SOP: Visual Inspection Process of Manufactured Drug Product for Particulate and Cosmetic/Functional Defects.

Approvals:

Preparer: Dr. Sengyong Lee — Date: 11JUL17
Reviewer: Dr. Matt Marshall — Date: 01SEP17

1. **Purpose:**
   1.1. To provide a process where manufactured drug product (finished product) is visually inspected for both particulate and cosmetic/functional defects.
2. **Scope and Applicability:**
   2.1. All drug product manufactured for use in regulated studies.
3. **Summary of Method:**
   3.1. Delivery of Product to Inspector(s)
   3.2. Verification of Delivered Product.
   3.3. Preparation of Delivered Product for Inspection
   3.4. Inspection of Product – General
   3.5. Inspection of Product – Process
      3.5.1. Inspector examines each vial for the defects listed in the Finished Product Inspection Form. Defects shall be categorized into 3 categories:
         3.5.1.1.Critical
         3.5.1.2.Major
         3.5.1.3.Minor
   3.6. Review of Inspection
   3.7. Product Status/Storage Location
4. **References:**
   4.1 21 CFR 210/211
   4.2 USP <790> Visible Particulates in Injections
   4.3 USP <1790> Visual Inspection of Injections
5. **Definitions:**
   5.1. **Critical** - defects which may cause serious adverse patient reaction or death if the product is used. This classification includes any non-conformity that compromises the integrity of the container and thereby risks microbiological contamination of the sterile product.
   5.2. **Major** - defects that carry risks of temporary impairment or medically reversible reaction, or involve remote probability of a serious adverse reaction. This classification is also assigned to any defect which causes impairment to the use of the product (which may result in a malfunctions that makes the product unusable).
   5.3. **Minor** - defects which do not impact product performance or compliance; they are often cosmetic in nature, affecting only product appearance and pharmaceutical elegance. Minor defects are not considered to be rejected product.
6. **Precautions:**
   6.1. None
7. **Responsibilities:**
   7.1 It is the responsibility of the operator/inspector to annually re-qualify inspection process to determine ability to distinguish known product rejects from acceptable product.

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7.2 It is the responsibility of the operator/inspector to annually partake in eye exams.
7.3 It is the responsibility of the operator/inspector to notify QA of product defects exceeding Acceptable Quality Limit (AQL).
7.4 It is the responsibility of the Quality Assurance personnel to perform investigations of failed inspections exceeding AQL.

8. Equipment and Materials:

8.1. A lighted non-glare white/matte black inspection booth of suitable design and configuration to meet required light intensity range (2000-3750 lux) at the viewing point.
8.2. A calibrated/traceable light meter at minimum at the commencement and completion of the inspection lot.
8.3. Stickers with the appropriate defect codes.
8.4. Finished Product Inspection Form

9. Procedure: Inspection Process

9.1. Delivery of Product to Inspector(s)
9.1.1. Operations personnel or designee delivers product to inspector.
9.1.2. Operations personnelor designee completes the following sections of the Finished Product Inspection Form.
9.1.2.1. Description
9.1.2.2. Batch Number
9.1.2.3. Lot Number
9.1.2.4. Quantity of Vials
9.1.2.5. Delivered By / Date
9.2. Verification of Delivered Product.
9.2.1. Inspector verifies that the quantity of vials delivered matches the number indicated on the form.
9.2.2. If the quantity matches, the inspector completes the "Received By/Date" portion of the Finished Product Inspection Form.
9.2.3. If the quantity does not match, the Inspector contacts Operations personnel or designee to resolve the quantity discrepancy.
9.3. Preparation of Delivered Product for Inspection
9.3.1. Product is staged in the "Product to be Inspected" area to the right of the inspection area in reach of the inspector. A second area is staged and labeled with two areas on the left hand side of the inspector and labeled as "Inspected Product - Good" and "Inspected Product - Defects".
9.3.2. Signs are posted as applicable to maintain segregation throughout the process.
9.3.3. Only one (1) lot of product is allowed at the inspection booth at any one time.
9.4. Inspection of Product – General
9.4.1. Inspection of product shall take place utilizing a lighted non-glare white/matte black inspection booth. The booth will be of suitable design and configuration to meet required light intensity range (2000-3750 lux) at the viewing point. Inspections may be performed utilizing either a standard inspection booth meeting

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these criteria, or a more advanced system employing integrated feedback and operator interface.

9.4.2. When utilizing a standard inspection booth for product inspection, light Intensity will be verified utilizing a calibrated/traceable light meter at minimum at the commencement and completion of the inspection lot. Additional verifications may be necessary as a subsequent verification will be performed if inspection of the lot is performed in multiple sessions, or if the light source is switched off for any reason during the process. The results of this verification will be noted on the Finished Product Inspection Form.

9.4.3. When utilizing an inspection booth with an integrated feedback system, the system will alert the inspector of out of range light intensity at any point in the inspection. This feedback system is to remain calibrated to maintain light intensity in the accepted range (2000-3750 lux) on an annual basis. Therefore, the verification step used for standard inspection booths is not necessary.

9.4.4. Inspection shall occur on 100% of product from each manufactured lot

9.4.5. Only one product at a time shall be inspected.

9.4.6. Product shall be appropriately agitated, inverted, and viewed for a minimum of 5 seconds per vial against both black and white backgrounds under the inspection light.

9.4.7. Qualified operations inspectors shall be qualified annually with eye vision checks, colorblindness checks, and ability to distinguish known product rejects from acceptable product.

9.4.8. Acceptable Quality Limits (AQL) shall be established for each type of manufactured product. AQLs dictate the maximum number of defective vials beyond which a batch is rejected. These limits are described in the batch record.

9.5. Inspection of Product – Process

9.5.1. Inspector maintains batch identity by utilizing caution when inspecting and / or placing inspected product on labeled trays by keeping product within the inspection area.

9.5.2. Inspector examines each vial for the defects listed in the Finished Product Inspection Form. Defects shall be categorized into 3 categories:

9.5.2.1. **Critical** - defects which may cause serious adverse patient reaction or death if the product is used. This classification includes any non-conformity that compromises the integrity of the container and thereby risks microbiological contamination of the sterile product.

9.5.2.1.1.1.GB: Broken or cracked glass vial

9.5.2.1.1.2.SB: Seal on vial broken, missing or jagged

9.5.2.1.1.3.St: Stopper on vial missing, cock-eyed, or otherwise compromised

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9.5.2.2. **Major** - defects that carry risks of temporary impairment or medically reversible reaction, or involve remote probability of a serious adverse reaction. This classification is also assigned to any defect which causes impairment to the use of the product (which may result in a malfunctions that makes the product unusable). Sub-categories of critical defects may be classified as:

9.5.2.2.1.1.PG: Particle/spot/smudge inside vial, adhered to glass
9.5.2.2.1.2.PSt: Particle/spot/smudge inside vial, adhered to stopper
9.5.2.2.1.3.PS: Particle in solution (glass, fiber, stainless steel, etc.). Particles can be black, white, colored, translucent, etc.
9.5.2.2.1.4.P: Precipitation inside the vial
9.5.2.2.1.5.C: Cap broken / gone / lifted
9.5.2.2.1.6.OC: Cap over crimped
9.5.2.2.1.7.UC: Cap under crimped
9.5.2.2.1.8.O1 Other: Defect not already included on Finished Product Inspection Form. Defect described on the form.

9.5.2.2. **Note:** Categories and quantities of particles encountered may be counted and identified per type/color on the inspection form to aid in future trending purposes.

9.5.2.3. Major Lyophilized cake defects (some of which may be categorized as cosmetic depending on appearance specifications):

9.5.2.2.3.1.MB: Meltback
9.5.2.2.3.2.CC: Cake collapse
9.5.2.2.3.3.CP: Partial cake collapse
9.5.2.2.3.4.OW: Off white cake
9.5.2.2.3.5.DP: Dark particulate in cake
9.5.2.2.3.6.O1 Other: Defect not already included on Finished Product Inspection Form. Defect described on the form.

9.5.2.3. **Minor** - defects which do not impact product performance or compliance; they are often cosmetic in nature, affecting only product appearance and pharmaceutical elegance. Minor defects are not considered to be rejected product.

9.5.2.3.1.1.GC: cosmetic defect on outside of the vial, scratch, or glass defect
9.5.2.3.1.2.O1 Other: Defect not already included on Finished Product Inspection Form

9.5.3. If the Inspector encounters a defect, the defect is labeled appropriately by applying a sticker with the appropriate defect code to the vial.

9.5.4. The Inspector places inspected vials on the appropriate tray as inspections are processed.

9.5.4.1. "Inspected Product - Good"
9.5.4.2. "Inspected Product - Defects"

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9.5.5. When the inspection is complete, the Inspector indicates the number of vials containing defects by writing the appropriate number in the Initial Inspection: Quantity for Review column of the Finished Product Inspection Form.
9.5.6. The Inspector signs and dates the Form on the completion date.
9.5.7. The Inspector notifies Operations personnel or designee that the inspection is complete.

9.6. Review of Inspection

9.6.1. The inspection Reviewer or designee reviews both sets of "Inspected Product - Good" and "Inspected Product - Defects" sorted by the Inspector.
9.6.2. "Inspected Product - Defects" - the reviewer examines each vial to confirm that the recorded defect is appropriate.
9.6.2.1. If the recorded defect is incorrect and should be categorized differently, the Reviewer lines out the defect sticker on the vial and writes the appropriate defect code on the sticker.
9.6.2.2. If the defect is appropriate, the Reviewer does not take any action.
9.6.2.3. If the vial does not contain the recorded defect, the Reviewer examines the vial completely for any other defects.
9.6.2.4. If the vial does not contain any defects, the Reviewer performs the following actions:
9.6.2.1. Record the passing vial in the appropriate location on the Finished Product Inspection Form.
9.6.2.2. Remove the defect sticker.
9.6.2.3. Place the passing vial in a case in the Inspected Product - Good set of product
9.6.3. The Reviewer may retrain the inspector on a particular defect, if necessary.
9.6.4. The Reviewer records the number of vials that did not contain defects in the "Passed" column on the Finished Product Inspection Form.
9.6.4.1. AQL inspection: "Inspected Product - Good" - the Reviewer performs a statistical inspection of the vials in the Inspected Product - Good tray by a statistical process representative of the entire lot of product: Refer to the following table for the number of samples to reinspect. Unless otherwise noted in the batch record, the inspection level will be I.

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9.6.4.2. Table of Lot Size, General Inspection Levels and Code Letters/Sample Size.

Lot Size (Number of ordered products)			General Inspection Levels		
			I	II	III
2	to	8	A	A	B
9	to	15	A	B	C
16	to	25	B	C	D
26	to	50	C	D	E
51	to	90	C	E	F
91	to	150	D	F	G
151	to	280	E	G	H
281	to	500	F	H	J
501	to	1,200	G	J	K
1,201	to	3,200	H	K	L
3,201	to	10,000	J	L	M
10,001	to	35,000	K	M	N
34,001	to	150,000	L	N	P
150,001	to	500,000	M	P	Q
500,001	and over		N	Q	R

Code letter	Sample size
A	2
B	3
C	5
D	8
E	13
F	20
G	32
H	50
J	80
K	125
L	200
M	315
N	500
P	800
Q	1,250
R	2,000

9.6.5. The reviewer examines each of the randomly selected vials.

9.6.5.1. If the vials do not contain any defects, the Reviewer returns the vials to their respective locations.

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9.6.5.2. If the Reviewer encounters a vial containing a defect, the Reviewer takes the following actions:

9.6.5.1. The Reviewer appropriately labels the defective vial with a sticker and defect code.

9.6.5.2. The Reviewer examines the appropriate number of vials to fulfill the statistical inspection criteria detailed above.

9.6.5.3. The Reviewer may retrain the inspector on a particular defect, if necessary.

9.6.5.4. The Reviewer may also recommend to management the inspector be retrained on all inspection procedures or is a candidate for disqualification as an inspector.

9.6.6. The Reviewer completes the Product Inspection Form by documenting the following information:

9.6.6.1. Total Quantity Delivered

9.6.6.2. Quantity of Passed vials

9.6.6.3. AQL inspection quantity

9.6.6.4. Status

9.6.6.5. Review Inspection Performed by / Date

9.6.7. The Reviewer records all vials containing defects in the appropriate locations on the Finished Product Inspection Form.

9.6.7.1. The AQL values in the table below are industry standard. These should be used to gauge finished product rejection or release. However, if differing acceptance limits as dictated by the client are included in the approved manufacturing batch record, those limits supersede the values below.

9.6.7.2. AQL Acceptance Values

Defect Category	AQL range (%)
Critical	0.010-.10
Major	0.10-0.65
Minor	1.0-4.0

9.6.7.3. If the above values are exceeded, open an investigation per the SOP, Deviations and Investigations to determine proper course of action. A second 100% re-inspection of the batch may be warranted and/or batch rejected.

9.6.8. The Reviewer appropriately labels the two categories of product containing defects and product passing inspection with the following information:

9.6.8.1. Description

9.6.8.2. Batch Number

9.6.8.3. Lot Number

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9.6.8.4. Quantity
9.6.8.5. Status: (Choose one)
9.6.8.1. Ready for Release,
9.6.8.2. Ready for Reject,
9.6.8.3. Management Review Required

9.6.9. Management or Designee completes the Final Product Quantity and Status table after the Reviewer has signed.

9.6.10. The Form is then reviewed, final dispensation assigned, and approved by a QA representative.

9.7. Product Status/Storage Location

9.7.1. Inspected product is stored in Quarantine status in a segregated area until product is released.

10. Trending

10.1. Data obtained from the in-process 100% inspection followed by AQL inspection are used for batch release. Both 100% and AQL data should be analyzed for adverse trends on a periodic basis, typically at least annually.

History

Revision Number	***Effective Date***	***Preparer***	***Description of Change***
0	11JUL17	Sengyong Lee	Initial release