Information Pills

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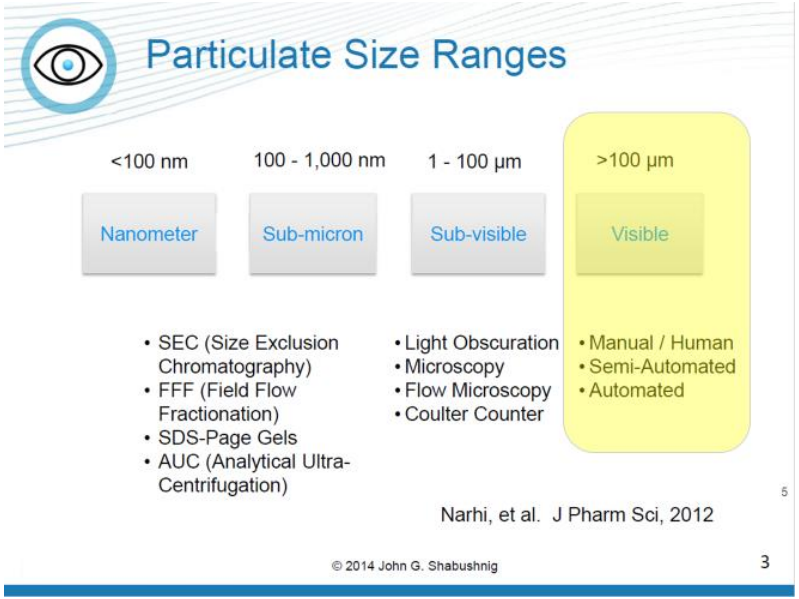
Agenda

- Common Myths and Misconceptions
- Pro & Cons CCI Methods

Particle Size and Capability of Detection



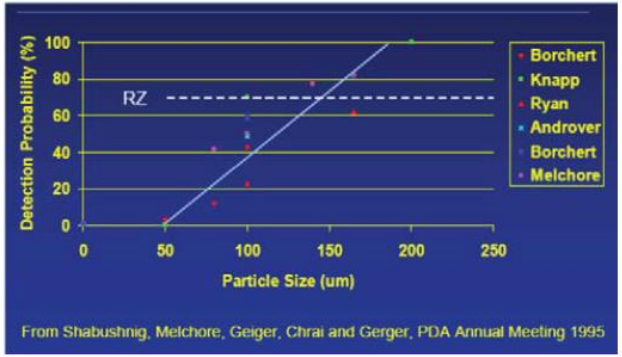
Source: USP Chapter <1790> Visual Inspection of Injections

Understanding human performance is critical to establishing visual inspection criteria. The threshold for human vision is generally accepted to be 50 µm. Individual receptors in the eye have a resolution of 11 µm, but typical resolving power is reported as 85–100 µm *[4]*. The detection process is probabilistic: the likelihood of detection is a cumulative function of visible attributes such as particle size, shape, color, density, and reflectivity. Analysis of inspection results pooled from several studies *[5]* *[6]* shows that the probability of detection for a single 50-µm particle in a clear solution contained in a 10-mL vial utilizing diffuse illumination between 2000 and 3000 lux is only slightly greater than 0%. The detection probability increases to approximately 40% for a 100-µm particle, and typically exceeds 95% for particles that are 200 µm and larger. Thus, in a qualified visual inspection system, the vast majority of extraneous particles that might go undetected and be introduced into the pharmaceutical supply chain will be smaller than 200 µm. Changes to the container (e.g., increasing size and opacity), fill level, and particle characteristics beyond size (e.g., color, shape, and density) will all affect the probability of detection.

[4] Delly JG. Diffraction lines: the eyes have it. Microscope. 1989; 37:195-211

Particle Size and Probability of Detection

Historical Detection Data



- Demonstrated across multiple studies detection capability directly relates to size and negligible detection at 50 microns
- Demonstrated reliable detection (> 70%) begins at ~ 150 microns

Critical step forward in visual inspection process characterization

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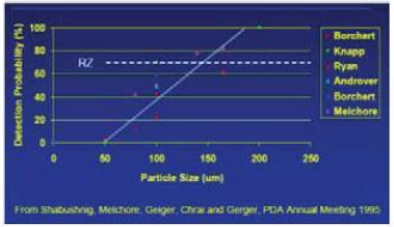
Understanding the Data

It is important to note that this 1995 study characterized particulate detection under highly idealized conditions:



- Clear liquid
- Vials
- Relatively large fill volumes
- Primarily Polystyrene particles – neutrally buoyant in water and therefore highly visible

Actual product inspection may have significantly different associated detection and poses a risk that the delta between published and actual may be misunderstood.

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Source: Shabushnig, Melchore, Geiger, Chrai and Gerger, PDA Annual Meeting 1995

Blue Dye Ingress

Pros	Cons
▪ Widely used industry standard, still accepted by regulatory agencies	○ Detectability of dye at which concentration?
	○ Qualitative (not linkable to leak size)
▪ Visual indication of the leakage	○ Destructive test
▪ Does not need aseptically filled units and is therefore suitable for development	○ False positive risks: ✓ Operator subjective, unreliable
	○ False negative risks: ✓ Poor sensibility with small leakages
▪ Detects clogs	○ Not reliable/repeatable in the detection of small-size closure integrity failure (< 20µm)

Vacuum Decay

Pros	Cons
▪ Can be used for 100% testing, non-destructive	○ Needs a special fixture for every container size
▪ Applicable to most package systems	○ Protein based liquid products at high concentration may prevent leak detection
▪ Overall package system is tested	○ Pre-filled Syringes stopper movement to be prevented during CCIT execution
▪ Easy validation: ✓ Flexibility in positive control choice (Laser-drilled holes, capillary tubes…) ✓ Quick sample preparation	○ Not a quantitative method ○ Sensitivity is a function of the vacuum chamber dead volume ○ Impact on the drug product – May produce product degradation (leakage below the threshold may cause non sterile ambient air ingress into the headspace) ○ Headspace sterile condition to be checked

High Voltage Leak Detection

Pros	Cons
▪ Can be used for 100% testing, non - destructive	○ Requires electrically insulated package system and nonflammable electrically conductive liquid product
▪ Quick	○ Not quantitative
▪ Applicable to protein based liquid products at high concentration	○ Headspace volume / filled volume: access of product in or near the leak
	○ More challenging validation (Laser-drilled holes only)
	○ Impact on the drug product – May produce product degradation

Headspace Gas Analysis

Pros	Cons
▪ Non-destructive, non-invasive, 100% inspection possible	○ Needs headspace bubble
	○ Requires unique standards for each container
▪ Quick	○ Requires inert headspace
▪ Potential Container Closure Integrity Testing	○ Requires quarantine after capping to perform Container Closure Integrity Testing