VISUAL INSPECTION IS KEY TO ENSURING PATIENT SAFETY in US Pharmaceutical Compounded Products

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Visual inspection is nothing new to professionals who make, prescribe, prepare, and/or administer pharmaceutical parenteral products to patients of all backgrounds, especially those who may have immunity concerns. The pharmaceutical industry has tried to ensure that companies enact the best quality standards that are consistent with Current Good Manufacturing Practices (CGMPs) to prevent an adulterated product from entering the market.

For companies that compound drug products in the United States—whether regulated as a 503A (Compounding Pharmacy) or 503B (Outsourcing Facility)—these procedures also apply, and if followed, will simultaneously meet requirements enacted by the US Food andDrug Administration (FDA) and/or multiple State Boards of Pharmacy(SBOP). While the concepts in this article reference FDA and SBOP standards, they may also apply to other regions. However, each region has specific requirements. Manufacturers should be aware of regulatory requirements in regions where they operate.

Visual inspection can be done via a manual process or through an automated process. Traditional pharmaceutical manufacturers are more likely to utilize automated Visual Inspection processes. However, compounding entities are likely to continue using manual Visual Inspection processes because developing automation when batch sizes are small may not be practical. The focus of this article is the manual aspect of Visual Inspection and not on specific products or defect troubleshooting.

Visual inspection may actually be a bit of a misnomer, as it isn't an assessment, but a step in the manufacturing process by which defects are found and removed from the batch. This can encompass multiple aspects, including examining the physical characteristics of the container (cracks, defects, bad crimp), but it primarily focuses on inspection for visible particulates. Per the FDA Draft Guidance for Industry, "Inspection of Injectable Products for Visible Particulates" (December 2021), the following definitions should be utilized in visual inspection [1]:

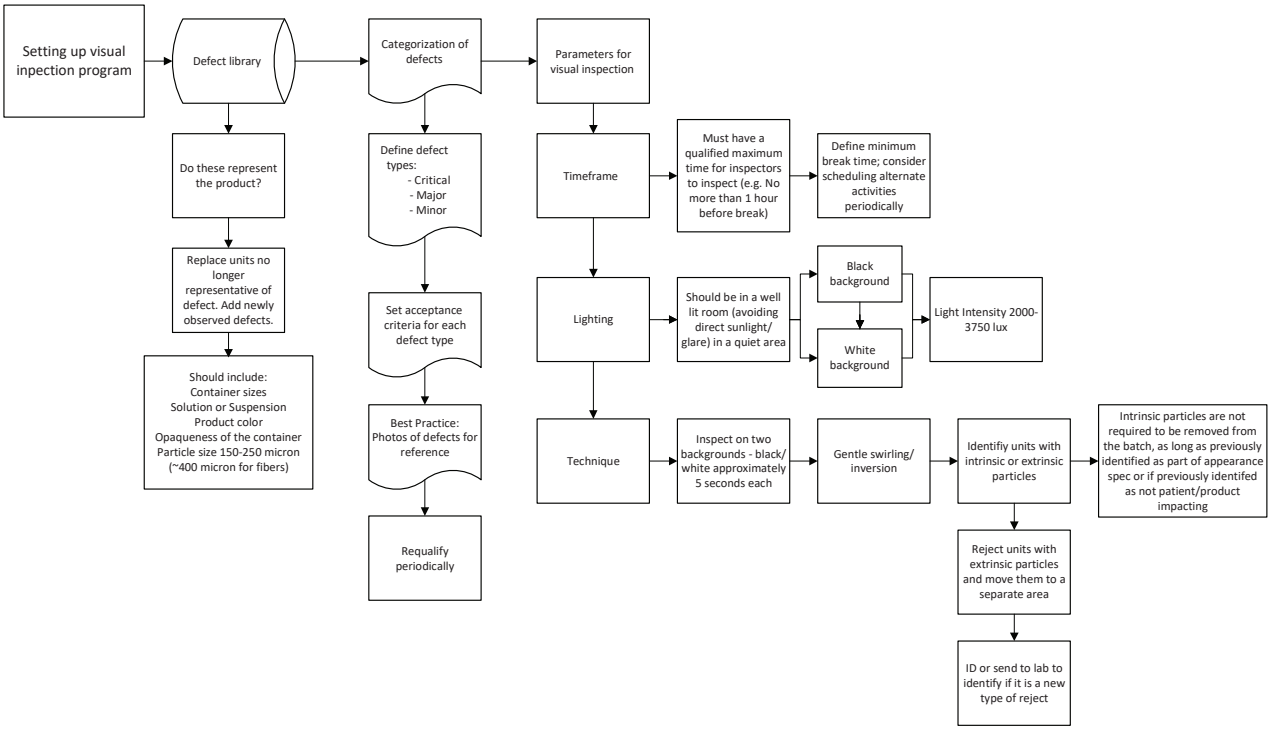
- Particulates refer to mobile, undissolved particles—other than gas bubbles—that are unintentionally present in an injectable product. They vary in nature (e.g., metal, glass, dust, fiber, rubber, polymer, mold, degradant precipitate) and can be categorized into three types:
  - Inherent particulates are an innate product characteristic (e.g., protein aggregation).
  - Intrinsic particulates originate from the manufacturing equipment, product formulation, or container system (e.g., syringe fibers).
  - Extrinsic particulates originate from the manufacturing environment and are foreign to the process (e.g., metal particulates).

This article focuses on 503B Outsourcing Facilities, which produce tens of thousands of units daily across the United States for patients in all fifty states. Currently, there are more than 90 registered Outsourcing Facilities [2], ranging from small producers (<1,500 units per batch) to large producers (>5,000 units per batch), using both manual and automated visual inspection processes. Therefore, the focus on visual inspection and the creation of uniform practices is vital to ensuring patient safety across 503B compounded products.

REGULATORY OVERVIEW

Section 501(b) of the Federal Food, Drug, and Cosmetic Act [3] states: "A drug shall be deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing,

Figure 1: Flow diagram of the components of a visual inspection program [7]



packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."

The information in the United States Pharmacopeia (USP) <790>, "Visible Particulates in Injections" (official as of May 2016) [4] and <1790>, "Visual Inspection of Injections" (official as of May 2017 [5], provides the basis of how visual inspections can be conducted. However these chapters are not detailed enough to guide implementation or address regulatory expectations.

The FDA Draft Guidance for Industry, "Inspection of Injectable Products for Visible Particulates" (December 2021) [1] states: "The guidance also clarifies that meeting an applicable United States Pharmacopeia (USP) compendial standard alone is not generally sufficient for meeting the current good manufacturing practice (CGMP) requirements for the manufacture of injectable products. The guidance does not cover subvisible particulates or physical defects that products are typically inspected for along with inspection for visible particulates (e.g., container integrity flaws, fill volume, appearance of lyophilized cake/suspension solids)."

503-registered outsourcing facilities are expected to comply with FDA CGMP requirements as outlined in 21 CFR Parts 210 and 211, with some minor exemptions. As of December 2020, the FDA has exercised enforcement discretion during 503B inspections, in alignment with its Draft Guidance for Industry, "Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act" [6]. The guidance states that limits and tests for visible particles shall be established for drug solutions purporting to be sterile. The guidance also references USP Chapter <790>, "Visible Particulates in Injections" [4], implying that the FDA may enforce visual inspection requirements consistent with those outlined in the USP chapter. However, the draft guidance does not provide sufficient detail on how a company should establish and implement its visual inspection program.

Each company must develop a program tailored to its unique products and manufacturing environment. However, the following principles must always be met and form the core of any approach a site chooses to adopt:

- The inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates.
- Every container that shows evidence of defects (e.g., visible particulates) shall be rejected.

MANUAL VISUAL INSPECTION

Most 503B compounders reference the following sources when developing their visual inspection programs: 21 CFR 211, FDA guidance, USP Chapters <790> and <1790>, International Society for Pharmaceutical Engineering (ISPE) guides, and Parenteral Drug Association (PDA) publications. However, these documents do not provide sufficient detail to ensure consistency and uniformity,

particularly when addressing manual visual inspection.

A robust visual inspection program should include several key components: a defect library, test sets, a defect categorization system, reference photos, limits for each defect category, and a method for analyzing relevant data. These elements should all be managed through the site's change control system. See Figure 1 for a depiction of how to set up a visual inspection program.

In addition, there must be a training program and a process to qualify and requalify personnel performing visual inspections (hereafter referred to as operators).

Each site will need to develop (or could purchase from a vendor a defect library [5] specific to their products. The library should include defects that may be observed for each product family and container size, and should consider the following (non-exhaustive) elements:

- Examples of the types of defects that could occur and have been observed during visual inspection.
- The defect library will be used for training and serve as a baseline for images and examples to be included in the site SOP.
- The defect library can be organized by product or designed to account for the different container sizes, solution or suspension types, product color, and the opaqueness of the container.
- Ensure particle sizes are appropriate. Particles should not be too large or too obvious—typically 150-250 µm (approximately 400 µm in length for fibers).
- Defect libraries should not be used indefinitely; they should have a requalification date. Any units no longer representative of the defect should be replaced.
- Defects should be analyzed annually (or more frequently) to determine if the defect library needs to be expanded to include newly observed defects.

Each company will need to develop a test challenge set [5] (also known as a training set) specific to irts products, which may be organized by product family or other bracketing approach. The test set is used to train operators and assess their ability to detect defects. The following recommendations apply to test sets (non-exhaustive):

- The test set should include all representative defects relative to the site's products. It must include examples of inherent, intrinsic, and extrinsic particulates. Vendors are available to create these sets.
- Test sets should include container defects, regardless of the product, for qualification purposes. These should include both naturally occurring defects and defect-free containers.
- A test set should include >90% of defect-free units, with defective units not to exceed greater than 10% of the total number of units in the test set.
- Defects within a test set should include critical, major, and minor rejects.
- The test key (identifying which units are defective) must be maintained separately by quality.
- Best practice is to use the entire test set for operator qualification. Justification is recommended if this is not the approach taken.
- Procedures must be established to ensure qualification container sets are updated as needed to remain representative of naturally occurring defects. The test set should be periodically re-evaluated to determine if units need to be replaced.
- Test sets should be periodically assessed to ensure only intended defects are present. Procedures should also be in place to ensure newly identified defects are included in the challenge set.
- For smaller test kits, rotate units frequently or maintain multiple sets so personnel do not memorize them.
- Each container within a test set should be identified with a unique ID in a non-readable format (e.g., barcode or QR code) that, when scanned, returns the ID number/code and its expected result.
- Each site should also establish a defect categorization system [5] for its products. Parameters should be defined for acceptability of each category, which typically include:
  - Critical: Defects that may cause patient injury, such as extrinsic particles, leaks, or container/closure defects compromising integrity of the container.
  - Major: Defects that reduce product usability but do not result in patient harm, such as underfill.
  - Minor: Defects that do not reduce usability of the product, such as cosmetic. (Note: Excessive defects in any category, even minor, may require 100% reinspection and lead to lot rejection.)
- Acceptance criteria for critical, major, and minor defects should be predefined and applied consistently across all products. Exceptions must be justified and acceptance criteria should be statistically justifiable.

It is beneficial to include photographic references of defects in SOPs and/or the defect library. These serve as visual aids for personnel during inspections.

A defined system must be in place for analyzing site data, including clear criteria for when re-analysis is permitted. There should be a periodic review of batch data to ensure the process has not shifted.

VISUAL INSPECTION CRITERIA

100% Visual Inspection

100% of the final containers of all parenteral preparations must be inspected, to the extent possible, for the presence of observable foreign and particulate matter in its contents [4]. This visual inspection should not be performed by the compounder of those units.

Operators should be trained to identify other defects, such as loose caps, cracks in the glass, or any other condition that would render the container unsuitable for use.

Manual visual inspection can be variable. Factors that can be minimized include fatigue, visual acuity, and distractions. These variables must be considered when setting up the visual inspection process as well as during training.

- Maximum inspection times followed by rest breaks must be provided to operators to maintain visual acuity.
- Inspection should not be performed by an operator for more than one (1) hour (or another qualified interval) continuously without a break.

Table 1: Example of a normal AQL inspection plan

Normal AQL Inspection Plan							
Lot/Batch Size	Minimum Sample Size	Critical (0.1%)		Major (0.4%)		Minor (4%)	
		Accept	Reject	Accept	Reject	Accept	Reject
281 to 500	80	0	1	1	2	7	8
3,201 to 10,000	315	1	2	3	4	21	22

Table 2: Example of a tightened AQL inspection plan

Reduced AQL Inspection Plan							
Lot/Batch Size	Minimum Sample Size	Critical (0.1%)		Major (0.4%)		Minor (4%)	
		Accept	Reject	Accept	Reject	Accept	Reject
281 to 500	32	0	1	0	2	3	6
3,201 to 10,000	125	0	2	1	4	10	13

- The duration of time each operator spends performing visual inspection must be documented.

Inspection Stations/Equipment

- The backdrop of the inspection station must include a background consisting of matte black and non-glare white panels to facilitate effective inspection [4] (see Figure 3).
- Inspection stations should be located in areas where background noise and distractions are minimized, preferably in a darkened room. At minimum, the inspection station must be shielded from natural light and other glare.
- Light intensity at the inspection station must be maintained between 2,000 to 3,750 lux. More difficult-to-inspect items may require higher lux levels to identify defects; however, this may also increase visual fatigue.
- Manual inspection stations must be periodically checked using a calibrated light meter to ensure that light levels remain within the required range.

ACCEPTABLE QUALITY LIMIT (AQL) INSPECTION

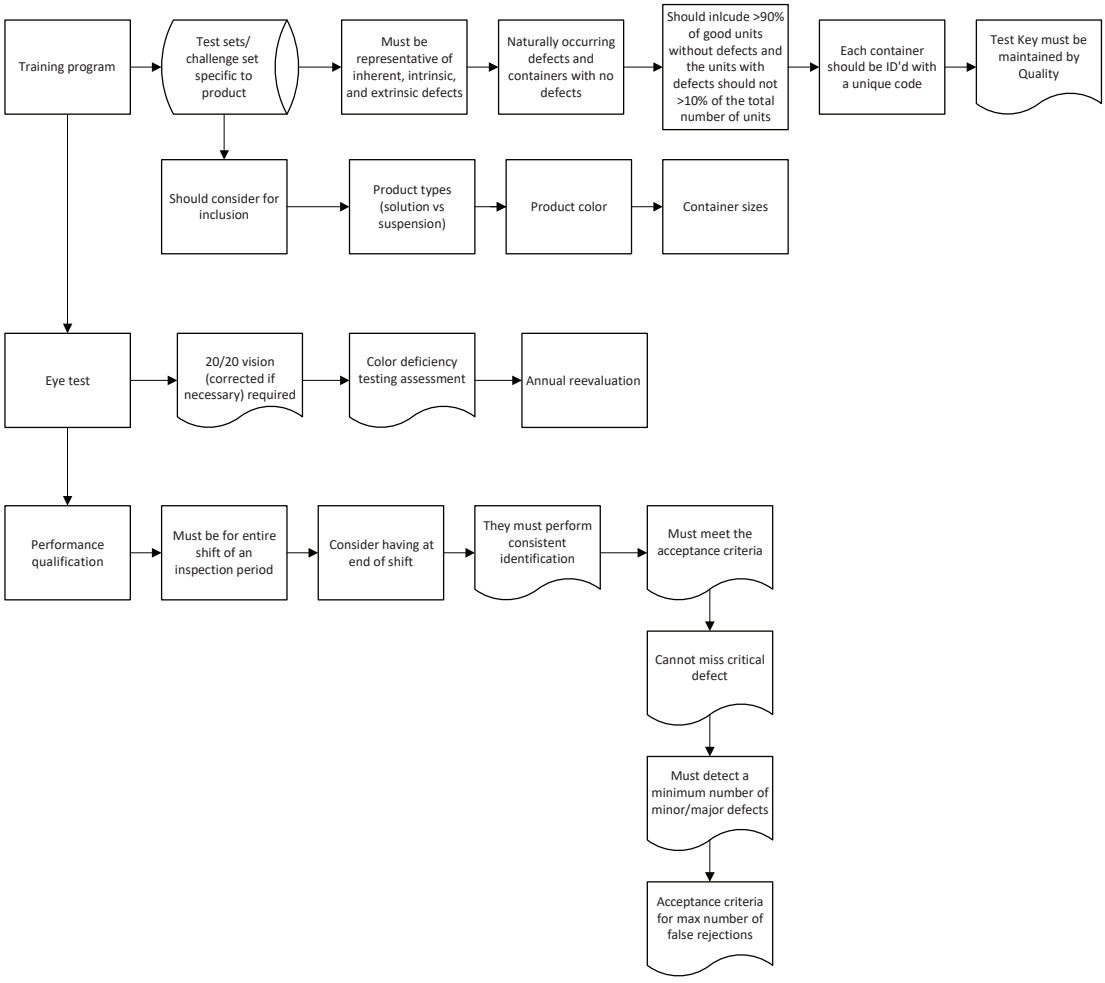
AQL testing is conducted by the quality unit on a selected sample set. It is used to assess a statistical representation of the batch and determine whether the inspection process was effective in identifying and removing defects—much like potency testing is performed by quality after manufacturing is complete [5].

- A statistical sampling must be conducted to determine AQL across the lot of all conforming material. These samples must be manually inspected.
- This AQL subset is part of the release criteria and serves as a verification of the 100% inspection performed on the lot. It must be done by the quality unit or under its supervision.
- The AQL samples should not be inspected by the compounder of the units or the operator who performed the initial 100% inspection.
- The number of samples selected for AQL [4,5] should be based on ANSI/ASQ Z1.4 [7] or ISO 2859-1 [8].
- Three general inspection levels—Levels I, II, and III—are outlined in Table 1. Unless otherwise indicated, Level II is the default. Level I may be selected when less stringent inspection is acceptable, while Level III is appropriate when more rigorous inspection is required. Four additional special inspection Levels—S-1 through S-4—are also provided in Table 1. These are intended for situations where smaller sample sizes are sufficient and a higher degree of sampling risk is acceptable [7].
- The general practice is to use inspection Level II with the single sampling plan when dealing with larger batch sizes. However, Level III may be used when targeting smaller batch sizes and when a higher level if risk is acceptable. Regardless of which inspection level is selected, a documented justification must be provided for that decision [7].
- AQL samples must be selected randomly across the lot.
- Depending on the circumstances, companies may apply normal, reduced, or tightened AQL acceptance criteria. For example:
  - Based on historical data, normal AQL inspection levels can be used and then reduced when consistent and acceptable justifications are available to do so.
  - If AQL results are routinely trending upwards, a tightened AQL may need to be applied. An example of a normal AQL inspection plan (see Table 1), a Tightened AQL inspection plan (see Table 2), and a reduced AQL inspection plan (derived from ANSI table, inspection Level III). However, the limits should be based on site data and must be justifiable based on a risk evaluation.
- The AQL inspection must follow the same inspection and qualification process as the 100% inspection.
- Any lot that fails to meet the AQL acceptance criteria must be investigated.

TRAINING AND QUALIFICATION

Paramount to the successful execution of any process is the consistent evaluation and enhancement of both the process itself and, more importantly, its personnel. Training is essential for processes

Figure 2: Visual inspection training program [7]



that rely on human intervention and activity. To ensure effective training, qualification is essential—particularly for consistent and robust evaluation of 503B products, especially when manual visual inspection is involved. Figure 2 outlines key components that a visual inspection training program should include.

In general, for manual visual inspection [5]:

- Inspectors must have 20/20 vision (corrected, if necessary) and pass a color deficiency test to be eligible for inspection duties. An annual re-evaluation is required.
- Inspectors must successfully pass manual performance qualification requirements, demonstrating consistent defect identification. Additionally, acceptance criteria must be clearly established for the performance qualification process.
  - Individual operators may not miss a critical defect during qualification.
  - Operators must detect a minimum number of defects for minor and major defects.

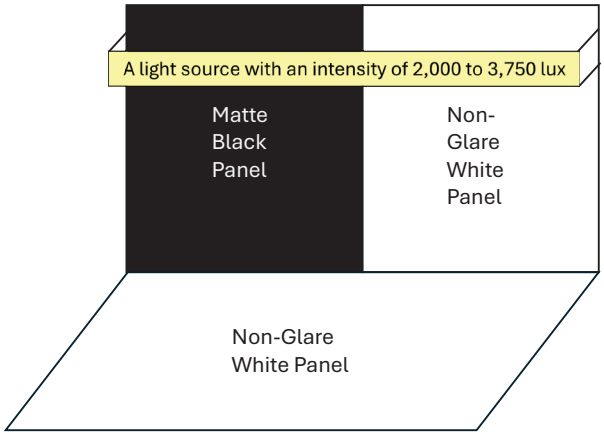
Acceptance criteria must be set for the maximum number of false rejections allowed.

- Performance qualification appraisal must also consider:
  - Ranges of container sizes
  - Product types (solution versus suspension)
  - Product color (yellow, red, clear, etc.)
  - Must be conducted in the same environment as inspections will be conducted (lighting, ergonomic considerations)
  - Must encompass the same amount of time as an inspection period to account for potential fatigue. Ideally, it should be conducted at the end of a shift to simulate real inspection conditions, and a reasonable time limit for completion should be established.

Technique

- Each container must be inspected on two backgrounds, one black and one white [5].
- Each container should be inspected for about 10 seconds—or approximately 5 seconds against eacch background.
- No magnification should be used.
- Gentle swirling/inversion should be done to place into motion any

Figure 3: Illustration of a visual inspection station



particles laying on a surface. Swirling should not be so vigorous as to cause excessive air bubbles.

- The operator is looking for particulates that are intrinsic or extrinsic (e.g., glass, fibers, stainless steel, etc.). These units should be removed to a separate area and are considered to be rejects.
- Units with particulates considered inherent product characteristics, such as product aggregates or precipitates, are not required to be removed from the batch as rejects, provided they have been previously identified as non-detrimental to product quality and are included as part of the product appearance specification.
- When intrinsic or extrinsic particulates are found and are not readily identifiable, the unit should be sent to a laboratory for particulate identification.



Inspection Challenges

- When the nature of the contents or the container-closure system limits full inspection of the unit, 100% lot inspection must be supplemented with destructive testing of a subset of the lot.
  - This may include inspection of reconstituted samples for dried samples (e.g. lyophilized), or for a dark amber container withdrawal of the contents of a sampling of containers from the lot may be required.
  - Samples must be selected randomly across the lot.
  - The number of samples selected should be based on ANSI Z1.4 [6] or ISO 2859-1 [8] using Inspection Level S-1.
  - Alternative sampling plans that provide equivalent or greater protection are acceptable, provided that appropriate justification is documented.
- An investigation must be conducted when an AQL failure occurs. If adequate justification is established supported by a risk evaluation, reinspection may be performed in acccordance with site SOPs [5]. Furthermore:
  - A deviation should be initiated.
  - The process should be pre-defined in the standard operating procedure (SOP or equivalent guiding document).

- Acceptance criteria for the reinspection must be pre-defined and should have tightened limits for the categories.
- A tertiary re-inspection is not typically justifiable.

In traditional pharmaceutical manufacturing, there is more time allocated for the development, testing, and refinement of production processes that support large-scale, long-term manufacturing. This allows for extensive research, validation, and optimization.

In contrast, pharmaceutical compounding often requires a time-sensitive response, whether due to the need to address drug shortages or in response to changing customer needs and shorter shelf life of their products. As a result, there is generally less opportunity for comprehensive process development, with greater emphasis placed on the rapid production of needed medications.

CONCLUSION

Visual inspection is a critical component in the compounding and manufacturing of parenteral products. Each facility should establish a program tailored to its specific products, environment, and applicable regulatory requirements. Effective training and clearly defined criteria are essential for the successful implementation of a visual inspection process, which serves as a cornerstone in demonstrating product quality.

Acknowledgements

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