SOP Title: Inspection of Unlabeled Vials of Finished Products
SOP Number: 15113
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1. PURPOSE

This SOP specifies Biopharmaceutical Development Program (BDP) requirements for the visual inspection of unlabeled vials of finished product produced under CGMP.

2. SCOPE

All vials will have been filled with container closure in place prior to inspection. Inspection of vials is a joint effort by Manufacturing and Process Analytics/Quality Control (PA/QC) personnel with assistance by Biopharmaceutical Quality Assurance (BQA) personnel as indicated in the SOP. Each qualified inspector may perform Manufacturing or PA/QC inspection during a run but may not perform both functions on the same pan of vials.

Manufacturing performs a 100% inspection of unlabeled vials of finished product. Vials with irregularities categorized as “minor”, “major” and “critical” are culled from the batch. A subsequent sampling of vials is screened by PA/QC to monitor the quality of the inspection performed by Manufacturing. This sampling is conducted according to ANSI/ASQC Z1.4, General Inspection Level II. Acceptable Quality Levels have been established for minor (AQL = 6.5), major (AQL = 1.5) and critical (AQL = 0.1) defects. After screening by PA/QC, any sublot exceeding the applicable alert limits will require the sublot to undergo a 100% screening by BQA. After the entire lot has been processed, defects detected by all phases of inspection (Manufacturing, PA/QC, and BQA) are tabulated and investigated if the total lot defect rate exceeds established limits.

For each lot, the complete cycle of inspection (Manufacturing inspection, PA/QC inspection, BQA inspection) is performed in sublots associated with pans of material so that individual pans can be cleared for labeling (to be performed at another location) while later sublots are simultaneously working through the unlabeled vial inspection process. This organization of the inspection process allows screened and acceptable sublots to proceed to labeling eliminating the need to wait for the unlabeled vial screening process to be completed for the entire lot before labeling can start. This reduces the interval that product is exposed to ambient conditions.

In addition, for products that are particularly labile and could likely be adversely affected during the inspection process, a focused inspection to detect critical defects is described. This focused inspection reduces the scope of inspection to detect critical defects only and therefore reduces the time required to complete the inspection. Focused inspections for labile products protect product identity, strength, quality, purity, and safety by minimizing the potential adverse impact to a product that could result from a prolonged standard inspection process.

Inspectors are trained on visual inspection of unlabeled vials by reviewing a training panel that contain both acceptable and unacceptable vials. When ready, inspectors then are tested by performing a vial inspection as they would for a final vialed product on a qualification panel that contains a mixture of acceptable and unacceptable containers. In order to pass the qualification, they must correctly detect 80% of acceptable vials and correctly detect 80% of unacceptable vials. Inspectors are recertified for visual inspection every two years.

3. RESPONSIBILITIES

3.1 Director, Technical Operations, BDP

- Defines this procedure.

3.2 Manufacturing

- Screens (and documents) 100% of unlabeled vials of finished product.
- Calculates (and documents) of total lot defects.
- Investigates for lots or sublots that exceed quality limits.
- Recertifies every two years for visual vial inspection using the Vial Inspection Requalification Panel.

3.3 Process Analytics/Quality Control (PA/QC)

- Screens of sublots (and documentation).
- Screens (and documents) 100% of unlabeled vials during validation lots.
- Calculates of total sublot defects from PA/QC screening.

- Evaluates the disposition of each sublot (need for additional QA screening).
- Recertifies every two years for visual vial inspection using the Vial Inspection Requalification Panel.

3.4 Biopharmaceutical Quality Assurance (BQA)

- Provides Quality oversight.
- Performs 100% screening of each sublot that fails quality limits.
- Inspects each rejected vial (if quantity of rejects exceeds limits) using enhanced vision (lighting and magnification) to confirm the PA/QC failure of the rejected vial.
- Assists in investigation for lots or sublots that exceed quality limits.
- Recertifies every two years for visual vial inspection using the Vial Inspection Qualification Panel.

4. EQUIPMENT

- Light boxes with black and white backgrounds
- Inspection Station (Eisai)
- Magnifier Illuminated (VWR #36935-100 or equivalent)
- Microscope

5. PROCEDURE

5.1 Check that the lamp(s) used in the inspection equipment are working. Should any lamp not be illuminating, do not use that station until the lamp is repaired or the bulb replaced with another of the same output.

5.2 Manufacturing Screening

5.2.1 Designation of Sublots

5.2.1.1 Manufacturing Filling Staff will designate pans of material as specific sublots. The first pan of material will be designated as “Sublot A,” subsequent pans would be designated “Sublot B,” “Sublot C,” et cetera.

5.2.1.2 **Form 15113-01** is initiated by Manufacturing for each sublot of glass vials.

5.2.1.3 **Form 15113-03** is initiated by Manufacturing for each sublot of cryovials.

5.2.1.4 **Form 15113-05** is initiated by Manufacturing for each sublot or lyophilized product vials.

5.2.1.5 The number of vials contained in each pan/tray (sublot) is recorded on **Form 15113-01, 15113-03, or 15113-05**.

5.2.2 Examination and Culling of Vials

5.2.2.1 For each sublot, Manufacturing will conduct a visual inspection of all vials.

5.2.2.2 Choose an area that has good lighting and adequate counter space to perform the operation. In some instances, product may be light sensitive and special precaution should apply that may change illumination light type/source, duration of the inspection, et cetera. Any such special handling should be noted on the inspection forms.

5.2.2.3 Choose equipment as appropriate from Section 4.0 to perform the vial inspection.

5.2.2.4 Place each vial, illuminated from below, against the black and white backgrounds and inspect for defects. If an inspector is uncertain whether any vial is acceptable, the inspector may look at the vial using enhanced visual inspection.

5.2.2.5 Cull and segregate any vials possessing a minor, major, or critical defect.

5.2.2.6 Segregate culled vials by minor, major, and critical defects. If desired, additional categorized “cull boxes” can be used to categorize and segregate culled vials during the inspection process.

5.2.2.7 Retain culled vials until the need for an investigation has been determined.

5.2.3 Tabulation and Documentation of Results

5.2.3.1 For each sublot, Manufacturing will document the results of their inspection using **Form 15113-01, 15113-03, or 15115-05**.

5.2.3.2 A subtotal of minor, major and critical defects for each sublot is performed and recorded on **Form 15113–01, 15113-03, or 15113-05.**

5.2.4 Document Sign-off

Manufacturing inspectors will indicate the inspection equipment used and sign off on the document.

5.3 Process Analytics/Quality Control Screening

5.3.1 Sampling

PA/QC will collect a random sampling of vials throughout the batch according to ANSI/ASQC Z1.4, General Inspection Level II. This sampling plan is reproduced in Table 1, below.

NOTE: Table 1 is not used when PA/QC is performing 100% inspection.

Sublot (pan) Batch Size	**Sample Size**	**ACCEPTANCE/REJECTION CRITERIA**		
		Minor Defect AQL = 6.5	**Major Defect AQL = 1.5**	**Critical Defect AQL = 0.1**
2 to 8	2	Accept with 0, Reject with 1	Accept with 0, Reject with 1	Accept with 0, Reject with 1
9 to 15	3	Accept with 0, Reject with 1	Accept with 0, Reject with 1	Accept with 0, Reject with 1
16 to 25	5	Accept with 0, Reject with 1	Accept with 0, Reject with 1	Accept with 0, Reject with 1
26 to 50	8	Accept with 1, Reject with 2	Accept with 0, Reject with 1	Accept with 0, Reject with 1
51 to 90	13	Accept with 2, Reject with 3	Accept with 0, Reject with 1	Accept with 0, Reject with 1
91 to 150	20	Accept with 3, Reject with 4	Accept with 0, Reject with 1	Accept with 0, Reject with 1
151 to 280	32	Accept with 5, Reject with 6	Accept with 1, Reject with 2	Accept with 0, Reject with 1
281 to 500	50	Accept with 7, Reject with 8	Accept with 2, Reject with 3	Accept with 0, Reject with 1

5.3.2 Examination and Culling of Vials

Perform this operation in the same manner as Manufacturing, (See Section 5.2.2).

5.3.3 Tabulation and Documentation of Results

Perform this operation in the same manner as Manufacturing, (See Section 5.2.3).

5.3.4 Evaluation and Documentation of Screening Results

For each sublot, PA/QC will total the defects encountered by Manufacturing and PA for minor, major, and critical defects. PA/QC will evaluate and document the results of their inspection on **Form 15113-01, 15113-03, or 15113-05** according to **Table 1** as:

- Inspection results ACCEPTABLE, sublot may proceed to labeling (BQA inspection not required).

OR

- 100% BQA inspection and/or Investigation required of sublot before proceeding to labeling. PA/QC will indicate which Acceptable Quality Limit (AQL) has been exceeded (major, minor, or critical).

5.3.5 Document sign-off

PA/QC will sign off on **Form 15113-01, 11513-03, or 15113-05**.

5.4 Quality Assurance Screening

5.4.1 Quality Assurance (as requested) will inspect the rejected vials using enhanced vision (lighting and magnification) to confirm the correct classification of the rejects. QA may change the reject classification to another classification including acceptable. This change will be documented and justified.

5.4.2 Quality Assurance will perform a 100% screening of individual sublots when PA/QC inspection results exceed alert limits.

5.4.3 The screening process is conducted in a similar manner to Manufacturing Screening (See SOP Section 5.2)

5.4.4 QA Screening is documented on **Form 15113-02, 15113-04** or **15113-06**.

5.5 Summary of Results

5.5.1 **Forms 15113-07** and **15113-08** will be completed to capture inspection results for all sublots comprising the entire lot.

5.5.2 The overall lot defect rate (in %) will be calculated and evaluated against established limits (critical < 2%, major < 10%, minor <15%).

5.5.3 An investigation will be conducted for lots exceeding established limits.

5.6 Additional Inspection Criteria

NOTE: Depending on the product, additional inspection criteria may be appropriate.

5.6.1 Justification for Additional Inspection Criteria

5.6.1.1 The need for additional inspection criteria is indicated on **Form 15113-01, 15113-03, or 15113-05**, and will be justified in a memo attached to the screening forms signed by the Project Scientist and BQA.

5.6.1.2 The memo will specify how the additional inspection criteria will be documented and the acceptance/rejection criteria that will be applied.

6. FOCUSED PROCEDURE FOR LABILE PRODUCTS

NOTE: For labile products, where the time required to complete a standard inspection could affect the product's potency or integrity, a focused screening may be conducted at the initiation of the Project Scientist with approval from BQA.

6.1 Justification for Focused Screening

6.1.1 The need for a focused screening is indicated on **Form 15113-01**, Form **15113-05 or 15113-03** and will be justified in a memo attached to the screening forms and signed by the Project Scientist and BQA unless justification for focused inspection is included in the BPR.

6.1.2 Any screening performed by Manufacturing, PA/QC and BQA will be identical to that described in Section 5.0 except that the focus will be on critical defects only.

6.2 Acceptance/Rejection Criteria

Acceptance/rejection criteria for a focused inspection will apply only to results for critical defects.

7. GLASS VIAL DEFECTS

NOTE: Glass vials and their closures may possess a variety of irregularities that may or may not affect a product's identity, strength, quality, and/or purity. Irregularities that may have a detrimental effect on a product are considered defects and are culled from the lot. Defects are categorized as minor, major and critical based on their potential to impact the product.

7.1 Vial Irregularities and Defects

7.1.1 Scuffing and minor scratches - Scuffing and minor scratches are not considered defects and are not culled from the lot.

7.1.2 Significant scratches – Significant scratches are considered a minor defect and shall be culled from the lot. Scratches are the result of vial handing and can vary in depth and length.

7.1.3 Pitting Significant pitting of the vial is considered as a major defect and shall be culled from the lot. Pitting is a result of glass manufacturing defects.

7.1.4 Internal glass strands - fisheyes, glass particles. Internal glass strands, fisheyes, and glass particles are considered critical defects and shall be culled from the lot.

7.1.5 Cracks/Chips - Cracks and chips are considered critical defects and shall be culled from the lot.

7.1.6 Vial residue - Residue on the inside or outside of the vial is considered a defect and shall be culled from the lot. Residue on the outside is considered a minor defect if it cannot be removed with minor wiping and residue on the inside is considered critical.

7.2 Crimp Irregularities and Defects

7.2.1 Physical deformities. Dents and other physical deformities of the crimp including damage to or a missing flip off cap are considered defects and shall be culled from the lot.

7.2.2 Inconsistent rounding-under. Crimps that are not consistently rounded under the neck of the vial are considered a defect and shall be culled from the lot.

7.2.3 Loose crimps. Crimps that are loose are considered a defect and shall be culled from the lot.

7.3 Product Irregularities and Defects

7.3.1 Particulate material. Particulate material including “floaters”, “sinkers”, fibers or other foreign material is considered a defect and shall be culled from the lot.

7.3.2 Cloudiness. Atypical cloudiness is considered a defect and shall be culled from the lot.

NOTE: Certain products (e.g. emulsions, suspensions) which under normal conditions appear cloudy should not be rejected unless the cloudiness is atypical, as would be the result of contamination, et cetera.

7.4 Fill Irregularities and Defects

Overfills and underfills. Vials determined visually to be overfilled or underfilled are considered a defect and shall be culled from the lot.

8. CRYOVIAL DEFECTS

NOTE: Cryovials and their closures may possess a variety of irregularities that may or may not affect a product’s integrity. Irregularities that may have a detrimental effect on a product are considered defects and are culled from the lot. Defects are categorized as minor, major and critical based on their potential to impact the product Cryovial Irregularities and Defects.

8.1 Vial Irregularities and Defects

8.1.1 Scuffing and scratches. Scuffing and minor scratches are not considered a defect and are not culled from the lot.

8.1.2 Physical deformities. Dents and other physical deformities are considered a defect and shall be culled from the lot.

8.1.3 Internal plastic strands or plastic particles. Internal plastic strands or plastic particles are considered a defect and shall be culled from the lot.

8.1.4 Cracks. Cracks are considered a defect and shall be culled from the lot.

8.1.5 Cryovial residue. Residue on the inside or the outside of the cryovial is considered a defect and shall be culled from the lot.

8.2 Cap Irregularities and Defects

8.2.1 Physical deformities. Caps missing gaskets, damaged threads or other physical deformities are considered a defect and shall be culled from the lot.

8.2.2 Loose caps. Caps that will not thread properly or are otherwise loose are considered a defect and shall be culled from the lot.

8.3 Product Irregularities and Defects

8.3.1 Particulate material. Particulate material including “floaters”, “sinkers”, fibers or other foreign material are considered a defect and shall be culled from the lot.

8.3.2 Cloudiness. Atypical cloudiness is considered a defect and shall be culled from the lot.

NOTE: Certain products (emulsions, suspensions) which under normal conditions appear cloudy should not be rejected unless the cloudiness is atypical as would be the result of contamination, et cetera.

8.4 Fill Irregularities and Defects

Overfills and underfills. Cryovials visually determined to be overfilled or underfilled are considered a defect and shall be culled from the lot.

9. LYOPHILIZED PRODUCTS IN GLASS VIALS

NOTE: Lyophilized products present inspection challenges that are not encountered with liquid filled vials. The product is usually in the form of a dry “cake” at the bottom of the vial. The Director of Manufacturing and QA shall be notified of any vials exhibiting discoloration, meltback/collapse, missing or shredded cakes, or other irregularities. An investigation may be necessary. Most cake related defects are considered critical.

Sample lyophilized vials should be provided by the Project Scientist as example vials for use by inspectors during inspection. Whenever possible, examples of acceptable cakes and non-acceptable cakes should be provided.

9.1 Vial Irregularities and Defects

Inspect vials as per Section 7.1 and 7.2 above.

9.2 Product Irregularities and Defects

9.2.1 Particulate material - Particulate material including “floaters” (visible on the top of the cake), “sinkers” (visible by looking through the bottom of the vial), and fibers or other foreign material that can be viewed through the sides of the vials are defects and shall be culled from the lot.

9.2.2 Discoloration and/or irregular cake appearance - Atypical appearance, such as cake discoloration, altered matrix/crystal structure, or irregular shape, thickness, etc., that differs from the expected appearance is considered a defect and shall be culled from the lot.

9.2.3 Meltback and collapse - Meltback/collapse usually results from insufficient water being removed from the product. If there was only a limited amount of moisture present, the cake can appear to be shorter, compressed, lopsided, or have depressions/holes in them. Greater amounts of moisture can result in what looks like dried amorphous material in the bottom of the vial. Occasionally, meltback can be expressed as small flat hard disks (buttons) at the bottom of the vial. The cake will usually appear dry. Any vials exhibiting meltback or collapse are defective and culled from the lot.

9.2.4 Missing or shredded cake - Some products require low solute concentration formulation buffers. Such products often have very light weight, “fluffy” or tenuous cakes that fail to hold together or stay in the vial. If it appears that all or part of the cake is missing and cannot be accounted for elsewhere in the vial, then such vials shall be culled from the lot. A missing cake may also be the result of product not being filled into the vial.

9.2.5 Irregular cake size - Vials determined visually to have a difference in cake height (too large or too small) are considered defective and shall be culled from the lot. Variation in cake size may be the result of overfilling the vial, under filling the vial and no product filled into the vial.

10. DOCUMENTATION AND RECORDS

10.1 Complete **Forms 15113-01, 15113-02** (when needed for glass vials), **Forms 15113-03, and 15113-04** (when needed for cryovials), and **Forms 15113-05** and **15113-06** (when needed for lyophilized product vials). **Forms 15113-07** and **151113-08** are completed for lyophilized products, glass and cryovials. All completed forms are attached to the BPR.

10.2 Any investigations required are to be documented and included as part of the BPR or a reference added as to where the investigation documentation is located.

11. REFERENCES AND RELATED DOCUMENTS

Document Number	Title
15113-01	Inspection of Unlabeled Vials of Finished Product Manufacturing and Process Analytics Inspection
15113-02	Inspection of Unlabeled Vials of Finished Product Quality Assurance Inspection
15113-03	Inspection of Unlabeled Cryovials of Finished Product Manufacturing and Process Analytics Inspection
15113-04	Inspection of Unlabeled Cryovials of Finished Product Quality Assurance Inspection
15113-05	Inspection of Unlabeled Lyophilized Vials Finished Product Manufacturing and Process Analytics Inspection
15113-06	Inspection of Unlabeled Lyophilized Vials Finished Product Quality Assurance Inspection
15113-07	Inspection Summary of Unlabeled Product Vials
15113-08	Acceptable Unlabeled Product Vial and Defect Limit Summary