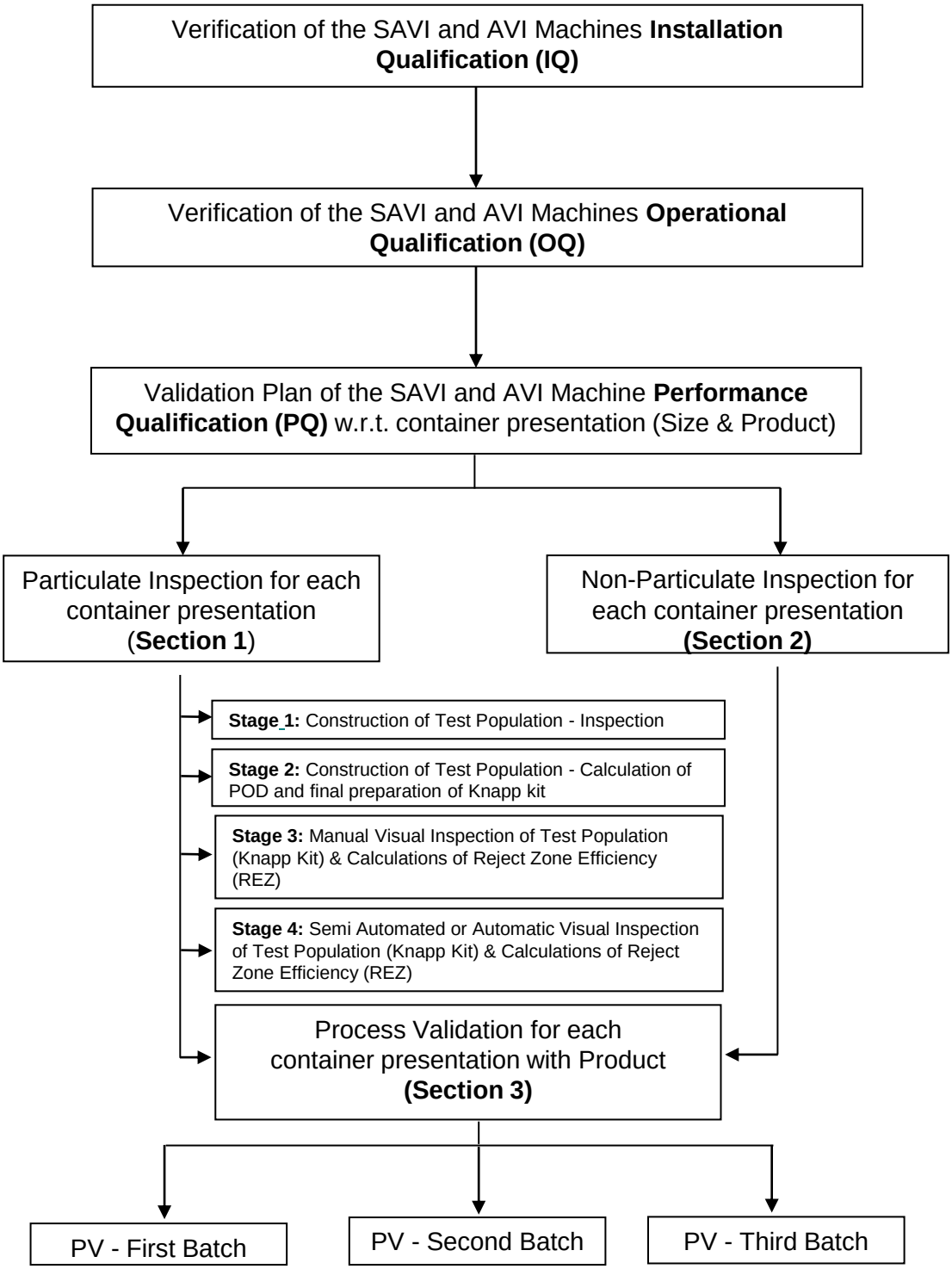
Annexure 5

Automatic Inspection Validation

QUALIFICATION OF SEMI-AUTOMATED VISUAL INSPECTION (SAVI)
AUTOMATIC VISUAL INSPECTION (AVI)

A. QUALIFICATION PLAN

The overall qualification strategy for the Semi-Automatic Visual Inspection (SAVI) and Automatic Visual Inspection (AVI) is outlined in following flowchart:



B. PARTICULATE INSPECTION FOR EACH CONTAINER TYPE (SECTION 1)

1. Study Strategy :

The particulate inspection qualification of each presentation will be divided into four stages, covered by four qualification document packages as summarized below.

Here the aim is to keep the manual inspection processes (Stages 1 and 3) of the qualification exercise separate from the data analysis processes as these are quite involved and may possibly cause unnecessary confusion to personnel not involved in Stages 2 and 4.

❖ **Qualification Document Package 1 (Stage 1)**

This document package will cover the data for generation of the initial test population. All the tests within this document will be performed by Production – Packing Department. The results will be analyzed by and the associated report will be generated by Validation/QA personnel.

❖ **Qualification Document Package 2 (Stage 2)**

This document package will cover data of all the analysis of the work performed during Stage 1 and the establishment of a test population of known reject/accept probabilities (Knapp Kit). All the work within this document will be performed, the results will be analyzed, and the report will be generated by Validation/QA personnel.

❖ **Qualification Document Package 3 (Stage 3)**

This document package will cover the processing of the test population by manual inspection. All the tests within this document will be performed by Production – Packing Department. The results will be analyzed by and the associated report will be generated by Validation/QA personnel.

❖ **Qualification Document Package 4 (Stage 4)**

This document package will cover the processing of the test population via the inspection machines (SAVI/AVI). All the tests within this document will be performed by Production – Packing Department. The results will be analyzed by and the associated report will be generated by Validation/QA personnel.

2. Knapp and Kushner Method

➢ References

The following documents were used when preparing the methods described in the qualification plan:

- ❖ Carleton, F.J., and Agalloco, J.P., "Validation of Aseptic Pharmaceutical Processes", 1986, Marcel Dekker Inc., New York.
- ❖ Knapp, J. Z., Kushner, H. K., and Abramson, L. R., "Automated Particulate Detection for Containers with Use of the Probabilistic Particulate Detection Model", Journal of Parenteral Science and Technology, Volume 35.

➢ Introduction

- ❖ The particulate inspection of parenteral containers is probabilistic in nature. An inspector may not always make the same accept/reject decision every time he inspects a container.
- ❖ If a container undergoes multiple inspections, the container can be categorized by its frequency of rejection.
- ❖ If a container is rejected seven out of ten times it is inspected, the probability of rejection is 0.7.
- ❖ If a large population of containers undergoes multiple inspections, we can categories the containers in the population by their probability of rejection.
- ❖ At the extremes of the population are very, very good containers (0.0 probability of rejection) and very, very bad containers (1.0 probability of rejection).

➢ Nomenclature

POPULATION	AZN NUMBER OF ACCEPT ZONE CONTAINERS	GZN NUMBER OF GREY ZONE CONTAINERS	RZN NUMBER OF REJECT ZONE CONTAINERS
AVERAGE REJECT RATE	RAG MEASURE OF INSPECTION DISCRIMINATION		RZE REJECT ZONE EFFICIENCY
ZONE	ACCEPT ZONE	GREY ZONE	REJECT ZONE

➢ Methodology

General

- ❖ The population is divided into three categories according to the probability of rejection of the container:

Category	Probability of Rejection (Single Inspection)
Accept Zone	0.00-0.30
Grey Zone	0.31-0.69
Reject Zone	0.70-1.00

- ❖ By comparing the performance of an inspection process in these categories, definitive statements can be made about the validity of the inspection process.
  - ❖ The ability of the inspection process to properly reject those containers in the reject zone is measured by the Reject Zone Efficiency (RZE).

    The RZE is calculated by Equation-1:

$$RZE = \frac{\text{Number of Reject Zone Containers Rejected in the Inspection Process}}{\text{Reject Zone Population}} = \frac{RZR}{RZN}$$

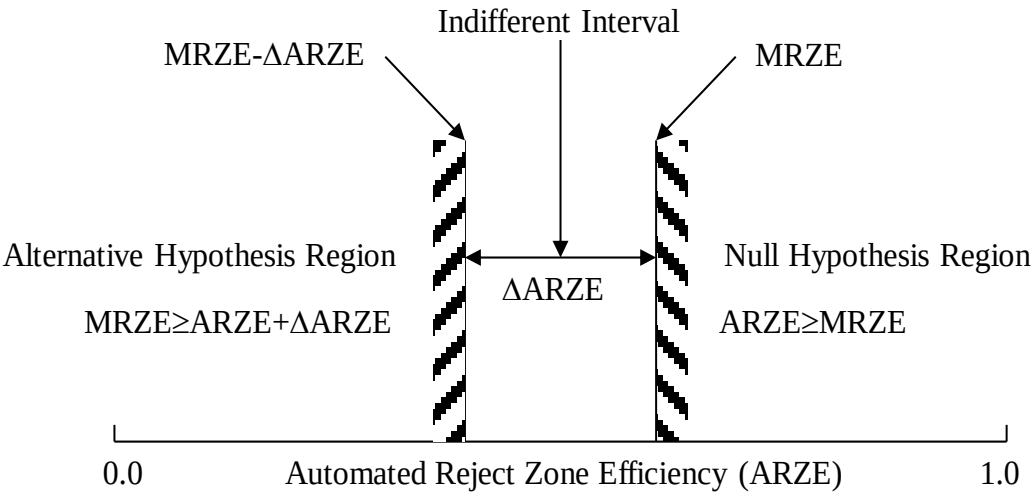
  - ❖ The ability of the rejection process to minimize the rejection of acceptable containers in the Accept and Grey Zones is measured by the undesired rejected rate (RAG).

    The RAG is calculated by Equation-2:

$$RAG = \frac{\text{Number of Accept and Grey Zone Containers Rejected in the Inspection Process}}{\text{Population of Accept and Grey Zones}} = \frac{AGR}{AZN + GZN} = \frac{AGR}{AGN}$$

  - ❖ These two parameters, RZE and RAG, characterize the inspection process from perspectives of security and discrimination, respectively.
  - ❖ As RZE increases, there is greater assurance that the production will meet quality standards.
  - ❖ As RAG decreases, there is greater assurance that acceptable units are not being rejected and the inspection process is economically more acceptable.
  - ❖ RZE and RAG can be optimized resulting in a more cost-effective inspection process at an equivalent level of security.
  - ❖ In comparing two inspection methods (i.e., manual inspection and automatic inspection), there are two hypotheses that must be considered:
    - ❖ Null Hypothesis: The two methods being compared produce equivalent results.
    - ❖ Alternative Hypothesis: The manual method is better than the automated method by a probability of 0.05 (RZE).
  - ❖ If the null hypothesis is satisfied, ARZE > MRZE and the automated inspection procedure is acceptable for use in normal production. If the alternative hypothesis is satisfied, MRZE > ARZE + ・ARZE, the automated inspection procedure is not acceptable for use in normal production.

- The values of N (total rejects from multiple inspections of the test population by each inspection procedure sufficient to satisfy the hypothesis with a 0.95 confidence level) are calculated based on a ・ARZE of 0.05.



THIS IS ILLUSTRATED IN FIGURE 1.

b) Determination of number of inspections of test population

- It is important to determine how many times the test population must be inspected in order to ensure that the hypotheses are satisfied for various types of inspection procedures. Let us consider the following assumptions:
  - The reject zone efficiency (RZE) of both the automated and manual inspection procedures is at worst 0.75.
  - The manual inspection procedure is “single-pass” and the automated inspection procedure is also “single-pass”.
- To calculate the number of inspections (N) required to satisfy the null and alternative hypotheses at pA=0.05, the following equation may be used:

$$\frac{1}{N_M}+\frac{1}{N_A}=\left[\frac{\Delta p_A}{t_\alpha+t_\beta}\right]^2\frac{1}{p_O(1-p_O)}$$

Where

N_M is the number of manual inspections required

N_A is the number of automated inspections required

p_O is the inspection Reject Zone Efficiency (assumed here to be 0.75)

t_α is the 100(1-・)th percentile of the normal distribution (1.645 in this case)

t_β is the 100(1-・)th percentile of the normal distribution (1.645 in this case)

So, assuming that $N_M = N_A = N$ (that is the number of manual inspections required is equal to the number of automated inspections required):

(1)
$$\frac{1}{N} + \frac{1}{N} = \left[\frac{0.05}{1.645 + 1.645}\right]^2 \frac{1}{0.75(1 - 0.75)}$$

$$N = 1623.6 \approx 1624$$

- The number of required inspections of the test population is calculated using the following equation:

(2)
$$\text{Number of Inspections} = \frac{\text{N}}{\text{RZN}} = \frac{1624}{\text{RZN}}$$

- The number of inspections shall be an integral number.
- The RZN must not exceed 25% of the test population or fall below 12.5% of the population, this lower figure having been chosen as an arbitrary value half that of the maximum allowable value, in order to still provide a significant challenge to the process.

  (For example, for a test population of 300 containers, the RZN can be in the range of 38 to 75. This value will be determined during the validation exercise.)

c) Stage 1: Construction of Test Population (Inspection)

- Rejected containers from real time inspection (Manual Inspection) should be collected from the production batches (e.g., number of containers is 300).
- If rejection is not obtained during manual inspection, then defects related to particulate matter should be created by manual addition, and/or a readymade defective kit should be obtained from certified party/laboratory.
- Rejected containers shall be considered to be the following:
  - Those that incorporate all types of particle defects found in product batches.
  - For particulate and fiber defects, size of seeds for preparation of rejected containers shall include bracketed range of sizes (also densities).
  - Bracketed range extends from near the lower limit of humanly visible range (100 µm) to the largest routinely observed in rejects collected. (Reference – USP chapter 1790).
  - Only one type of particle per container should be used for preparation of defect containers.
- Containers from a normal production batch should be selected at random as good containers (e.g., number of containers totaling 200).
- These should be identified as described in the table below. In addition, the numbering given below is recommended to avoid the possibility of skewing the results by prediction (this is provided as guidance; other numbering systems can be followed).

#	Container Serial Number	Type of Container
1	1 to 100	**Reject vials**
2.	101 to 150	**Good vials**
3.	151 to 200	**Reject vials**
4.	201 to 250	**Good vials**
5.	251 to 300	**Reject vials**
6.	301 to 350	**Good vials**
7.	351 to 400	**Reject vials**
8.	401 to 450	**Good vials**
9.	**451 to 500**	**Reject vials**

- Two experienced inspectors shall inspect these 500 containers five times each.
- The order in which the containers are inspected shall be randomized and the observations recorded.

b) Stage 2: Construction of Test Population (Calculation of PoD and final preparation of Knapp Kit)

- The probability of rejection/detection (PoD) for each container from Stage 1 should be calculated. Observations and record the details should be recorded in detail.

Category	Probability of Rejection/Detection (PoD)
Accept Zone	0.00-0.30
Grey Zone	0.31-0.69
Reject Zone	0.70-1.00

- From the 500 inspected containers, between 38 and 75 containers should be selected whose probability of rejection is 0.7 or higher; the total number of containers should be made up to 150 by adding containers whose probability of rejection is 0.3 to 0.69.
- It is important to number the 150 containers randomly selected from the production batch (Good Units) with the numbers of the “unused containers” from the inspected population of 300 rejects.
- A test population (aka Knapp Kit) of 300 nos. sequentially numbered containers has thus been constructed.
- The total number of required inspections shall be calculated using the information from the section “Determination of number of inspection of test population” detailed above.

c) Stage 3: Manual Visual Inspection (MVI) of Test Population (Knapp Kit) Calculations for Reject Zone Efficiency (REZ)

- The total number of required inspections shall be calculated using the information from the section "Determination of number of inspection of test population" detailed above.
- The manual inspection process should be performed as follows:
    - Five trained inspectors should be selected. Each inspector should be instructed to inspect the test population in accordance with current procedural SOP on Manual Visual Inspection.
    - Each inspector must perform no more than 3 inspections of the test population in a single day.
    - These inspections must be performed sequentially and preferably in the early hours of the shift to minimize the effects of lethargy and laziness in the inspection.
    - Any breakage shall be recorded. Broken container shall be replaced.
    - The order in which the containers are inspected shall be randomized.
    - Each inspector shall perform no more than 10 inspections in total. This restriction is required in order to prevent the observations of a single inspector skewing the results.
- Production Supervisor (not an inspector involved in the validation) shall document all raw data with respect to the inspection.
- All raw data shall be passed to Validation Department upon completion of the manual inspection process.
- Recorded data shall be analyzed for calculation of average rejection probability in Reject Zone (aka Reject Zone Efficiency [REZ]) and average rejection probability in Grey + Accept Zone, aka RAG).
- Refer procedure outlined below for calculations and compilation of results.

d) Stage 4: Semi-Automated OR Automatic Visual Inspection (SAVI or AVI) of Test Population (Knapp Kit) & Calculations of Reject Zone Efficiency (REZ)

- The semi-automated or automated inspection machine should be run in validation mode.
- The critical set parameters should be selected as per development study report.
- The activity should be performed in accordance with the operational SOP for machine.
- Any breakage shall be recorded. Broken container shall be replaced.
- The total number of inspections required will be based on the number of manual inspections performed.
- After the completion of runs, the printout should be collected and the data should be reviewed.
- All data shall be passed to Validation Department upon completion of the automated inspection process.
- Recorded data shall be analyzed for calculation of average rejection probability in reject zone (aka Reject Zone Efficiency [REZ]) and average rejection probability in Grey + Accept Zone, aka RAG).
- Refer procedure outlined in the section below for the calculations and compilation of results.

e) Stage 4: Semi-Automated OR Automatic Visual Inspection (SAVI or AVI) of Test Population (Knapp Kit) & Calculations for Reject Zone Efficiency (REZ)

- For each container in the test population, there are the following parameters that make up the data point:
- P_m, the probability of rejection (one manual inspection).
- P_a, the probability of rejection (one automated inspection).
- P_{mn}, the probability of rejection (multiple manual inspections).
- P_{an}, the probability of rejection (multiple automated inspections).
- Using the matrix below (Matrix 1), each parameter can be grouped into 11 partitions, thus creating 121 data points. The number of containers occurring at each point may be totaled.

		1			2	3	4	5	6	7	8		9	10	11	12
					Data											
Rows					Accept Zone				Grey Zone				Reject Zone			
1	N(A) Automated Method Distribution		P(A) Automated Method Rejection Probability	1.0												
2				0.9												
3				0.8												
4				0.7												
5				0.6												
6				0.5												
7				0.4												
8				0.3												
9				0.2												
10				0.1												
11				0.0												
			M		0.0	0.1	0.2	0.3	0.4	0.5	0.6		0.7	0.8	0.9	1.0
					P(m) Manual Standard Rejection Probability											
12																
		Total			N(m) Manual Standard Distribution											

- The reject zone efficiency (RZE) for a single manual inspection (m1) and a single automated inspection (a1) can now be calculated.
  - Total each column 2-12 and record the totals in row 12.
  - Total each row 1-11 and record the totals in column 1.
  - The reject zone population (RZN) for a single manual inspection can be calculated by adding the values in row 12, columns 9, 10, 11 and 12.
  - This is demonstrated by equation 3:

(3) $$RZN = N_{0.7} + N_{0.8} + N_{0.9} + N_{1.0}$$

- The reject zone rejects (RZR) for a single manual inspection (m1) can be calculated by multiplying the population (N) of each partition within the reject zone (row 12, column 9, 10, 11 and 12) by its respective probability of rejection, P(m1), and then total the resulting product from each zone. This is demonstrated by equation 4:

(4) $$RZR(m_1) = 0.7N_{0.7} + 0.8N_{0.8} + 0.9N_{0.9} + 1.0N_{1.0}$$

- This can be modified for multiple inspections. The reject zone rejects (RZR) for multiple inspections (mn) can be calculated by multiplying the population (N) of each partition within the reject zone (row 12, column 9, 10, 11 and 12) by its respective probability of rejection, P(mn), and then total the resulting product from each zone. This is demonstrated by equation 4a:

(4a) $$RZR(m_n) = 0.7^n N_{0.7} + 0.8^n N_{0.8} + 0.9^n N_{0.9} + 1.0^n N_{1.0}$$

- The reject zone efficiency (RZE) for a single manual inspection (m1) can be calculated by equation 5:

(5) $$RZE(m_1) = \frac{RZR(m_1)}{RZN}$$

- This can be modified for multiple inspections. The reject zone efficiency (RZE) for multiple manual inspection (mn) can be calculated by equation 5a:

(5a) $$RZE(m_n) = \frac{RZR(m_n)}{RZN}$$

- The reject zone rejects (RZR) for a single automated inspection (a1) can be calculated by adding the values in columns 9, 10, 11 and 12 for each row 1-11. Multiply each total by its respective probability of rejection, P(a1), via a single automated inspection. The total of the products can be shown by equation 6:

(6) $$\begin{aligned} RZR(a_1) = {} & 0.1(N_{0.1,0.7} + N_{0.1,0.8} + N_{0.1,0.9} + N_{0.1,1.0}) \\ & + 0.2(N_{0.2,0.7} + N_{0.2,0.8} + N_{0.2,0.9} + N_{0.2,1.0}) \\ & + \ldots + 1.0(N_{1.0,0.7} + N_{1.0,0.8} + N_{1.0,0.9} + N_{1.0,1.0}) \end{aligned}$$

- This can be modified for multiple inspections. The reject zone rejects (RZR) for multiple automated inspections (an) can be calculated by adding the values in columns 9, 10, 11 and 12 for each row 1-11. Multiply each total by its respective probability of rejection, P(an), via multiple automated inspections. The total of the products can be shown by equation 6a:

(6a) $$\begin{aligned} RZR(a_n) = {} & 0.1^n(N_{0.1,0.7} + N_{0.1,0.8} + N_{0.1,0.9} + N_{0.1,1.0}) \\ & + 0.2^n(N_{0.2,0.7} + N_{0.2,0.8} + N_{0.2,0.9} + N_{0.2,1.0}) \\ & + \ldots + 1.0^n(N_{1.0,0.7} + N_{1.0,0.8} + N_{1.0,0.9} + N_{1.0,1.0}) \end{aligned}$$

- The reject zone efficiency (RZE) for a single automated inspection (a1) can be calculated by equation 7:

(7) $$RZE(a_1) = \frac{RZR(a_1)}{RZN}$$

- This can be modified for multiple inspections. The reject zone efficiency (RZE) for multiple automated inspection (an) can be calculated by equation 7a:

(7a) $$RZE(a_n) = \frac{RZR(a_n)}{RZN}$$

- If RZE(a1)>RZE(m1) or RZE(an)>RZE(mn), then the automated inspection method is more secure than the manual inspection method.

The same matrix can be used in the calculation of the reject rate in the accept and grey zones (RAG) for both the manual and automated inspection procedures.

- The population of the accept and grey zone (AGN) for a single manual inspection (m1) can be calculated by adding the values in columns 2-8, row 12. This is demonstrated by equation 8:

(8) $$AGN = N_{0.0} + N_{0.1} + N_{0.2} + N_{0.3} + N_{0.4} + N_{0.5} + N_{0.6}$$

- The accept and grey zone rejects (AGR) via a single manual inspection (m1) can be calculated by multiplying the population (N) within each partition of the accept and grey zones (columns 2-8, row 12) by their respective probability of rejection, P(m1). The sum of these products is AGR(m1), as shown by equation 9:

(9) $$AGR(m_1) = 0.0N_{0.0} + 0.1N_{0.1} + 0.2N_{0.2} + 0.3N_{0.3} + 0.4N_{0.4} + 0.5N_{0.5} + 0.6N_{0.6}$$

- This can be modified for multiple inspections. The accept and grey zone rejects (AGR) via multiple manual inspections (mn) can be calculated by multiplying the population (N) within each partition of the accept and grey zones (columns 2-8, row 12) by their respective probability of rejection, P(mn). The sum of these products is AGR(mn), as shown by equation 9a:

(9a) $$AGR(m_n) = 0.0^n N_{0.0} + 0.1^n N_{0.1} + 0.2^n N_{0.2} + 0.3^n N_{0.3} + 0.4^n N_{0.4} + 0.5^n N_{0.5} + 0.6^n N_{0.6}$$

- The reject rate in the accept and grey zones for a single manual inspection, RAG(m1), is calculated by equation 10:

(10) $$RAG(m_1) = \frac{AGR(m_1)}{AGN}$$

- This can be modified for multiple inspections. The reject rate in the accept and grey zones for multiple manual inspections, RAG(mn), is calculated by equation 10a:

(10a) $$RAG(m_n) = \frac{AGR(m_n)}{AGN}$$

- The accept and grey zone rejects (AGR) via a single automated inspection (a1) can be calculated by adding the values in columns 2-8 for each row 1-11. Multiply each total by its respective probability of rejection, P(a1), via a single automated inspection (a1). The total of these products can be shown by equation 11:

(11) $$\begin{aligned} AGR(a_1) = {} & 0.1(N_{0.1,0.0} + N_{0.1,0.1} + N_{0.1,0.2} + N_{0.1,0.3} + N_{0.1,0.4} + N_{0.1,0.5} + N_{0.1,0.6}) \\ & + 0.2(N_{0.2,0.0} + N_{0.2,0.1} + N_{0.2,0.2} + N_{0.2,0.3} + N_{0.2,0.4} + N_{0.2,0.5} + N_{0.2,0.6}) \\ & + \ldots + 1.0(N_{1.0,0.0} + N_{1.0,0.1} + N_{1.0,0.2} + N_{1.0,0.3} + N_{1.0,0.4} + N_{1.0,0.5} + N_{1.0,0.6}) \end{aligned}$$

- This can be modified for multiple inspections. The accept and grey zone rejects (AGR) via multiple automated inspections (an) can be calculated by adding the values in columns 2-8 for each row 1-11. Multiply each total by its respective probability of rejection, P(an), via multiple automated inspections (an). The total of these products can be shown by equation 11a:

$$\begin{aligned} AGR(a_n) = {} & 0.1^n (N_{0.1,0.0} + N_{0.1,0.1} + N_{0.1,0.2} + N_{0.1,0.3} + N_{0.1,0.4} + N_{0.1,0.5} + N_{0.1,0.6}) \\ & + 0.2^n (N_{0.2,0.0} + N_{0.2,0.1} + N_{0.2,0.2} + N_{0.2,0.3} + N_{0.2,0.4} + N_{0.2,0.5} + N_{0.2,0.6}) \\ & + \ldots + 1.0^n (N_{1.0,0.0} + N_{1.0,0.1} + N_{1.0,0.2} + N_{1.0,0.3} + N_{1.0,0.4} + N_{1.0,0.5} + N_{1.0,0.6}) \end{aligned} \tag{11a}$$

- The reject rate in the accept and grey zones for a single automated inspection, RAG(a1), is calculated by equation 12:

$$RAG(a_1) = \frac{AGR(a_1)}{AGN} \tag{12}$$

- This can be modified for multiple inspections. The reject rate in the accept and grey zones for multiple automated inspections, RAG(an), is calculated by equation 12a:

$$RAG(a_n) = \frac{AGR(a_n)}{AGN} \tag{12a}$$

3. Acceptance Criteria

- **If RZE(a_n) >= RZE(m_n) then the validation will be deemed to be acceptable.**
- **It is also desirable for RAG(a_n) =< RAG(m_n); however this is not critical.**

13 Glossary

- Particulate matter: extraneous, mobile, undissolved substances other than gas bubbles (like glass particles, fibers, etc.) unintentionally present in parenteral products.

- Intrinsic particulate matter (from within the process): particulate matter generated from materials of construction of equipment, tools, accessories, reagents, etc. used in manufacturing process; e.g., processing equipment, primary package qualified product contact materials (e.g., stainless steel, glass, rubber, silicone oil, etc.).

- Extrinsic particulate matter (from outside the process): atypical particles generated from non-process precursor materials. These may need to be further identified by optical microscope, polarized light microscope, micro FTIR etc. These may include environmental contaminants, such as insect parts, hair, fibers, paint, rust, etc.

- Visible particulate matter: any matter in product associated with objectionable condition or practices in production, storage or distribution; included are matter such as glass, metal, wood, plastic, fibers, hair, rust, paper/cardboard pieces and other particulates.

- Inherent particulate matter (part of the formulation): particles generated from materials found in formulation of product.

- Critical defects: any defect that will harm patient and those which may impact the integrity of the sample.

- Major defects: affects the functionality of the product (these may reduce the performance of drug product), but will not impact the patient.

- Minor defects: defects which do not affect the function, and may impact the appearance of the product, but will have no impact on patient safety.

- AQL (Acceptable Quality Level): when a continuous series of lots is considered, the AQL is the maximum % defects that have been determined tolerable as a process average for the purposes of sampling and inspection.

- Visual Inspector: he or she is the trained and qualified person for visual inspection.

- PoD: probability of detection.

14 References

- American National Standard – Sampling Procedures and Tables for Inspection by Attributes - ANSI/ASQ Z1.4 – 2003 (R2018).
- USP40-NF-35, Chapter 790 – Visible Particulates in Injections.
- USP40–NF35 Supplement I: Chapter 1790 – Visual Inspection Of Injections
- Parenteral Drug Association (PDA), Technical Report No. 43: Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing. (2013).
- FDA, Sterile drug process inspections: Compliance Program Guidance Manual, Program 7356.002A. (2012).
- http://www.fda.gov/downloads/ICECI/ComplianceManuals/CompliancePrograMManual/ucm125409.pdf. Accessed 12 October 2016.
- ICH. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH Q10 Pharmaceutical Quality System (PQS). (2008).
- http://www.ich.org/_leadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Presentation/Q10_General_Presentation.pdf. Accessed 12 October 2016.
- Code of Federal Regulations Title 21 Food and Drugs, 21 CFR 210.3 Definitions (2014).

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