Visual Inspection of Medicinal Products for Parenteral Use

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Acknowledgement

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1. **Scope**

This paper aims to highlight best practice for carrying out visual inspection of medicinal products for parenteral use in the pharmaceutical industry. It should be seen as additional to and complimentary with the different Pharmacopoeias. Visual inspection of medicinal products for parenteral use should detect any readily identifiable visible container defect and ensure constant quality of the product in terms of absence of particular matter and/or turbidity, correct or uniform appearance of a lyo cake.

Deviations from the herein proposed procedures and figures are possible any time. But sticking to the proposed procedures and figures may lead to safer inspection processes and less discussions in GMP inspections, as the described approach has shown its suitability during many years of industrial operation and GMP inspections.

2. **Manual inspection**

2.1 **Workplace**

The premises where the manual visual inspection takes place should be suitable for carrying out this operation. Besides the common GMP requirements for manufacturing or quality control areas, of substantial importance for suitable inspections conditions are:

**Illumination:**

The intensity of the illumination at the inspection point should have at least 2000 lux. For Blow-Fill-Seal Products an illumination of 10,000 lux is recommended. The total uncertainty of the lux-meter should be considered. The color reproduction n, using the CRI index, should have an RA value > 90% and not less then 80%.
Illumination should be regularly qualified and part of the maintenance programme. An appropriate interval for checking the illumination is 6 months. It is recommended that a technical measurement be used to determine the light intensity on a prefixed point, which should be very close to the inspection point of the operator.

The ambient illumination must not interfere with the illumination of the workplace and should be turned down during inspection, if possible. Reflecting surfaces should be avoided.

Ambient conditions:
The ambient conditions are of enormous importance for carrying out this operation. Temperature should be ambient and should not exceed 25 °C in the summer if not otherwise justified. The relative humidity and air velocity should be controlled and ensure comfortable working conditions. The noise level should therefore be below 55dB.

2.2 Personnel
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.

Personnel carrying out the visual inspection must be qualified, comprising initial qualification and periodic requalification.

Initial qualification should follow a predefined schedule, starting with the introduction of the new employees to training kits. These training kits should contain all kind of defects and must be updated constantly with new evolving defects out of production. These
training kits should be specific for the dosage form. Following the training via training sets there should be a side to side training with an experienced operator. The new employee should have the chance to ask questions and the experienced operator does perform in parallel a 100 % inspection of the inspected species of the new operator.

Following the initial side by side training the initial qualification should be performed with a qualification set. This set should focus on critical and major defects and also contain a limited number of minor defects.

The number specimen to be inspected should represent the number of objects which are inspected in the duration from one eye break to the other eye break.

Acceptance criteria for the qualification should be predefined. In the initial qualification all critical defects and a predefined level for major defects should be found.

Routine requalification must be performed at least every 12 months. After a second failure the operator must undergo a repeated eye test and a subsequent new qualification with the training kit and a subsequent new qualification via a qualification kit.

It is recommended to do the Requalification under worst case conditions, which is at the end of a shift instead of at the start of a working day.
2.3 Operation

Each object should be inspected for at least 5 seconds against a white background and an additional 5 seconds against a black background. Times may be shorter when using a semi-automatic system. The objects should be slightly twisted or slowly rotated whereby formation of air bubbles will be avoided.

The post inspection recovery time for the employees carrying out the Visual Inspection is of essential importance. The maximum time for continuous inspection activity between break periods and the total maximum inspection time for a shift/workday must be limited.

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.

3. Automated inspection

3.1 Qualification / Validation

The central element of qualification/validation of a fully automated inspection system should be the verification that the automated system is at least as good as human inspector (without magnification) with regards to failure detection rates. Qualification and validation can be done consecutively or combined. The performance qualification can be rated as validation if it is carried out product-specific. Bracketing is possible. In this case it has to be carried out using product specific qualification sets. During machine qualification the inspection of a qualification set should be repeated at least 10 times. The detection rate should be compared to the results of a qualified manual inspection and
should be at least as good as manual inspection. It is worth mentioning that an automated inspection machine is not capable of removing certain categories of cosmetic defects.

3.2 Routine Operation
During routine operation the performance of the automated system should be demonstrated to be within the acceptable range of the pre-defined (during PQ) defect detection limits, before and after the inspection process by using a test set containing the range of defects that has been used in Qualification. An abridged or reduced function set may also be used.

3.3 Requalification
Requalification of an automated inspection system should be ideally carried out annually, or every two years at the latest. This must be done by evaluation of the changes and deviations that occurred during the period of operation. This review must include a statistical trend analysis of the performance data obtained during routine inspection and system suitability determinations using the function sets before and after every machine use.

3.4 Revalidation
An automated visual inspection machine should be seen as a critical system. Therefore a periodic revalidation should be carried out, e.g. every 3-5 years. Revalidation (as validation) is product specific. Bracketing approaches for the revalidation are possible.
Different approaches may be used:

3.4.1 Revalidation can be done by repeating the verification human inspection versus the inspection results from the machine, for example by manual re-inspection of an automatically inspected batch. The acceptance criteria are the same as in the initial validation.

3.4.2 Revalidation can be done by continuous revalidation:
Revalidation can also be done using the AQL results. The AQL is a manual inspection of a representative batch quantity performed for every inspected batch (man-machine comparison). Within this a repeated verification of human inspection versus the automated inspection machine is performed on batch level. The acceptance criteria herein are the acceptance criteria of the manual inspected AQL and ends up in a batch to batch revalidation of a product.

Independent from the approach used, the result and its evaluation should be documented in a revalidation report.

4. Defect Classes

There should be at least two product-specific defect classes defined. Defining more defect classes may be appropriate, e.g.:

**Critical defects**: may cause a lack of sterility, container integrity or cause harm to patients

**Major defects**: may alter the content or the function of the product
Further defect classes can be:

**Minor defects**: Defects that do not affect patient health or product functionality

If a company performs additional visual inspection for culturally sensitive cosmetic defects it is recommended not to include them into the GMP defect classification.

5. **Evaluation of defect classes and trending**

5.1 **Manual, semi-automated and Fully automated (non-inline) inspection**

Based on the trend analysis of the production process a limit for each defect class should be defined. There should be limits for individual defects and for the sum of all defects within a defect class. Yields should also be monitored.

Limits should be defined on process history (overall max reject rate, rate per defect / particle category) and should reference the process capability index (CpK) for the process step.

Typical limits for individual defects are

- **Critical defects**: 0.5 % to 1 % *
- **Major defects**: 1 % to 3 %
- **Minor defects**: 3 % to 5 %

There should be a limit for the sum of defects.

There could additionally also be a limit for the sum of defects.

*There are critical defects (e.g. turbidity) with an acceptance limit of 0.*
The measures to be taken for batches, exceeding these limits are to be predefined. For example: batches exceeding one fold of the limit should be investigated (Initiate a failure investigation).
Batches exceeding two fold of the limit should be additionally 100% re-inspected. Re-inspection should be performed independent whether a manual, semi-automatic or automatic visual inspection has been performed, but not more than 3 times.

Re-inspection of rejected containers is not recommended and must not be performed without judgment done within in an investigation.

NOTE:
“Grey Channel” for fully automated inspection systems: The usage of a “grey eject channel” in automated inspection may be useful for containers for which the inspection result is not clear. On a technical point of view a grey channel is also meaningful due to e.g. machine stops, when it is uncertain whether a vial has been fully inspected or not.

Examples for the Grey Channel:
1. Air bubbles: Air-bubbles might be the reason for an unclear inspection result. Camera systems cannot distinguish between particulate matter and air-bubbles. Therefore re-inspection of containers from the grey channel using a holding time of the product vials in order to reduce the air-bubbles is allowed but should not be performed more than once.
2. Other defects in the grey channel: On a technical point of view some small defects (e.g. small scratches) should be re-inspected manually if the camera system is not feasible for the defect detection. The feasibility is shown during the validation.
Objects in the grey channel should only be re-inspected one time. Trending is done over the whole batch after the objects have been classified as good or defects.

5.2 Automated inspection: In-line

An in-line fully automated inspection system needs trend analysis of the production process. Due to the in-line process and the fact that camera systems cannot trend defect categories a trending system has to be established on the technical level e.g. side-wall defect, crimping-defect, shoulder defect etc. Limits of these cameras have to be established on a historical process basis and need to be evaluated. This gives a reference to the process capability index (CpK) for the process step.

The measures to be taken during the batch production exceeding these limits are to be predefined and should lead to actions during the batch production process. Herein a re-inspection of the batch is not needed due to the immediate corrective action.

Re-inspection of rejected containers is not recommended and must not be performed without judgment done within in an investigation.
6. **Batch release**

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 (see above).

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.
For release of the batch, the minimum AQL should be

Critical: 0
Major: AQL 0.65 or 1
Minor: AQL 4 to 6.5

If an AQL limit is exceeded, the whole batch may be re-inspected 100% followed by a second AQL manual inspection. This process can be repeated, but 3 times in maximum. It is recommended to have tighter AQL limits for the repeated AQL testing. The number of AQL manual inspection steps should be evident in the batch documentation, the Qualified Person uses for the release decision.

AQL manual inspection can be carried out in a separate area, without constraint in time for the personnel doing the visual inspection.
7. Definitions

AQL
Acceptable Quality Limit, using ANSI/ASQ Z1.4 or ISO 2859-1, general inspection level II

CRI-Index:
The Color Rendering Index (CRI) is a unit of measure that defines how well colors are rendered by different illumination conditions in comparison to an ideal or natural light source. The Ra value uses only the first eight from the 14 test colors of the DIN 6169. Light sources have different Ra values, e.g. a white LED 80-95; fluorescent lamps 50-90.

Function set:
A function test kit (system suitability test kit) used before and after the inspection of each batch to demonstrate the functionality of the fully automated inspection system. It may contain an abridged set of more crude defects such as big particles, cracked or empty containers.

Particle:
A particle in this context means a readily visible particle with a diameter or span of 150 µm or bigger. Smaller, for example colored particles may be visible down to a size of 50 µm or smaller. These particles have also to be counted to the visible particles.
**Qualification set:**
A set of product specific containers with real product, with 10-20% but less than 30% of the containers containing randomly distributed defects. All known defects should be contained in the test set. New defects should be added to the test set after they have been identified. Units of tests sets for the manual inspection containing a defect should be invisibly marked or encoded. Obvious and clear readable numbers or letters should not be used. The sets should be cleaned after usage and routinely checked for defects at least every 6 months. There should be a logbook for each test set.

**Training set:**
A test set used for the training of the operators of the manual inspection, to teach the possible defects. Similar to the qualification set but contains only containers with defects.

**Visual Inspection:**
The process of sorting unacceptable units from acceptable units by human visual inspectors and/or through qualified equipment.

**Fully automated visual inspection:**
The process of sorting unacceptable units from acceptable units by equipment (camera system). Detection and handling of units to be inspected is performed by equipment.

**Fully automated (non-inline) visual inspection:**
The process of sorting unacceptable units from acceptable units by equipment (camera system) after the batch production has been finished.
In-line fully automated visual inspection:
The process of sorting unacceptable units from acceptable units by equipment (camera system) parallel or at the same time of the batch production.