ECA Foundation
Fostering harmonisation of GMP/GDP regulations

Visual Inspection of Medicinal Products for Parenteral Use

A document by the ECA Foundation
Version 5.0; October 2025

Table of Contents

Visual Inspection of Medicinal Products for Parenteral Use

Authors – Acknowledgements

This ECA Good Practice Guide was developed by the Steering Committee of the ECA Visual Inspection Working Group:

Dr Tobias Posset (Roche Diagnostics)
Felix Krumbein (Head of ECA Inspection Group)
Dr Helmut Gaus (Winsol, formerly Boehringer Ingelheim)
Martin Dearden (M&F Quality Pharma Solutions Ltd)
Dr Martin Becker (formerly Baxter Oncology)
Al Goodwin (Amgen)
Christof Langer (OSConsulting)
Dr Robert Eicher (Concept Heidelberg)

Version	Changes
Version 1.0	New Document
Version 2.0	Editorial adjustments Inclusion of a false reject rate into the qualification of human inspectors Clearer description of revalidation (chapter 3.4) Inclusion of new chapter 4: Inspection of lyophilized product Addition of the ASTM E2587-2 standard (Standard Practice for Use of Control Charts in Statistical Process Control) in chapter 6 (Trending) More detailed description of the batch release concerning the visual inspection data (chapter 7) Harmonization of the AQL limits with USP in chapter 7 Explanation on how to tighten AQL limits in chapter 7 Number of possible re-inspections adjusted to 2 (Chapter 6 & 7) Inclusion of new chapter 8: Concerns regarding distributed product
Version 3.0	Editorial Adjustments Usage of artificial test sets amended in chapter 2.2 Test of the color vision of human inspectors amended in chapter 2.2 Usage of format specific sets possible in qualification phases before PQ (chapter 3.1) Precision section 7 "Batch Release" including visible particles being allowed within the AQL manual inspection according USP<790> Reference list added as chapter 10
Version 3.1	Adding CCI statement (being out of scope for this document) Precision of minimum AQL level for batch release Deletion of the requirement for "sum of defects"
Version 3.2	Statement added regarding the Annex 1 changes: 1. manual inspection qualification condition under worst case conditions (section 2.2) 2. use of glasses/corrective lenses within manual inspection (section 2.2)
Version 4.0	Editorial adjustments Description of uninterrupted inspection times & breaks in manual visual inspection adapted (2.3) New chapter on semi-automated visual inspection (3) Routine Operation: usage of test sets clarified (4.2) Method reinspection may differ from method of original inspection (7.1)

Version 5.0	New chapter 5 on inspection of difficult-to-inspect items added Precision of the use of the functional test set in routine practice Adjustment of the chapters on requalification and revalidation for automatic inspection systems Elaboration of the procedure in case particles found in the AQL test Editorial adjustments, among others: "must" changed to "should". Consistent use of "kit" instead of "set" Regulatory adaptions in chapter trending Chapter batch release: Adaptation to other changes in the document Addition of PQ and PV in the Section "Definitions"

Technical Review

Klaus Feuerhelm (former GMP Inspector, Germany)
Dr Bernd Renger (Past Chair of the European QP Association – deceased)

Legal Representative

ECA Foundation
c/o VHP Auditing Firm and Legal Trustee
Attn Mr J. Ruland
Hebelstr. 7
68161 Mannheim
Germany

Disclaimer

The information contained in this publication is provided for general informational and educational purposes only. While every effort has been made to ensure the accuracy and completeness of the content, the publisher and the authors assume no responsibility or liability for any errors, omissions, or inaccuracies.

This publication does not constitute legal, regulatory, or professional advice. Readers are encouraged to consult the relevant regulations, guidelines, and competent authorities before making any decisions or taking any actions based on the information provided herein.

1 Scope

This paper aims to highlight best practices for carrying out 100 % visual inspection of medicinal products for parenteral use in the pharmaceutical industry. It should be seen in addition and complementary to the monographs of 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 particulate matter and/or turbidity, and correct or uniform appearance of a lyo cake.

Modifications of procedures and figures proposed in this paper are possible at any time. However, following the proposed procedures and figures may lead to safer inspection processes and may avoid discussions in GMP audits and inspections, as the described approach reflects current practice and has shown its suitability during many years of industrial operation and GMP inspections.

The CCI (Container Closure Integrity) topic is out of scope of this paper (see ECA position paper "Container Closure Integrity testing of medicinal products for parenteral use").

2 Manual Inspection

2.1 Workplace

The area where manual visual inspection is performed should be suitable for this operation.. Besides common GMP requirements for manufacturing or quality control areas, the following inspection conditions are of substantial importance:

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 (see also chapter 5). Accuracy of the lux-meter measuring light intensity should be considered. The colour reproduction, using the CRI index, should preferably have an RA value > 90%.

Illumination should be regularly qualified and part of the preventive maintenance programme. An appropriate interval for checking the illumination is at least every 6 months. It is recommended that the technical measurement used to determine the light intensity is performed at 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:
Ambient conditions have a high impact on the quality of this operation. Ambient temperature should normally be at room temperature and should not exceed 25 °C in summer, unless otherwise justified. Relative humidity and air velocity should be controlled and ensure comfortable working conditions. The noise level should therefore be below 55dB [source: German Workplace Ordinance ArbStättV].

2.2 Personnel

Personnel involved in the visual inspection should regularly undergo eye tests. The optometrist should focus on the ability to discriminate small differences in uniform structures, e.g. open/closed circles. Also, colour vision of the inspector should be tested.

Personnel performing visual inspection should be qualified, comprising initial qualification and periodic requalification. Qualification should be specific for each dosage form (e.g. syringe, vial, ampoule).

Initial qualification should follow a predefined schedule, starting with the introduction of the new employees to training kits. These training kits should contain all kinds of defects and should be updated constantly with new evolving defects out of production. These training kits should be specific for the dosage form. In case of unstable defects or defects which are not available photos of defects or artificial defects may be used.

A bracketing approach for different products is acceptable when process equivalence is scientifically justified. Following the training via training kits there should be a side-by-side training with an experienced operator. The trainee should have the chance to ask questions with the experienced operator performing a parallel 100 % inspection of the inspected units of the trainee.

Following successful completion of the side by side training, the initial qualification should be performed using a qualification kit. This kit should focus on critical and major defects and also contain a limited number of minor defects. The number of units to be inspected should represent the number of objects which are inspected in the routine process from one eye break to the next eye break.

2.3 Regulatory expectations

The European GMP requirements with regard to the visual inspection are – among others - included in EU GMP Guide, Annex <1> "Manufacture of Sterile Products" in the section "Finishing of sterile products". This guidance document addresses expectations relevant to visual inspection.

Despite the fact that current regulations cover many topics concerning visual inspection, situations may occur where expectations of a regulatory inspector differ from to the scientific understanding of the pharmaceutical company.

Expectation 1:
There is sometimes the expectation for operators to wear corrective lenses when undergoing visual inspection qualification, if they are worn during daily life.
Corrective lenses are used to shift an observed object into the focus point of the human eye. It is a known fact that individuals may shift an observed object into their (individual) eye focus point simply by varying the distance to the object, without the use of corrective lenses. Operators that need corrective lenses in everyday life might be able to perform visual inspection without.
The requested medical check examines e.g. three-dimensional sight, color identification, stigmatic corrections and most importantly reflecting the normal "daily life" visual capability. This ensures that the operator can see defects.

The medical check is not related to the competence of performing visual inspection activity. This is checked during qualification of the operator and whether he has to wear visibility aids is determined during this process.

Expectation 2:
There is sometimes the expectation for operators to be qualified considering different stress factors, including fatigue at the end of shift. It can be doubted that a fatigue effect can be simulated in an examination situation which has an impact on the operator whether he/she can keep his/her job. With this there is always nervousness, and some people have even examination anxiety which leads to release of Adrenalin in the human body which counters a fatigue effect. Additionally, when performing initial qualification, the fatigue at the end of shift can't be simulated anyway, as the operators are not yet allowed to perform a "normal" visual inspection workday.
As Annex 1 requests that operators performing visual inspection should be following a work and rest regime specifically designed to minimize distractions, there should be no fatigue effects at end of shift, which would impact the validity of the visual inspection.

Keeping this in mind, it should be considered to address these two topics/aspects/expectations by a Quality Risk Management approach.

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. Also, a limit for the False Rejects (rejection of samples without defects) should be predefined (e.g. 5-10%).

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

2.4 Operation

Routinely, during the 100 % inspection each object should be inspected for at about 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 to swirl up particles whilst avoiding the formation of air bubbles.

The post inspection recovery time for visual Inspection staff is of essential importance. The maximum time for continuous inspection activity between breaks and the total maximum inspection time for a shift/workday should be defined.

Industry practice is 20-60 minutes of inspection. A current good practice goal is 30 minutes of inspection followed by a break of at least 5 minutes continued for a total maximum duration goal of no longer than 4 hours. All maximum uninterrupted inspection activity should be qualified.

3 Semi-Automated Inspection

Semi-automated visual inspection is the combination of manual visual inspection and an automated transporting system of the units. The inspection system presents the object to a human inspector allowing inspections using a defined set-up (inspection booth) and a qualified human operator.

The complete inspection of each unit is ensured by the following aspects:

1. To avoid disturbances of the inspector, an inspection booth should exclude external light sources.
2. At least a full 360° rotation of the unit in the inspection field facilitates inspection.
3. Inspection of the top and the bottom of the unit ensures complete inspection of the unit.
4. For liquid products, particle inspection can be supported by pre-rotating the objects before inspection to get the particles moving within the solution.
5. Due to the nature of a semi-automated inspection the inspection field is typically illuminated higher than in manual inspection (for example 8.000 lux) and may be adjusted to suit for difficult to inspect objects. Inspection of difficult to inspect objects are described in chapter 5.
6. For an undisturbed visual inspection, the surrounding of the booth should be designed in such a way to prevent extraneous light and/or reflections.
7. Magnification or other suitable aids should be used in order to bring the visual focus point of the operator's eyes to the point of inspection using an ergonomic sitting situation of the operator.

Risk Management Principles via assessments should be used during qualification of all the variable parameters noted above. Pre-start up tests should be established and then implemented in a controlled manner to be used periodically. Functional control kits should be used to ensure variable parameters are within the validated state before commencement of the inspection process, whereas potential drifts of the equipment (e.g., Illumination) is more suited to be verified periodically, e.g. at least every six months.

The most important parameters are:

- Conveyor Speed
- Illumination
- pre-spinning / if applicable
- Rotation within the inspection field to ensure 360-degree inspection of the unit

Validation of the semi-automated inspection process should show at least equivalence to manual inspection results.

For lyophilized products, inspectors are qualified at maximum inspection speed and may inspect during routine operation at maximum or any lower inspection speed.

For liquid products, inspection at the qualified speed should be routinely used at all times due to the influence of speed on the inspection validity.

After an inspection process of an uninterrupted and predefined duration, operators require an eye break. Semi-automated visual inspection requires greater concentration by the operator. For that, times of uninterrupted inspection are typically shorter than manual visual inspection and times of breaks may differ from the numbers given in chapter 2.3 (Operation of the Manual Visual Inspection).

4 Automated Inspection – Qualification, Validation and Routine Operation

4.1 General

The central aspect of qualification and validation of a fully automated inspection machine is the verification that the machine is at least as good as the comparative group of human inspectors (without magnification) with regards to defect detection rates. Qualification and validation can be done consecutively or combined.

Basically, qualification is the documented evidence that the inspection machine is fit for purpose, while validation is the documented evidence that the machine achieves reproducible results of desired quality in the manufacturing process. In simple terms, the qualification is done to ensure that the machine works as specified (URS), whereas the validation ensures that it consistently delivers the desired (inspection-) results in the manufacturing process.

4.2 IQ & OQ – Installation and Operational Qualification

Qualification begins with the development of the user requirements and ends with the verification of proper implementation. As part of the qualification phases, it should be confirmed that the machine complies with the user requirements specifications (URS).

Installation Qualification (IQ) usually includes verification of the correct installation of components and equipment against technical drawings and specifications and the provision of the agreed operating and work instructions and maintenance requirements by the supplier.

Operational Qualification (OQ) covers cross-product and format-specific functionality tests such as

- the management of users, recipes, alarms, and warnings
- proper transport, handling, and ejection of units for all formats
- counting of units, batch report and audit trail functionality
- presentation of the units in front of the cameras, such as correct positioning, rotation, illumination, etc.

4.3 PQ – Performance Qualification

As part of the PQ, documented evidence should be provided demonstrating that the automated inspection machine (AIM) fulfills the defined performance requirements under intended (real) production conditions. The central aspect of performance qualification is the verification that the AIM performs at least as well as the comparative group of qualified human inspectors (without magnification) regarding defect detection capability. PQ should be performed product specific.

Throughout performance qualification, product-specific qualification kits should be used to evaluate detection rates after an appropriate number of inspections. These kits should consist of production materials, qualified substitutes, or simulated products that have been demonstrated to exhibit equivalent physical and optical characteristics relevant to automated visual inspection (e.g., size, shape, and color of defects, particle mobility), irrespective of their pharmaceutical relevance. The qualification kit should be inspected at least ten times to ensure statistical robustness.

Detection rates should be compared with the results of a representative group of qualified human inspectors and should be at least equivalent to manual inspection, assessed at the level of defined defect categories (comparison of individual container results is not required).

When evaluating particle detection performance, the principles of the so-called *Knapp Test* should be considered. Julius Knapp demonstrated that a ratio of not more than 25% defective units within a set of conforming (good) units provides optimal statistical accuracy for determining detection performance while avoiding bias. In practice, however, qualification kits typically contain around 10% defective units to prevent rejection bias. Such enrichment with good units is required whenever the *Knapp Test* is applied in the context of a man-machine comparison to demonstrate the performance of the automated inspection system, which is typically the case for the confirmation of particle detection capability. If, however, the machine's performance is evaluated against predefined acceptance criteria, i.e., detection rates, the inclusion of good units may be omitted, as automated systems are not subject to operator bias and fatigue.

Success is demonstrated when the machine's detection performance, based on a predefined number of at least ten repeated inspections, is statistically equivalent to that obtained from the same number of repeated manual inspections. If a higher number of repeated inspections are required, the corresponding number shall be adjusted accordingly for both the automated and manual inspections to ensure statistical comparability. This constitutes the so-called *Knapp Test*.

Bracketing approaches may be applicable, provided that they are justified by quality approved rationales.

4.4 Validation

Validation provides documented evidence that the automated inspection machine consistently produces results of the required quality during routine manufacturing. Tests should cover the operating range, simulating the intended process supported by quality-approved rationales.

This includes confirmation of process capabilities in terms of product stability, defined AQL limits, and trend limits. Furthermore, validation is intended to provide guidance on the information and data to be provided in the regulatory submission.

Validation may be performed by comparing the results of manual human inspection with those obtained from the automated inspection machine. For example, this can involve manual re-inspection of a previously inspected batch or sub-batch (e.g., 5000 units) to confirm that the machine's performance is at least as good as the comparable group of human inspectors. Alternatively, validation can be confirmed by assessing the achievement of the expected AQL limits based on a defined number of batches (e.g., three consecutive production batches).

4.5 Requalification and Revalidation

Requalification of an automated inspection system should ideally be carried out annually, or every two years at the latest. Requalification should include a review of all changes and deviations that occurred during the period of operation. This review should include statistical trend analysis of performance data obtained during routine inspection and system suitability testing based on functional test kits assessed before and after every batch production. If necessary, additional inspections of representative defect kits may be carried out during production to ensure the inspection equipment remains in a state of control.

Revalidation can be performed by repeating the verification of the human inspection versus the inspection results of the machine, for example by manual re-inspection of an automatically inspected batch or part of the batch (e.g., 5000 units). The acceptance criteria are the same as during the initial validation.

In addition to such periodic revalidation activities, continuous revalidation of the automated inspection machine performance may be established through the ongoing statistical evaluation of AQL results. Since the AQL represents a manual inspection of a representative sample from every batch, this data provides continuous evidence of the machine's inspection performance. Statistical trending of AQL results in accordance with Quality Risk Management (QRM) principles enables early detection of performance shifts. Consistent performance within predefined limits demonstrates maintained process control and can be considered a continuous confirmation of the AIM's validated state – thus fulfilling the intent of revalidation on a batch-by-batch basis.

Results and evaluations should be documented in a revalidation report.

4.6 Routine operation

During routine operation the overall functional performance of the automated system should be demonstrated to be within the acceptable range of the normal operating conditions and validated state. This is achieved by using the functional test kit containing representations of the range of defects that has been used in the qualification, which should be applied before and after the inspection of a batch. An abridged or reduced functional test kit may also be used. In the event of a risk, such as a malfunction or machine drifts (misalignments of visual components, camera defects, etc.) of the inspection system or in the case of a prolonged inspection time (e.g. campaign production, large volume batches), the described functional test can also be useful within a batch.

5 Inspection of difficult-to-inspect Products and Containers

All drug products must be 100% visually inspected, even if they are difficult to inspect due to their product characteristics or container. A difficult to inspect product may be defined as either cloudy (suspension products) and/or turbid/oily products (emulsions) or a mixture of these characteristics. Difficult-to-inspect containers can be defined as amber, coloured, opaque, or plastic, essentially any material that is not 100% transparent. Additionally, a small product volume sometimes may be considered as difficult to inspect.

If any characteristics of the product cannot be visually inspected by the 100% inspection, suitable inspection methods should be used additionally, e.g. destructive random sampling. Samples are taken according to a sampling plan, please refer to DIN ISO 2859-1 or ANSI/ASQ Z1.4. In case the additional testing is carried out to test for particles, the destructive testing should be performed in a grade A (ISO 100) environment or at similar conditions to avoid sample contamination with particles from the environment. During the testing process, product solution is withdrawn from the container and filtered through a filter membrane (e.g. 0.8 µm pore size similar to <USP 788>), prewetted with particle free water. After residues of the product are washed away with particle free water, the dried membranes are visually inspected with a stereomicroscope for particles > 100 µm (see USP <790>, AQL 0.65).

5.1 Inspection of lyophilized product

In case of lyophilised products, particles can only be detected on the cake, not within the cake during 100% visual inspection. For within-cake-inspection, a number of samples are reconstituted and visually inspected for particulates. The result must be within the predefined particle limits.

5.2 Brown glass, coloured/turbid solutions

Visual inspection of products in brown glass containers or with coloured solutions are difficult to inspect in terms of particle detection for example. Detectability of other defects like fill level, closure defects or glass defects is usually not affected with such products.

As with brown glass containers or coloured solutions, the contrast between particles and the product is lower than with clear glass containers and clear solution, and consequently the probability to detect particles is decreased. Especially detection of small particles is more difficult and compliance to <USP 790> (detection of particles >100 µm) may be hard to achieve.

Decreased visibility of particles in brown glass containers of slightly coloured or slightly turbid solutions may be improved by increasing illumination, as described in Ph. Eur. 2.9.20 or JP 6.06, or by extending the inspection time. Also, other measures like using Tyndall light or different illumination wavelength may be helpful in special cases.

If particles are not visible due to strong coloration of a product, milky products or in lyophilized products, destructive testing must be used as mentioned in case of lyophilised products.

If the product is also non-transparent (opaque) or very cloudy, microscopic examination, e.g. as described in JP 6.06. Method 2, has to be applied.

6 Defect Classes

There should be at least two product-specific defect classes defined. Additional defect classes may be defined, for example:

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.

Other: If a company performs additional visual inspection for e.g. specific cosmetic appearance for products intended to be placed to culturally sensitive markets, it is recommended not to include them into the GMP – and with-it product quality related - defect classification.

7 Evaluation of Defect Classes and Trending

7.1 Manual, semi-automated and fully automated 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 maximum reject rate, rate per defect / particle category) and should reflect and reference the process capability index (CpK) for the process step.

Action limits must be determined product specific, based on production history. In case there is no previous experience, typical action limits for individual defects are for example:

Critical defects: 0.5 % to 1 % *

Major defects: 1 % to 3 %

Minor defects 3 % to 5 %

*For critical defects, indicating severe GMP issues such as sterility-impairing defects (e.g., turbidity, cracks) or mix-ups, the acceptance limit is 0, triggering an investigation.

Typical action limits can also be based on specific defects (e.g. particles) instead of using the categories critical, major and minor.

Setting alert limits may be reasonable e.g. to identify a production specific problem as early as possible.

According to ASTM E2587-2 (Standard Practice for Use of Control Charts in Statistical Process Control), control limits for trending should be calculated from process data and not be based on fixed specification limits. However, the evaluation should optimally be based on at least 30 representative data points of the process. This would require preliminary control limits to be defined based on experience prior to the first calculation deriving from measured data points.

If a batch exceeds a trending limit, the reason for this should be investigated. Batches exceeding the acceptance limit for critical defects should also trigger the company's failure investigation process.

Once the root cause has been identified and the inspection method is suitable for sorting out the defects causing the problem, the batch can be re-inspected. Re-inspection should never be performed without prior evaluation of suitability. Under certain circumstances, depending on the defect detection rate, the test method used in the initial inspection may not be suitable for re-inspection. E.g., if an automated system fails in identifying certain defects in the first run, it is likely to fail also in a second run. The decision on the re-inspection method should be made by an authorised and qualified person.

When frequent re-inspections must be performed, a failure investigation should be initiated with the aim to improve the sensitivity of the primary inspection process or of the manufacturing controls to prevent defects in the upstream process as determined by root cause analysis.

Re-inspection of rejected containers should not be performed.

NOTE:

"Grey Channel" for fully automated inspection systems: Defining a "grey eject channel" in automated inspection may be useful to separate containers for which the inspection result is not clear. From a technical point of view, a "grey channel" is also meaningful in case of e.g. machine stops, when it is uncertain whether a unit has been fully inspected according to procedure or not.

Examples for the Grey Channel:

1. Air bubbles: Air-bubbles might be a 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 after a certain time of rest in order to reduce air-bubbles is allowed. In this example, time reduces the number of air bubbles, which reduces the false reject rate whilst maintaining a more stringent machine set-up.
2. Other defects in the grey channel: from a technical point of view some small defects (e.g. small scratches) should be re-inspected manually if the inspection system is not able to differentiate predefined characteristics, for example due to ambiguities caused by the intrinsic characteristic of the product (air bubbles) at the time of inspection. The feasibility is shown during the validation.

Objects in the grey channel usually do not require more than one re-inspection. Trending is done over the whole batch after the objects have been classified as good or bad.

8 Batch Certification/Release

For the release decision two criteria need to be evaluated:

1. Trending analysis of the 100% batch inspection (see chapter 7) and

2. The result of the AQL manual inspection.

The results of 100% visual inspection trending, done as part of manufacturing process, are an integral part of batch documentation, specifying the types of defects found (fibre, turbidity, crack, etc.) as well as a classification of the defect such as critical, major or minor. Acceptance criteria should be pre-defined for at least the defect classes defined from all defects found during the 100% inspection process (see above). For automated inspection, these classifications needs to be done on a technical level (side-wall defect, crimping defect,…) and cannot be done using the classification such as critical, major or minor (see above).

For the AQL manual inspection, a randomized sampling out of the accepted containers coming from 100% inspected batch should be performed according to a pre-determined AQL procedure. AQL manual inspection may be carried out by production staff under a quality oversight or the quality unit.

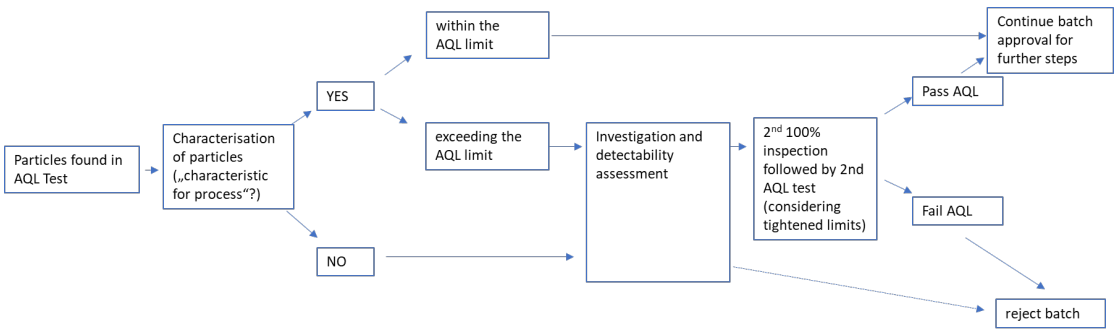
For release of the batch, the minimum AQL is typically:

Critical:	0 defects within the AQL samples
Major:	≤ 0.65 AQL
Minor:	≤ 4.0 AQL

If an AQL limit is exceeded, the whole considered-to-be-acceptable batch should be re-inspected 100% followed by a second AQL manual inspection with tightened AQL limits. This process is usually not repeated several times. Tightening of AQL limits can be considered and is possible by two ways: Stay on the AQL sample size and use the next (tighter) AQL limit- OR: Stay on the AQL limit and use the next (higher) AQL sample size.

Particles found in AQL testing must be characterized and evaluated according to their nature. If characterization shows that the particle is not process-related the origin must be investigated and assessed prior to further actions. Particular attention during investigation should be paid to possible adulteration, sterility, or other cGMP-related issues of the affected batch.

If the characterization shows that the particle is process-related, the number of units found in AQL must be within the given AQL limits. AQL limit violation of those particles triggers an investigation followed by a 100% reinspection of the batch. A second AQL test of the reinspected batch must then demonstrate successful particle clearance. Using tightened AQL limits should be considered. When particles are rated as major defects (according to USP <790>), and characterization shows that the particle is process-related while AQL limits are met, the batch can be approved for further processing. If AQL limits are exceeded again, a decision on further reinspection must be taken after the investigation has been closed (see figure).



The number of AQL manual inspection steps should be evident in the batch documentation.

AQL manual inspection may be carried out in a separate area without time constraints for the inspectors.

The results of the 100% visual inspection and the results of the AQL testing are part of the finished product release assessment that should embrace all relevant factors of the batch. After assessment by quality control or quality assurance, these data should be made available in an easily readable format to the Qualified Person, responsible for batch certification and release decision

9 Concerns regarding distributed Product

When concerns arise regarding particulate matter of product already distributed to the market, it is recommended to inspect several samples following a practical DIN ISO 2859 compliant sampling plan.

As visual inspection for particulates is a probabilistic and not a deterministic process, sampling plans for non-critical defects with a limit of zero are not practical as an assessment tool and should be avoided.

The inspection needs to be performed under the same conditions as the routine inspection was performed. The relative batch and sample size will determine the acceptance criteria, if these criteria are met by inspection of these samples, the batch can be considered essentially free of particles.

It is good practice to isolate particle(s) of any complaint sample and to determine the size and to characterize the nature of the particle(s) during investigation.

10 Definitions

AQL	Acceptable Quality Limit, using ANSI/ASQ Z1.4 or ISO 2859-1, general inspection level II
CRI-Index:	The Colour Rendering Index (CRI) is a unit of measure that defines how well colours 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 colours of the DIN 6169. Light sources have different Ra values, e.g. a white LED 80-95; fluorescent lamps 50-90.
Function testkit:	A functional 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 kit of more apparent defects such as big particles, cracked or empty containers.
Particle:	A particle in the context of this paper means a readily visible particle with a diameter or span of 150 µm or bigger that allows reliable detection (70% probability or higher) in a clear solution. Smaller, for example coloured or shiny particles may be visible down to a size of 50 µm or smaller and thus have also to be counted to the group of visible particles.
PQ	Performance qualification (PQ) is intended to confirm the capabilities of the machine to which extent a specific set of defects (qualification kit) is detectable. This test is conducted by inspecting the samples with the machine several times by finally calculating the detection rate which is the quotient of the number of detected samples by the total amount of samples in a specific category. Thus, the PQ serves to confirm the sensitivity of the machine.
PV	Validation of the inspection system examines the entire inspection process (incl. two-stage AVI + SAVI/MVI, impact of light, etc.). This is part of the process validation (PV). PV shows the suitability of the process under routine conditions.
Qualification kit:	A set of product specific containers with real product, A test kit 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 kit. Any new defects should be added to the test kit after they have been identified. Units of tests kits for the manual inspection containing a defect should be marked or encoded invisibly. Obvious and clear readable numbers or letters should not be used. The kits should be cleaned after usage and routinely checked for defects at least every 6 months. There should be a logbook for each test kit.

Training kit:	A test kit used for the training of the operators of the manual inspection, to teach the possible defects. Similar to the qualification test kit 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.

.

11 References

- DIN/ISO 2859-1/
- ANSI/ASQ Z1.4
- USP <790> and <1790>
- Ph. Eur. 2.9.20
- Ph. Eur. 5.17.2
- ASTM E2587-12
- EU GMP Annex 1
- German Workplace Ordinance (=ArbStättV)