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A Review Article on Visual Inspection program for sterile injectable product

A complete solution for manual inspection process

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FROM THE AUTHOR'S DESK

Dear Readers,

Through PRES we are trying to connect with the Global Pharma community. Where we discussed, share and explore lots of pharmaceutical hot topics. Being a Pharma professional it is very difficult to get time for own to do something different from the routine responsibilities. Hope you all professionals are agreed with my views. That's you, the readers and followers of my blog, who always encouraged me a lot to do something different than my routine assignment.

We know most of the information's are easily available in web media; I am just trying to collate all those information in a single article.

I have collated the information's broadly from the major regulatory guidance document including FDA, PIC,s, MHRA and other pharmaceutical knowledge resources like ISPE, PDA & other websites.

Once again I would like to thanks to my readers, followers and seniors, who has encourage me a lot.

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PREFACE

Inspection program is one of the tuff challenges for pharmaceutical industry. As it is a manual program hence probability of& the failure rate in very high. Success of the study depends upon the various human factors. Semi-automatic and automatic inspection machines are available in the market, which requires separate set of experience and expertise to establish for routine usages. In our upcoming article we will focus on that machine also. However this article completely dealing with manual inspection process.

Before coming to my next section I would like to take this opportunity to thank

Mr. John G. Shabushing, Founder and Principal Consultant at Insight Pharma Consulting LLC for his support to clear my view on several aspects of inspection process. He is an encyclopaedia of pharmaceutical quality, regulatory requirements and manufacturing with specific expertise in the visual inspection of sterile injectable products.

I am thankful to Mr. Jim Agalloco, President, and Consultant & Everything Else at Agalloco & Associates, who has inspired me a lot to start technical writing. His contribution is huge in the subjects of sterilization, aseptic processing and process validation.

Apart from that I would like to thank to my Guru's and Guide from the industries,

- Pradipta Swain, Vice President Operations at SUN PHARMA
- CH V V SATYANARAYANA, Head Quality.QA/QC. Aurobindo Pharma

Addition to this I would like to convey my gratitude to my principle & teacher Dr. Arnab Samanta. Last but not least I would like to thanks my colleague Md. Azad Khan and VD Prasad Chikkala for their unconditional support and help me to understand the practical difficulties of implementation manual inspection and patient risk.

Contents

1. Introduction

Objective of this article is to conduct a thorough review and understanding on the manually conduct visual inspection process for liquid Injectable products in liquid and lyophilized form and to explore the complications identified during the routine process. Along with that troubleshot to overcome from the challenges. Evaluation quality of product during batch release and consider continuous process improvement opportunities. Following topics are considered in the review,

- Process controls
- Regulatory expectation
- Current trend
- Identifying further scope of improvement
- Inspector training and evaluation process
- Defect Kit preparation and maintenance

The scope of this review is limited to the inspection process of liquid and lyophilized Injectables products filled in clear or amber colour glass container manufactured through aseptic process by considering conventional / Isolator technology and inspected through manual process.

2. Background

Sterile injectable products are used extensively in health care. Patients, caregivers, manufacturers, and regulators have an inherent expectation for safe and effective injectable drug products. This expectation requires injectable pharmaceuticals to be produced to standards of quality, purity, and sterility that include being essentially free of extraneous matter such as particles. Despite guidance in producing product that is “essentially free” of particles, manufacturing such product is very challenging. A gap exists between the observation of small quantities of particles in injectable pharmaceutical products and patient documented safety concerns resulting from the inadvertent administration of particles to patients. Thus, a need exists to create a framework to describe and assess the potential risk.

3. Overview of Manufacturing Process

Injectable manufacturing process is design such a way that it provides a high degree of assurance for patient case towards health care system. Manufacturing consisting complex process steps, outcome is not only claim the sterility of the product. To provide the product safety, purity and efficacy it is mandatory that product should to be free from any visual particulate defects.

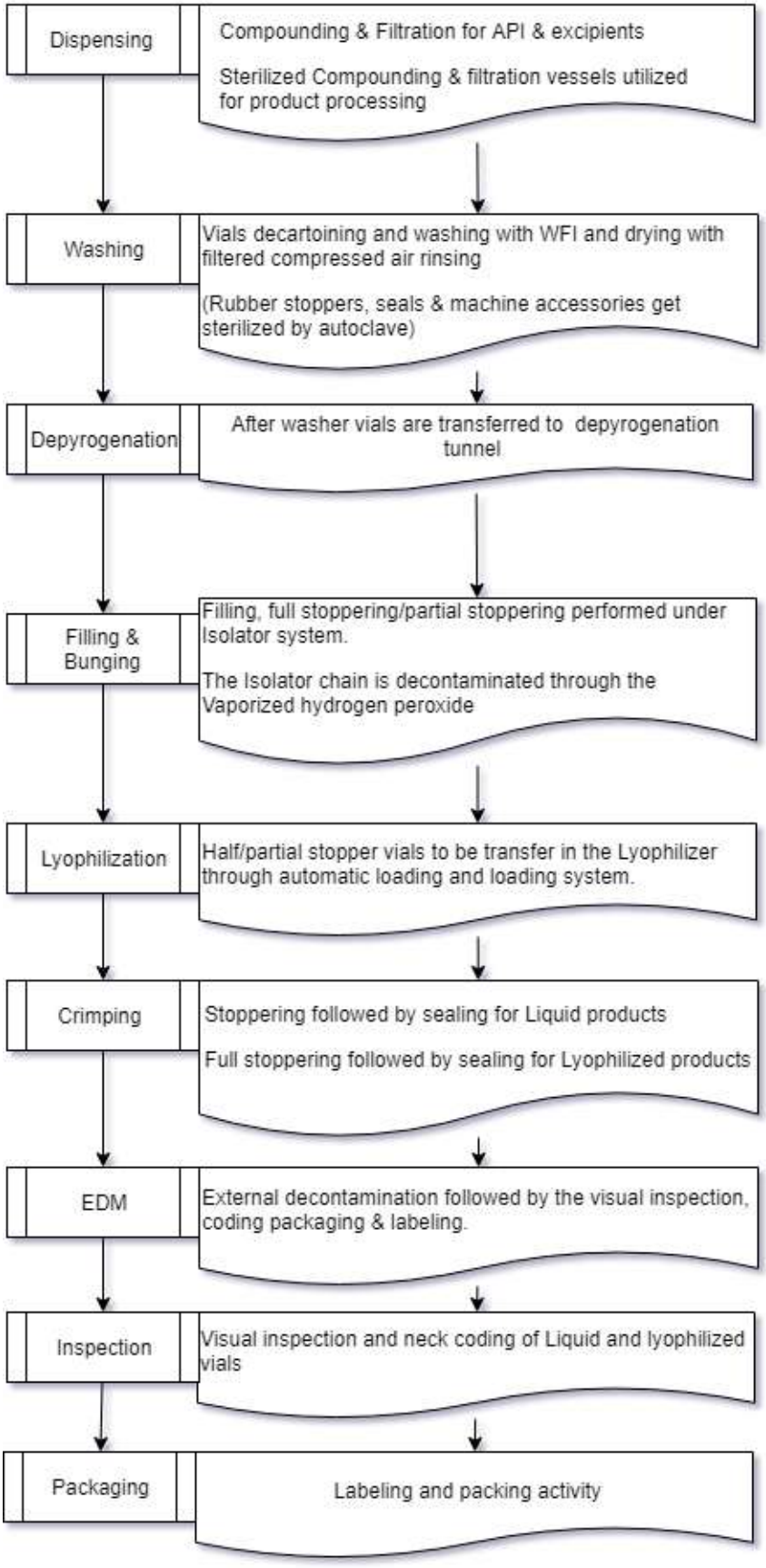
Each product is manufactured in either liquid filled or lyophilized powder form, sterile filtered bulk product solution is filled and over sealed (in liquid vials) or half stopper for lyophilisation (in lyophilized powder vials), lyophilized vials are full stopper and over sealed. The complete manufacturing and packaging is performed using qualified manufacturing equipment and facility by trained technical staff. API, excipients and primary packaging materials are sourced from the approved vendor source. All incoming material lots are subject to a strict incoming material checks for compliance to the respective approved specifications as per written and approved procedures. Material is approved for manufacturing only after demonstration of conformance to all specifications. Only approved lots are released for manufacturing.

The bulk product solution manufacturing steps are critically controlled and maintained in accordance with approved manufacturing procedures throughout the manufacturing process and actual observations / conditions are appropriately documented in the approved manufacturing record.

The entire aseptic manufacturing process is divided into major seven parts:

- Compounding of API and Excipients
- Depyrogenation of vials and sterilization of equipment/ accessories, compounding/ filtration vessels, closures and over seals
- *Decontamination of the Filling line Isolators
- Sterilizing grade filtration at point of fill and aseptic filling process
- Vial receiving, filling, stopper and sealing
- Transfer of filled and half stopper vials for Lyophilizer loading and unloading
- Transfer of stopper vials post lyophilisation to vials sealing

*Step to be consider for Isolator Technology



Flow Chart 1: Manufacturing process flow for liquid/lyophilized injectable product

4. Risk Assessment for Particle Contamination

Aseptic processes are some of the most difficult processes to conduct in the pharmaceutical industry. A robust aseptic processing provides assurance to reduce the particulate contamination in final product container. Particulate matter is defined in Particulate Matter in Injections ⟨788⟩ as "mobile undissolved particles, other than gas bubbles, unintentionally present in the solutions". Visual inspection is a probabilistic process and the specific detection probability observed for a given product for visible particles will vary with differences in product formulation, particle characteristics, and package design. Therefore inspection process will not be a single solution to detect and remove the particle content from the product. Build up the systemic control in the every stage of aseptic processing will be the objective.

Since the nature of aseptic processes, sterile products produced aseptically present a significantly higher risk to the patient. So, an effective risk-management program aids in the careful control of the process, reducing the risk of contamination as well as wasted effort in controlling insignificant risks.

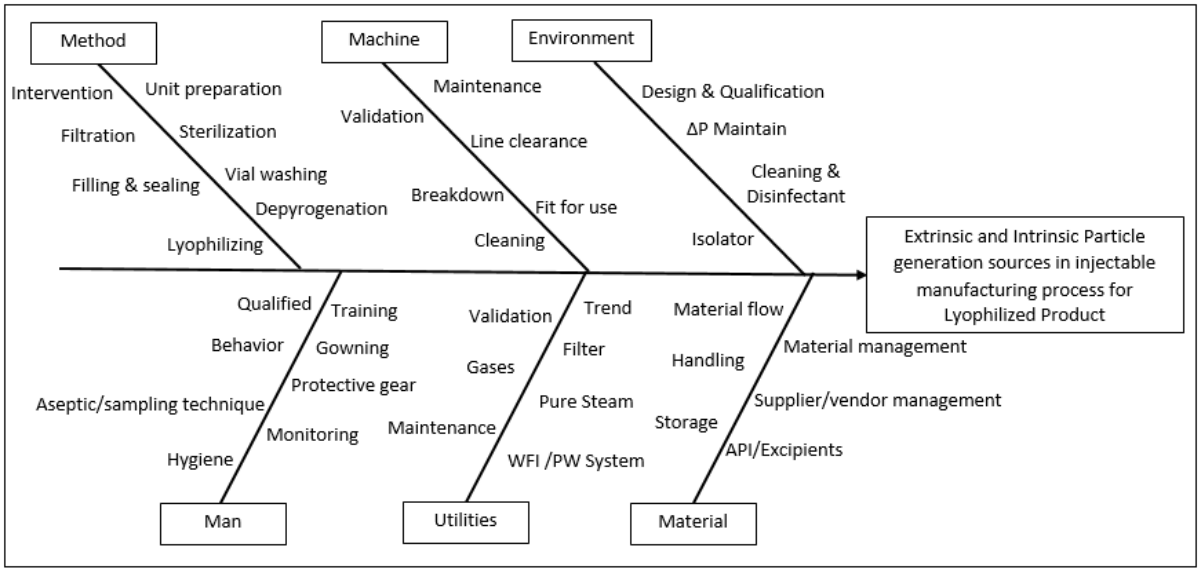


Figure 1: Fishbone for identifying the particle generation in injectable Lyophilized product

All the potential areas were identified as part Fishbone/Ishikawa diagram, from where the probable area for generating particle can be evaluated.

4.1 Environment :

Environment considered as the all clean areas where manufacturing activities were carried out. Filling activity performed in Grade A condition within the Filling room or Isolator

system and surrounding area of Isolator is Grade C. For conventional manufacturing Filling activity performed in Grade A condition with background of Grade B.

For conventional filling process,

- Area is design by following cGMP norms.
- Environmental monitoring is considered through EMS.
- AHU controls through integrated BMS
- Proper cleaning and disinfection process are established
- Maintenance of temperature, humidity and differential pressure
- Continues Monitor of non viable particle count in critical area during operation
- Replacement of HEPA filter and maintenance of air handling units
- Restricted operator access
- Defined man and material movement

For Isolator technology,

- Isolators has been introduced only after appropriate validation, following test are performed as schedule mention in VMP, Air velocity, ACPH, NVPC, Recovery, Gloves integrity, pressure differential, microbial monitoring, VHP and smoke study.
- Aseptic processing has been carried out using isolator system in positive pressure conditions.
- It is a barrier from external environment and minimizes human intervention.
- The transfer of materials into isolator through LTP (Liquid transfer port) and mouse hole.
- Rubber stopper and flip off seals are transfer in isolator aseptically through RTP port.
- The entire articles are sterilized as per validated load pattern and transfer in to the isolator aseptically.
- The air classification required for the background environment complying with the Grade D requirement in operation condition.
- Monitoring is carried out routinely and leak testing of the isolator and glove/sleeve system is carried out as per procedure.
- Inbuilt Interlock provided to the system as a part of additional safety measures that once leak test will successfully complete then system will allow for VHP run.
- Transfer system (e.g. RTP), gaskets and seal parts covered by maintenance program.

4.2 **Material :**

API, Excipients, primary packing material (Vial, Rubber bung & flip off) and including other consumables like silicon tubing, products filter all are considered as part of material category.

All the materials are procured from the authenticated and qualified vendor source after inspection.

However redundant filtration (0.22 μ) technique followed for filtration of bulk solution after compounding and pre & post integrity of filter is performed to assure the integrity. Filter compatibility with the product was studied as a part of initial process development. Hence chance of particle generation through API or other Excipients is remote. Controls and handling of primary packaging material are elaborated in the Section No 4.5.

4.3 **Machine:**

- Design and selection of equipment is done based on approved User Required Specification (URS).
- All critical equipment is qualified as per site VMP before release for routine use.
- A risk based qualification approach is adopted based on sound scientific rational as per ICH Q9.
- Requalification performed as per approved schedule mention in Validation Master Plan (VMP).
- Preventive maintenance procedure is available for routine maintenance.
- In case of any breakdown it is address through break down maintenance procedure.
- Major failures during operations are addressed through incident management procedure.
- Schedule calibration is performed for all measuring instruments (e.g. Pressure gauges, sensors).
- Routine operation and cleaning is carried out through respective approved procedures.
- Re-verification/revalidation shall be considered in case of major breakdown/maintenance or major modification/ changes.
- The design of equipment used in aseptic processing limiting the number and complexity of aseptic interventions by personnel.
- All critical process equipment power supply supported by UPS to prevent the unwanted power failure/interruptions.
- Routine operation and cleaning is carried out through approved procedure.
- In case of any breakdown it is address through breakdown maintenance procedure.
- Process implementation/Changes are evaluated through Change management procedure and major changes are evaluated through Risk assessment.
- As a part of cleaning validation/verification all product contact and non-contact part of equipment are evaluated through approved cleaning validation/verification protocol as per Validation Master Plan**.**

4.4 **Utility:**

Clean utilities like Purified water, Water for injection (WFI), pure steam, compress air and nitrogen all comes direct or indirectly contact of product. Purified water used for primary source for washing /CIP process, however final rinse of all cleaning/CIP is performed through WFI. After compounding bulk is transferred to the buffer vessel through redundant filtration, hence the chance of introduction of particles is remote. All the clean utilities are qualified and are being closely monitored to ensure an appropriate quality.

In addition, microbiologically the water system and the pure steam generation systems are closely monitored with comprehensive sampling and testing. The quality of water is being assessed through trending the results monthly wise and summarizing the observed results.

In-house established alert and action limits are in place to maintain the quality of purified water which is the fed water for WFI and steam generation. Pure steam condensate is being collected as per the procedure and tested to meet the WFI parameters. All these aforesaid controls are handled as per the procedures.

A compressed used for the process is assessed for appropriate purity (e.g., free from oil) and it's microbiological and particle quality after filtration is better than that of the air in the environment into which the gas is introduced. The sterile grade filters are used for autoclave air lines, Lyophilizer vacuum breaks, and tanks containing sterilized materials. Sterilized holding tanks and any contained liquids kept under positive pressure or appropriately sealed to prevent microbial contamination.

Filters that serve as sterile boundaries or supply sterile gases are tested for integrity upon installation and periodically thereafter (e.g., end of use). Integrity tests are also considered after activities. Integrity test failures are subjected for failure investigated as per operating procedure, and filters are replaced at appropriate, defined intervals.

4.5 **Method:**

The manufacturing process is designed to keep the final container and its contents clean within the control parameters established for process-related particulates. Subsequent steps are mentioned below through which the manufacturing processes are executed.

- Decartoning of vials activity:

  It is a part of preliminary inspection of incoming vials for verification of cracks or other significant defects.

- Vial washing activity:

  During washing the use of recycled WFI and the compressed air followed by fresh WFI with compressed air is sequentially instructed. Software has three levels of privilege wherein, the operator and supervision have the operation control

privilege and admin will have complete privilege to control the software access. As a part of qualification system were challenges to confirm the robust controls on removal of foreign particulate, broken glass pieces and any soluble or insoluble mater presence in glass vials. Online filtrations are available in the utility line (Compressed air, WFI and recycle water) to remove the particulate contamination in the final cleaned container.

- Depyrogenation and sterilization activity:

  Through the tunnel conveyer clean containers travelled to tunnel from washer. Pressures balancing of tunnel are set and maintain such a way it will not allow the Grade C air inside of the tunnel. Quality of the air in the tunnel maintained as Grade A. The tunnel sterilizer is being monitored for non-viable particulate count prior to start the Depyrogenation cycle. The cleaning is done with the lint free mops wetted with WFI followed by wiping with a dry lint free mope.

- Filling, bunging and sealing activity:

  The entire filling activity is performed under positive pressure isolator system. Since the isolator contains high pressure so the chance of getting contamination depyrogenation tunnel is remote. Same has been demonstrated during air flow visualization studies. Continues particle counter are installed on the filling line to monitoring the non-viable particle count. Isokinetic probes are installed in all the critical locations (e.g. Post tunnel Filling turn table, at filling stage, half stoppering/bunging stage and loading side of Lyophilizer) within the filling line to identify any excursion during process.

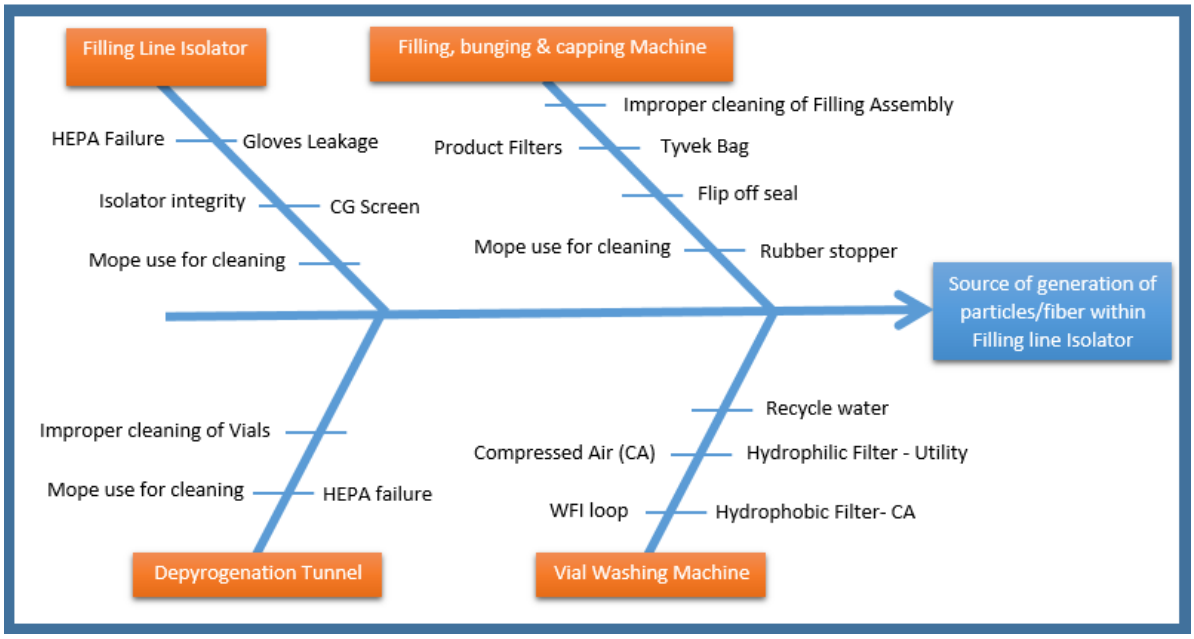
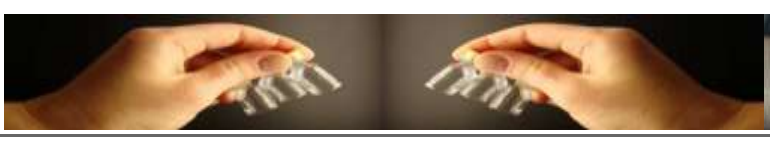


Figure 2: Fishbone for identifying the potential source of particle during filling activity

Components	Failure mode	Inbuilt failsafe design features
Vial Washing activity	Particle generation through, • Compressed air • WFI • Recycle water • Un-cleaned Vials • Filter failure	• Compressed air and recycle water line provided with 0.2µ and 1.2 µ filters respectively • Periodic integrity of Compressed air filters is performed. • During batch initial WFI clarity was verified and apart from that during batch washed vials clarity was verified with periodic interval.
Depyrogenation	Particle generation through, • Improper washing of vials • Shredding of mope lint used for tunnel conveyer cleaning • HEPA filter failure	• All vials sizes are qualified adequately before using for batches. • The cleaning is done with the lint free mops wetted with WFI followed by wiping with a dry lint free mope. • Mopes are lint free and procured from qualified vendor source. • HEPA filter integrity was verified 6 monthly basis. • The tunnel sterilizer is being monitored for non-viable particulate count prior to start the Depyrogenation cycle.
Filling Line Isolator	Particle generation through, • Isolator integrity • Gloves integrity • HEPA filter integrity • CG screen • Shredding of mope lint	• Visual verification is done before starting of gloves integrity as a part of pre-checks. • As a part of line clearance procedure gloves integrity test report was verified before clearance of any batch. • Post gloves integrity test is carried out after batch to assure the sterility of the product. • Gloves replacement frequency is established based on rational before they break down or degrade. • Aseptic processing has been carried out using isolator system in positive pressure conditions. • It is a barrier from external environment and minimizes human intervention • The transfer of materials into isolator through LTP (Liquid transfer port) and mouse hole. • Rubber stopper and flip off seals are transfer in isolator aseptically through RTP port. • Monitoring is carried out routinely and leak testing of the isolator and glove/sleeve system. Air balance between isolator and other interference are verified during smoke study. • Inbuilt Interlock provided to the system as a part of additional safety measures that once




Components	Failure mode	Inbuilt failsafe design features
		leak test will successfully complete then system will allow to process next stage. • HEPA filter integrity was verified 6 monthly • Within the isolator on the filling line online particle counter are installed to monitoring the NVPC (Non-viable particle count). • CG screen intactness is verified within the Isolator before line clearance activity. • Isolator internal surface moped with lint free mope. These mopes are procured from qualified vendor source.
Filling , Bunging and capping	Particle generation through, • Product filters • Filling assembly • Rubber stopper • Use of Tyvek Bag • Flip off seal • Shredding of mope lint	• Filter are product dedicated and one time use only • Pre and post integrity was performed for each batches • Filter compatibility study was per formed with each batches • Online particle counter probe available to monitor any excursion during assembling filling accessories. • Rubber stopper procured from approved vendor source and release based on the predefine specification. • Ready to use (RTU) rubber stopper are used for the process. • Tyvek bags are cut with the help of blunt end scissor from polyethylene film side to avoid the shredding of particle. • Vials are stopper after lyophization hence the particle contamination risk from the flip off is remote. • Filling machine internal surface moped with lint free mope. These mopes are procured from qualified vendor source.

Table 1: Design review and evaluation for identifying potential source of particle during filling activity

4.6 **Man:**

Visual inspection of the injectable products manufactured driven by manual inspection process. Trained visual inspectors are inspecting the entire filled unit at site.

As per the procedure follow controls are should to be in place for effective inspection process,

- Visual inspector are required to have at least a 5 minutes eye- rest period after 30 minutes of continuous Visual Inspection or when eyes get stressed/wet due to continuous Inspection (whichever is earlier).
- Individual Visual Inspector shall not extend the Visual Inspection activity beyond 6 hours in a day.
- For clear containers NLT 2000 Lux to NMT 3750 Lux and for amber colour containers [1]NLT 8000 Lux to NMT10000 Lux.

  [1]**Note:** 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.
- [2]During Inspection NLT 5 seconds is allowed for evaluation of visible particles against the black background and white background individually. Additionally for NLT 5 seconds for inspecting the vials from bottom, top and side walls any defects.

  [2]**Note:** Larger or more complex containers may require additional time for inspecting all attributes.
- Production Supervisor need to be collect randomly 20 vials from the inspected good vials for every one hour ± 10 minutes, as part of additional assurance
- AQL inspection performed by the Quality department after 100% inspection

Addition to this following mentioned good manufacturing practices are followed to enhance the environment/process controls,

- Only trained personnel/operators are permitted for in to the controlled area.
- Restricted Entry and Exit access for core manufacturing area for Injectable
- Microbial monitoring is performed by qualified personnel.
- Aseptic Working Practices inside the Filling Line Isolators performed by trained operator.
- Personnel are trained on the general practices like cleaning, preparation of autoclave load and CIP/SIP activity in critical area.
- Cleaning activity performed of area performed by trained personnel.
- Schedule medical check-up is performed for plant personnel and all personnel are instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.
- Single use disposable Tyvek suit use as a gown for injectable area entry
- Gloves should be sanitized frequently Prior to and throughout aseptic operations.

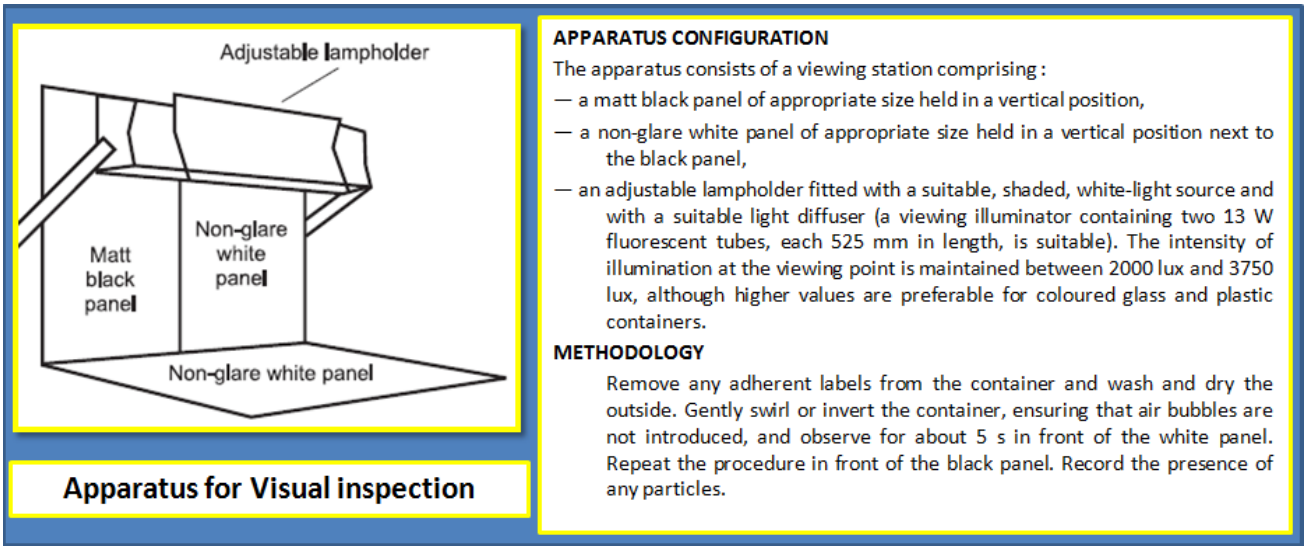


Figure 3: Inspection apparatus details

5. Inspection Kit preparation and challenges

The detection process is probabilistic; the likelihood of detection is a cumulative function of visible attributes such as particle quantity, size, shape, colour, density, and reflectivity. Understanding human performance is therefore critical to establishing visual inspection criteria. Individual receptors in the eye have a theoretical resolution of 11 mm, but typical resolving power is reported as 85–100 mm[1].

A single 50-mm particle in a clear solution contained in a clear 10-mL vial utilizing diffuse illumination between 2,000 and 3,000 Lux is only slightly greater than 0%[1].

The detection probability increases to approximately 40% for a seeded standard with a 100-mm particle and the threshold for routine, reliable detection (70% PoD) of individual visible particles is often near 150 mm in diameter and typically exceeds 95% for particles that are 200 mm and larger. The PoD for fibers of similar length is less than that discussed for spherical particles above, with reliable detection often commencing at or above 500 mm[1].

Thus, in a qualified visual inspection system, the vast majority of non-fibrous particles that might go undetected and be introduced into the pharmaceutical supply chain will be smaller than 200 mm.[1]

Changes to the container (e.g., increasing size and opacity), formulation (e.g., colour and clarity), fill level, and particle characteristics beyond size (e.g., colour, shape, and density) will all affect the PoD that can be achieved for a specific product and package.

5.1 Type of defect to be considered during development of kit,

Naturally occurring defects: These defects are considered from the actual defects observed in production,

- Represent the actual product and defects
- Expiry is short
- Need frequent inspection to verify its state of qualification
- Types of defects knowledge is based on the defect knowledge of the site
- Batch to batch variation

Intentionally created defects: These defects are created defects by an external laboratory or in-house laboratory,

- Not a true representation of actual rejects
- Comparability studies needs to be performed
- Creating defects ensures all defect types can be obtained at any point in time
- Longer Expiry
- Inspection frequency can be relaxed
- Types of defects knowledge is based on the overall defects in industry across sites
- UV marking for easy identification of defects from inspected units

5.2 Challenges in preparing Defect kits:

Defect kit preparation is very challenging task, before prepare we should understand about the inspection process and applicability of the kit on the selected process. Majorly inspection process is categorized in to part.

Manual / Semi automated inspection program

- Visual Inspector's training
- Visual Inspector qualification

Automated inspection program

- Automated inspection development
- Automated inspection setup
- Automated inspection qualification

5.3 Defect selection for kit development

Data analysis on deviations, complaints, production rejection trend to select the defects to be included in the defect library .Scientific Justification and rationale required for using Bracketing approach for selection of defects. It can be categorized as,

- Type of Container
- Size
- Fill Volume
- Typical Defect Type/Size

- Unique Product Characteristics-e.g. Aqueous , Non –Aqueous, Lyophilized powder
- Manufacturing Conditions-Equipment Setup, Filling Line Speed...etc.
- Inspection parameters-Equipment Setup/Solution Scan Time

5.4 Defect selection in qualification kits

- Having 5-20% defect containers mixed with acceptable containers
- Defect distribution (Critical: 5-7%, Major: 3-7%, Minor: 2-6%)
- Set-up kit needs to have 80% defect containers mixed with acceptable containers
- Batch size should to be considered that covers at least 2 eye rest

5.5 Defect kit particle size:

- Lowest particle which can be seen by an unaided eye
- The lowest detectable size for 20/20 human vision under controlled inspection conditions is generally accepted to be 50 µm. Now the question is, should particle size be ~50µ?

  The probability of detection for a single 50 µm particle is ~10%. This probability of detection increases approximately:
  - Up to 40% for a 100 µm particle
  - UP to 70% for a 150 um particle
  - UP to >80-90% for particles 200 µm and larger
- Particle size has to be of a size providing >70% detection probability

5.6 Qualification of defect kit

- Multiple inspections to be considered with a detection probability of >70%
- Qualified inspectors to be used for detection/identification
- No. of inspectors should be more to remove operator to operator variability
- No. of inspections depend upon detection probability
  - Higher detection probability, lower multiple inspection
  - Lower detection probability, higher multiple inspection
  - Generally varies between 10-30 inspection
- Defect categorization should be uniform
- Sufficient inspector pool (person to person variability)
- Acceptable units should not be rejected or should have a probability of detection less than 30%

5.7 Defect Kit maintenance: Defect sets are standards by which process is measured, they require careful maintenance,

- Should be ideally stored in the respective storage conditions for Naturally occurring defects
- Requalification is required frequently to ensure maintenance of detection probability
- Expiry to be defined
- Inspections prior to use to ensure the set is in good condition at all times
- Replacement and tracking of defects becomes damaged

Developing acceptance criteria: 100% defect identification by operator during qualification, its too stringent acceptance criteria. Guidance to setting acceptance criteria,

- Detection of 100% of critical defects
- Detection of ≥ 90% of major defects (For particulates)
- Detection of ≥ 80% of minor defects
- Also False Reject acceptance criteria are must. General acceptable value is LT 5%.

General recommendation to be considered for defect kit,

- It should be developed for each product/container family unless justified with scientific rationale
- All defect units should not have extraneous markings (UV preferred) or defects present that may result in false rejection or rejection for something other than the target defect.
- Need to have clear procedures with detailed descriptions of containers utilized in defect sets
- Clear benefits in having specialized group or specially trained individuals make sets
- Well designed and maintained defect sets are required to have successful manual and automated inspection operations
- Created defected should be evaluated as it provides lot of advantages

6. Typical inspection process flow

Manual visual inspection is the reference inspection method described in all of the major pharmacopeia. It consists of viewing filled and sealed containers under controlled conditions. 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.

Inspections of the vials are performed against black and white background. Defects are characterized in three categories,

- Critical type defects,
- Major type defects,
- and Minor type defects

Defect category	Critical defects	Major defects	Minor defects
Limit	NMT 1-2 %	NMT 2-3 %	NMT 3-4 %

Table 2: Limit of different category of defects for 100% inspection

Note: Limit can be set based on the in-house standard and historical trend data . Accumulated defect rate should not more than 5 %.

Lot or Batch Size	Sample Size Code Letter	Defect Category	Critical		Major		Minor	
		AQL	0.01%		0.4%		4.0%	
		Sample Size	Ac	Re	Ac	Re	Ac	Re
501 to 1200	J	80	0	1	0	1	7	8
1201 to 3200	K	125	0	1	1	2	10	11
3201 to 10000	L	200	0	1	2	3	14	15
10001 to 35000	M	315	0	1	3	4	21	22
35001-150000	N	500	0	1	5	6	21	22
150001 to 500000	P	800	1	2	7	8	21	22

Note: Reference for Sample and inspect the batch is taken from the ISO 2859-1.

Table 3: Proposed AQL values for inspection lot wise

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

Table 4: Typical AQL range of visual inspection process (as per USP<1790>)

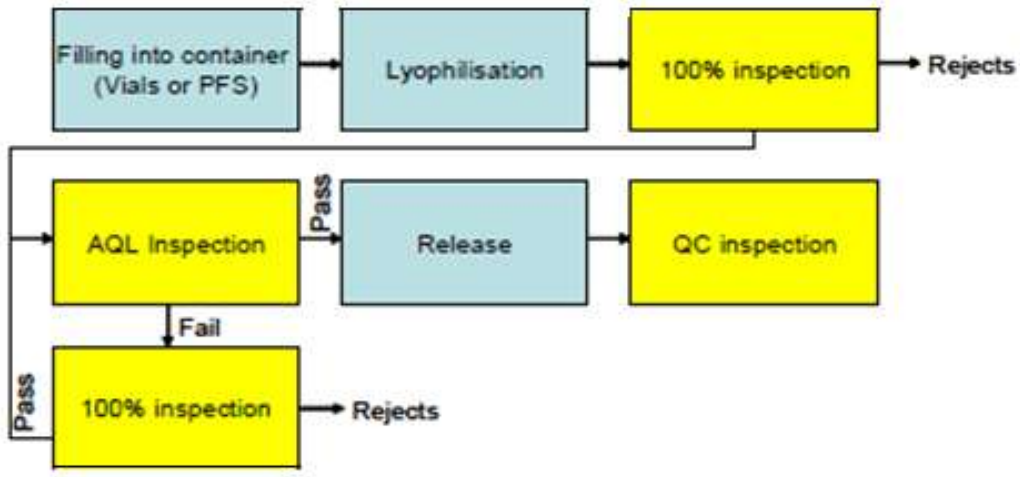


Figure 4: Inspection process flow for liquid & lyophilized product

Critical defects (those that pose the greatest risk to the patient) assigned an AQL with a very low value. The accepted number (the number of defective units allowed in the sample) for a critical defect is zero. **Major and minor defects**, which pose less risk to the patient, an increasing (less stringent) AQL values are assign and accept numbers greater than zero.

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 defined sample of units is reconstituted and inspected for visible particles in addition to the 100% inspection of the cakes for visible particles. Precaution has been taken during reconstitution of these samples to avoid contamination that can lead to false-positive results. Sample preparation was performed in a clean environment with appropriate particle-control measures. Then reconstituted samples were inspected using the same conditions as applicable for visible particles.

During AQL evaluation, if the acceptance limit is exceeded then entire batches are considered for 100 % re-inspected. Post 100 % Re-inspection, AQL sampling shall be performed and if the defect levels are well within the acceptance limit then batches are released for packing. If after re-inspection AQL is failed, the batches are considered for

their investigation disposition decision shall be taken based on the outcome of the investigation and in consultation with Head QA.

As per revised General Chapter <1790> Visual Inspection of Injections on dated May1, 2018 it is recommended to adopt sampling plans S-3 and S-4.

Guidance reference from USP <1790>:

"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."(6)

AQL Range 0.01%-0.25%								
Lot or Batch Size	S-3				S-4			
	Sample Size Code Letter	Sample Size	Ac	Re	Sample Size Code Letter	Sample Size	Ac	Re
501 to 1200	E	13	0	1	F	20	0	1
1201 to 3200	E	13	0	1	G	32	0	1
3201 to 10000	F	20	0	1	G	32	0	1
10001 to 35000	F	20	0	1	H	50	0	1
35001-150000	G	32	0	1	J	80	0	1
150001 to 500000	G	32	0	1	J	80	0	1

Table 5: Proposed AQL values of visual inspection of reconstituted Lyophilized vials

The degree of control in a sampling inspection is selected by specifying one of the following controls Level:

Normal Inspection: AQL = 2X the required quality level. This inspection is intended to detect a breakdown in process control signalling the need to shift to a tightened inspection. It is intended to protect against unusual quality deterioration by direct rejection of batches.

Tight Inspection: AQL = the required quality. The inspection itself is intended to give complete protection against unsatisfactory quality.

Reduced Inspection: AQL = 3X the required quality level. This inspection is intended to detect a breakdown in process control signalling the need to shift to a tightened inspection. It is intended to protect against unusual quality deterioration by direct rejection of batches.

The Normal Inspection as shown above is set equal to twice the required quality level. This quality level is selected to indicate major deviations from the quality level desired. It cannot provide the sensitivity required for sensitive monitoring of batch quality.

7. Qualification of Inspector

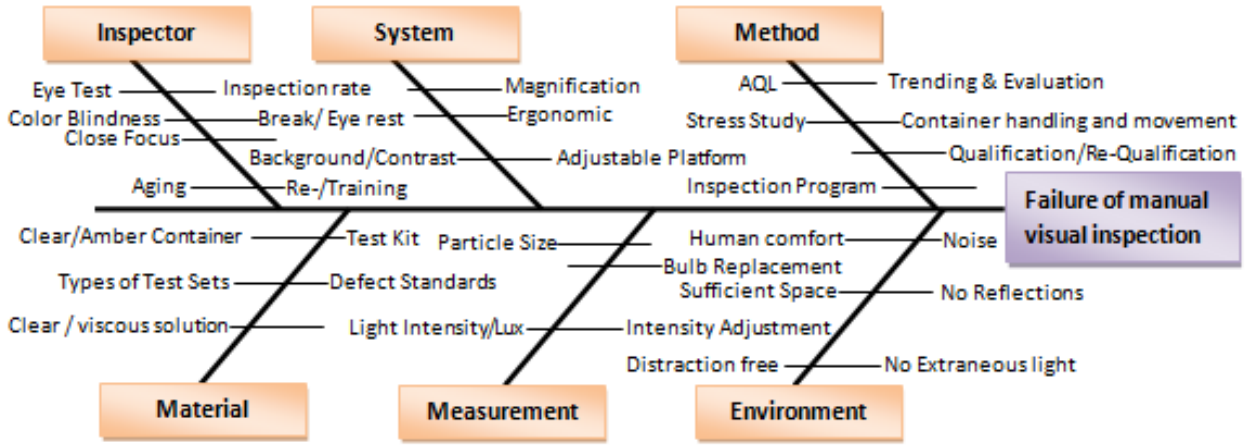


Figure 5: Fishbone for identifying the failure of inspection process

Manual visual inspection is very challenging procedure. Number factors are identified as parts of fishbone analysis (Ref. figure 5) which have direct or indirect impact on the inspection process. All the contributing factors are briefly describe below,

7.1 Inspector:

- Personnel involved in the visual inspection should regularly undergo an eye test. The optometrist should focus on the ability to discriminate small differences in uniform structures, e.g. open/closed circles.
- 20/20 vision test , Vision color acuity and depth perception test to be include
- Read & Understand - Procedures and Work Instructions
- Inspector age need to be considered, high age will decrease the detection capability
- ECA recommends, a good practice is 20 minutes of inspection, followed by a break of at least 5 minutes for a total maximum duration of not longer than 4 hours. Uninterrupted inspection activity should not exceed 40 minutes. This break should allow time to rest the eyes and mind, and may be achieved with a short rest (e.g., 5 min) or a longer meal break. This need for regular breaks may also be met through rotation to a non-inspection function, such as material handling or documentation.

7.2 System:

- Inspection stations should be designed and operated in a manner that minimizes the inspector's risk of repetitive-motion injury.
- Adjustable chairs and careful positioning of light sources as well as incoming and inspected product can reduce the risk of such injury.
- These adjustments can also reduce inspector fatigue and discomfort, both of which can be distracting and thus can decrease performance.
- The inspection room environment should also be considered. Temperature and humidity should be controlled for inspector comfort.
- Reduced ambient lighting is recommended to focus the inspection process and to reduce distraction from extraneous reflections.
- Special care should be given to inspection rooms with exterior windows that allow daylight into the room and thus changing ambient lighting throughout the day and with changing seasons.
- The three articles written by Budd [4,8,26] clearly discuss concepts on inspection environment. These articles demonstrate by illustration on how to hold the vial at the optimal angle for agitation and inspection. One illustration clearly demonstrates the angle of the eye to the object. Another illustration clarifies the distance between the pupil and the object being inspected. This information specifies the correct distance of close focus position of the eye and object being inspected (150–250 mm).
- According to the companies participating in the PDA surveys, the use of magnification has declined through the years. At present, approximately 26% of participating companies use magnification [21].
- As discussed by Budd [20], the curvature of a vial's circular shape and the index of refraction of filling fluid create an imperfect lens due to distortion. In a similar way, the curved surface of a magnifying lens creates similar distortion, which makes the particle size vary depending where it is located. Containers, such as small syringes, are difficult to examine and the use of magnification may be advantageous in such circumstances as long as the optical distortion is understood and controlled[18]. Once qualified, the use of magnification must be used consistently for that specific product. The line inspector is not free to make a decision on its use, once the process is qualified.

7.3 Method:

Defect Set Test should have:

- 80% good product; 20% defective product
- Approx. 120 containers
- 1 gross example of each categorized defect type
- Inspector must catch 100% of defective product
- Inspector must not false reject more than 5% of good product
- Visual inspection standards may be identified from known production rejects, or may be created manually with characterized particulate material.
- A single particle per seeded container should be used when determining detection thresholds. The use of multiple particles in a container is not recommended in order to avoid skewing the data by increasing the PoD.

7.4 Material:

The primary packaging materials that directly contact the product and the potential environmental contaminants can be divided into specific particle groups such as glass, stainless steel, elastomeric closure, plastic, and fibers (synthetic or natural). All such material shall be procured from qualified vendor source.

Apart from that the type of packaging material (e.g. clear or amber color) and type of product content (e.g. liquid or viscous) contribute more complication during inspection program.

7.5 Measurement:

- Selection of range of particle for kit preparation
- Measurement of Lux level occasionally and replacement of inspection bulb
- Variable intensity will be a useful entity for ember color or opec container
- Qualification test set: the qualification test set consists of product specific containers containing the product and having all known "static" defects (scratches, wrong flip-off, missing stopper...). Usually, about 10-20% of the containers of the set have a defect. New failures or defects are added to the qualification test set.
- Particle test set (Knapp-Test): Sets that contain only particles. These are particles having the size from 50µm to 1000µm and consisting of different materials (plastic, the material stoppers are made of, glass, metal). Hence, they are "non-static", i.e. the defect is in the container or in the drug solution. Particle test sets are part of the qualification test set at the same time.

7.6 Environment:

A well-designed inspection room is free from distractions, extraneous light and is ergonomically designed for inspector comfort. Inspection rooms may consist of a number of independent inspection booths operated as separate units or they may be connected in series on a paced line. Both arrangements are acceptable providing the pacing time provides effective inspection and is qualified[10].

Training and qualification for the manual visual inspection of finished product comprises of three phases.

Phase I: Training, Eye check-up and Defect recognition training

Phase II: Qualification / Re qualification

Phase III: On the Job training

Frequency of Eye Check-up:

Periodic eye check-up performed for every 6 months±15 Days. During periodic eye check-up if any discrepancy noticed in the inspector eye sight incident investigations to be initiate.

Inspector must meet the following acceptance criteria during phase II and phase III stage of qualification,

- Detection of ≥100% of Critical defects
- Detection of ≥90% of Major defects
- Detection of ≥70% of Minor defects
- False Reject Rate of ≤5%.

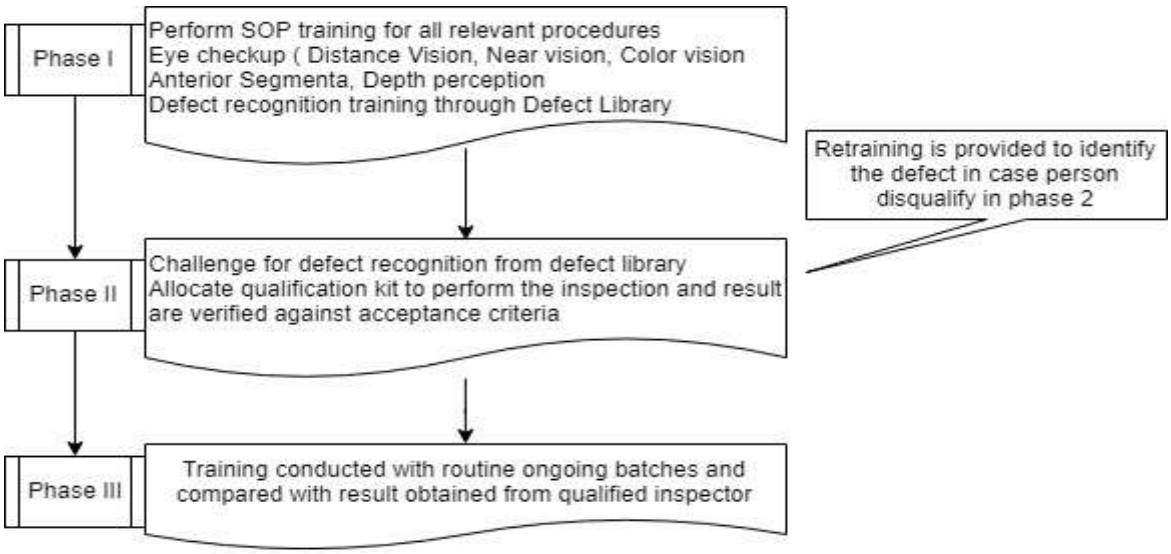


Figure 6: Process flow for qualifying the visual inspectors

8. Establishment of Inspection Process

Qualify an inspector using a test set that is representative of the product to be inspected.

For example, if the product to be inspected is lyophilized, qualify the inspector using the lyophilized test set.

- Inspectors are qualified if their detection of rejects is ≥ 70% detection of known rejects and ≤ 30% of blanks (false reject) in any given test set. The inspector must meet this requirement three (3) times before being considered a qualified manual visual inspector.
- The trainee is trained on the operation of the manual inspection booth.
- The trainee is shown the rejects within the test set to be trained upon.
- Each of the rejects is described as the trainee inspects the rejects within the test set. A blank is also given for inspection as well.
- Ensure that operators spend appropriate time (5+ seconds against each colored background) with each product container during the visual inspection process.
- The reject vials are then mixed in with the rest of the test set and the trainee inspects each vial while being observed by the trainer. The trainee inspects all of the vials and notes the defect code for the reject vials while maintaining separation of the rejects and the blanks.
- Upon completion the trainer compares the trainee's determinations to the actual defects/blanks. ≥ 70% detection of known rejects and ≤ 30% of blanks (false reject) is required to pass. The trainee repeats the inspection process until successfully passing three (3) times.
- The Trainer documents ea4.1ch trainee inspection on the Visual Inspector Qualification Form.

Inspector Re-Qualification Schedule:

- Visual inspectors are re-qualified annually.
- If inspection performance declines, re-qualification may be required in shorter time-frames.
- Common causes of declined performance that may lead to a need for requalification include fatigue, demonstration of an improper reject rate during operations, etc. and/or causing excessive product investigations.
- Annual eye sight exams at optometrist for visual acuity with 20/20 vision or 20/20corrected. If eyesight is corrected with eye glasses or contact lenses, then those must be worn during the product inspection process.

9. Evaluate Customer complaint

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

For the release decision two criteria need to be evaluated:

1. Trending analysis of the 100% batch inspection (see section 5) and
2. The AQL manual inspection.

The results of the 100% visual inspection, done as part of the manufacturing process, should be available in an easily readable format to the Qualified Person, responsible for the release decision. In addition to listing the defects found in the Visual Inspection process the batch documentation must contain a listing of the type of defect found (fiber, turbidity, crack, etc.) as well as a classification of the defect such as critical, major or minor. Acceptance criteria must be pre-defined for these defect classes as well as for a sum of all defects found during the 100% inspection process. For the AQL manual inspection a randomized sampling of the 100% inspected batch should be performed according to a pre-determined AQL procedure. AQL manual inspection can be carried out by production or the quality unit[1].

Upon receipt, suspect containers should be subjected to the same inspection conditions and methodology used in the release inspection. Particle(s) verified in the returned or re-evaluated supply must be carefully characterized by an analytical forensic process to determine their source and likely cause. Single particles of typical product-contact materials are unlikely to present a concern. Multiple particles, large particle sizes, and any particles indicative of physical or chemical change are significant events and should be subject to further investigation.[1]

10. Expectation of Regulators

Visual inspection remains to be an important part of the manufacturing process and the quality assurance of injectable products. Product inspection provides required information for lot release, and, additionally it provides clarity on defect identification and contributes for continuous process improvement. Particulate matter contamination has become the #1 reason for recalls of the US-FDA.

The current inspection methods and acceptance criteria for particle matter in injectable products may be found in the national or regional pharmacopeia. For the U.S. market, the

U.S. Pharmacopeia (USP) General Chapter <788> Particulate Matter in Injections has been official for many years. It defines two methods for counting sub visible particles and sets limits of 6,000 and 600 particles per container for ≥10 μm and ≥25 μm particles, respectively. These limits apply to containers ≤100 mL. As this is a harmonized chapter, the same methods and limits are found in the European Pharmacopeia (EP) and the Japanese Pharmacopeia (JP).

Requirements for visible particles are found in USP General Chapter <1> Injections. The requirement set in this chapter is that every final container is inspected for particles to the extent possible, and any showing the presence of observable foreign and particulate matter are rejected. It further requires that "the inspection process shall be designed and qualified to ensure that every lot of parenteral preparations is essentially free from visible particulates" (2). General Chapter <790> Visible Particulates in Injections was published in the first supplement to USP 37 and became official August 1, 2014 (1). This chapter establishes reference inspection conditions and provides quantitative limits based on acceptance sampling to meet the expectation for every lot to be essentially free from visible particles. The inspection conditions are harmonized with those found in the EP (3).

"The intent of USP General Chapter <790> was to move towards a global standard to define what is visible by defining a common set of inspection conditions:

- An inspection light intensity of 2000 to 3750 LUX
- Inspection for five seconds against black and white backgrounds
- The container should be swirled or inverted during the inspection provided that this does not damage the product.
- The inspection processes applies to extrinsic (coming from outside of the process) and intrinsic (coming from processing equipment and the primary packaging).
- Defines the use of accepting sampling for batch release, after 100% inspection, using a General Level II sampling plan from ANSI/ASQ Z1 .4 standards with an AQL of 0.65%. ISO 2859 also provides an equivalent sampling plan. "

The scope of USP <1790> includes manual inspection but also extends to other visible defects such as container integrity and other inspection methods such as semi - automated and automated systems.

USP <1790> provides the following information:

Introduces the concept of the inspection lifecycle to help identify types of particulates and their source with the goal of continuous improvement and reduction in particulates throughout the process,

- Provides more detailed discussion on the risk of particulates to patients to aid in risk assessments.

- Provides recommendations and methods for the proper preparation of test sets to assess manual inspection performance and to qualify inspectors. These procedures may be applied to the qualification and validation of semi-automated and automated inspection processes.

Additional requirements for products marketed in Europe can be found in the Finishing of Sterile Products section of the European Medicines Agency Annex 1. This section sets the requirement that "filled containers of parenteral products should be inspected individually for extraneous contamination or other defects." It also sets an expectation that inspectors pass regular vision tests and that frequent breaks be given to avoid fatigue. The EP, in Parenteral Preparations Injections (0520), specifies "solutions for injection, examined under suitable conditions of visibility, are clear and practically free from particles." It follows with an inspection method described in 2.9.20 Particulate Contamination: Visible Particles. This section specifies illumination intensity, background, and pace for the conditions suitable for inspection.

Visual inspection, and especially the detection of particles, remains at the centre of many discussions regarding product manufacturing control, quality assurance and regulatory compliance. From 2008 to 2012, 22% of all injectable product recalls in the USA were associated with visible particulate matter. Particle related recalls rise from 3 in 2008 to 41 in 2014.

During this same period, the number of particle related FDA 483 observations are reported. This is likely an indication of heightened sensitivity by both regulators and manufacturers', rather than a measure of decreasing product quality.

The Parenteral Drug Association (PDA) and the United States Pharmacopeial Convention (USP) have been working to educate and provide guidance to the industry in the hope of establishing consistent, practical guidelines and best practices that will lead to improved quality and reduced recalls due to visual defects. Technical Report No. 79, Particulate Matter Control in Difficult to Inspect Parenteral is the latest publication by PDA, this technical report is intended to provide logical pathways to DIP (difficult-to-inspect parenteral) inspection and testing to support continual process improvement in the industry.

The 100% inspection (100% inspection of injectable products including: cracks, visible particles and other significant defects) of the final filled and sealed product may occur via a manual, automated, or semi-automated inspection process. Manual and semi-automated inspection processes involve specified viewing fields and calibrated light sources. Semi-automated processes may use conveyor belts and rotational units that present the filled product to an operator for visual inspection. All conveyor and rotational speed set points

should be verified against established parameters. Automated inspection systems may inspect for one or all types of defects in a given filled product. Defect categories with relevant action levels should be defined.

Inspectors are intent to review the following things from your inspection process,

- The qualification of the equipment and the challenges performed to verify equipment functionality prior to routine use should be evaluated as well as the training program for operators performing manual visual inspections.
- Written procedures should define the defects to be removed from the lot and actions to take if the number of critical defects exceeds a pre-determined level.
- Significant defect categories should be identified.
- Results of inspection of each batch should be compared to established action levels.
- Evaluate the appropriateness of and the rationale or justification for pre-determined action levels.
- Evaluation of the investigations performed for the cause of rejects, including units rejected for cracks and as well as visible particulates (e.g., foreign matter).
- Evaluate the adequacy of written procedures for visual inspection.
- How the inspection process is conducted for routine commercial batches?
- Challenge visual/manual inspection rates through observation.
- Evaluate personnel qualification and requalification and equipment qualifications according to established procedures.
- Evaluate personnel qualification including the use of reference samples for qualification.
    - If a manual system is used, determine if employees are trained and qualified to verify they can recognize and remove defects under actual or simulated production conditions.
    - If an automated or semi-automated system is used, determine the equipment is qualified and the software program or equipment settings have been validated for all types of products being inspected (e.g., clear vials, amber vials, colour solution, suspensions).
    - If the equipment is an automatically controlled computer based system, an assessment of the system and validation is warranted.
- Evaluate the firm's program for sampling and examination of inspected vials and evaluate the effectiveness of inspection and action taken if the reject level is reached.
- Evaluate the firm's assessment of units rejected during filling operations (any separate inspection prior to the 100% inspection stage), established alert/action limits, and investigations where appropriate.

11. Summary and conclusion

11.1 Summary:

Visual inspection for particles and other visible defects continues to be an important part of the manufacturing process for injections. Good product development will lead to a stable product with a lower risk of particle formation. Identification of the type or types of particles found during product development and routine manufacturing is an important aid in source identification and reduction. Inspection results should be trended to further aid in continuous process improvement with the ultimate goal of defect prevention.

The capabilities and limitations of visual inspection illustrate the rationale for this principle. Neither human manual inspection nor fully automated inspection systems can provide assurance of particulate-free products. Visual inspection is a probabilistic process, with detection probabilities less than 100%, especially for particles less than 200 mm in diameter. Visible particle testing is influenced by multiple, highly variable factors such as drug and container clarity, lighting, particle size, optical density, refractive index, colour, contrast, and operator or automated inspection sensitivity and reliability.

And the most intensive prevention and inspection strategies should be targeted at the processes that control attributes most likely to affect patient safety. Manufacturing in conformance with cGMP assures that a drug is safe and has the characteristics of identity, strength, quality and purity that it purports or is represented to possess, by rigorously controlling the manner of production. If manufacturing processes do not comply with cGMP, the product is adulterated. The goal of cGMP is to assure that manufacturing processes consistently produce products that meet predetermined specifications by controlling all phases of drug product manufacturing, including particulate control.

11.2 Conclusion**:**

This paper provides insights towards the approaches followed for visual inspection process for identifying particle defects in Lyophilied product. Inspection process, inspector training, Kit preparation, process defect library maintain, source identification and failure investigation are the major key steps for robust visual inspection process. Based on the holistic review it can be concluded that current methodology are adequate and complies with the regulatory requirement.

However overall batch quality using internal systems to control particulate matter and the means to investigate these occurrences is key to the life-cycle approach for pharmaceutical production. Evaluation of retention and stability samples provides insight to batch quality, as do the field-use effects for any medication. While the presence of particles or product or container defects discovered in retained or returned product do not necessarily incriminate the quality of the batch, careful investigation should be conducted to exclude systemic risks.

12. Information about Inspection Process

Before we are discussed about the inspection process of particulate matter in the parenteral and particles nomenclature, we should understand the different range of particle size and its identification methodologies.

Particulate size range:

<100 nm	100 – 1,000 nm	1 – 100 µm	>100µm
Nanometer	Sub-micron	Sub-Visible	Visible
• SEC (Size Exclusion Chromatography) • FFF (Field Flow Fractionation) • SDS-Page Gels AUC (Analytical Ultra-Centrifugation)		• Light Obscuration • Microscopy • Flow Microscopy • Coulter Counter	• Manual / Human • Semi-Automated • Automated

Faulty Visual inspection process is one of the major burning issues of pharmaceutical industry. Industries had received number of 483 observations so far. Major drawback is none of the guidance is providing clear idea about the inspection process.

	USP <790>	Ep 2.9.20	JP 6.06
Illumination intensity (Lux)	2000-3750	2000-3750	2000-3750 (8000-10000)*
Inspection time (sec)	10 sec	10 sec	10 sec
Background	Black/white	Black/white	Black/white
Acceptance Criteria	"Essentially free from visible particulates" ANSI/ASQ Z1.4 AQL=0.65%	"Clear and practically partially-free "	"Free of readily detectable foreign insoluble matter "

13. Defect Library

Defect library is one of the most important thing what firm need to creat . It will not only helpful for the visual inspector qualification and additionally it will work as a refrance for qualified inspector too. Any newly observed defect should to be added to defect library.

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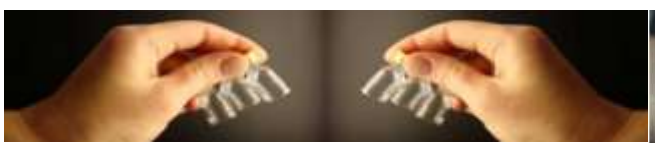


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