

Technical Brief

Subject: Establishing Compliant, Risk-Based Reject Limits for Automated Visual Inspection (AVI) Systems

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1.0 Executive Summary

This brief recommends a defensible, cGMP-aligned method for establishing in-process reject limits for pharmaceutical Automated Visual Inspection (AVI) systems.

A common pitfall is to transplant manual inspection AQL (Acceptable Quality Limit) rates into AVI operations. That conflates two different constructs: product quality sampling (AQL) versus real-time process control monitoring (AVI reject rates).

Recommended approach: adopt a Statistical Process Control (SPC) model that sets a “normal” reject baseline from the validated False Reject Rate (FRR) of the machine plus the process’s True Defect Rate (TDR). This is scientifically sound, regulator-defensible, and provides superior process understanding per USP <1790> and FDA’s Process Validation Guidance.

2.0 The Flaw in Using Manual Inspection Limits

Manual inspection limits (AQLs) must not be used as in-process control limits for AVI:

1. **Type I/II error exists for both humans and machines.** Human inspectors have non-zero false reject/false accept rates and must be qualified and periodically re-qualified per USP <1790>. An AVI system’s FRR is an inherent characteristic that must be quantified and accounted for.
2. **Detection bias (Probability of Detection, PoD).** Validated AVI is typically more sensitive than manual inspection, especially for Major/Minor defects. Porting a manual limit will trigger unnecessary deviations as the AVI detects more true defects.

Using a simple AQL-based limit creates a blind threshold. A 7% total reject rate could be 1% true defects + 6% false rejects (machine issue) or 6% true defects + 1% false rejects (process issue)—and you wouldn’t know which.

3.0 Recommended Methodology: A 4-Step Process for Setting AVI Limits

Establish a statistical baseline from validated machine performance and historical process capability.

Step 1: Characterize the Machine “Noise” (FRR).

Determine FRR during OQ using representative good sets per product/container format, speed, and illumination; confirm under routine conditions in PQ. Maintain format-specific FRR as a Continued Process Verification (CPV) parameter.

- *Example:* PQ for a 1 mL syringe shows a stable, validated FRR of **1.5%**.

Step 2: Determine the Initial Process Defect Rate (TDR).

Use historical manual-inspection quality data.

- *Example:* 0.1% Critical, 0.4% Major, 0.5% Minor → TDR = 1.0%.
- *Caveat:* Expect AVI to increase true-defect detection; re-baseline TDR after initial AVI campaigns (e.g., after 10–20 commercial batches) using CPV data.

Step 3: Calculate the Initial “Normal Operating” Center Line (p-bar).

This is the expected average for a normal batch and the basis for control-chart limits.

- $\bar{p} = \text{FRR} + \text{TDR}$
- *Example:* 1.5% + 1.0% = 2.5%

Step 4: Establish SPC Limits (sample-size dependent).

Use a **p-chart** (proportion nonconforming) at each monitoring interval (e.g., hourly) with actual sample size n :

- Center line: $\bar{p} = \text{FRR} + \text{TDR}$
- Std. dev.: $\sigma_p = \sqrt{\bar{p}(1 - \bar{p})/n}$
- Alert limit ($\approx +2\sigma$): $\bar{p} + 2\sigma_p$
- Action limit ($\approx +3\sigma$): $\bar{p} + 3\sigma_p$

Note: Consider EWMA (and/or Laney p') if over-dispersion or small n reduces Shewhart sensitivity.

4.0 Best Practice: Set Limits per Defect Category

For real process control, chart **each category** (and station where applicable), not just total rejects.

Example: Proposed Reject-Limit Structure

Reject Category	Historical TDR	Validated Machine FRR	Expected Rate (Center Line, $\bar{p}$)	Alert Limit	Action Limit
Critical defects (e.g., missing plunger)	0.10%	0.05%	0.15%	Statistical (+2 std. dev.)	Statistical (+3 std. dev.)
Major defects (e.g., particles, flange)	0.40%	0.85%	1.25%	Statistical (+2 std. dev.)	Statistical (+3 std. dev.)
Minor defects (e.g., cosmetic)	0.50%	0.60%	1.10%	Statistical (+2 std. dev.)	Statistical (+3 std. dev.)
Total rejects	1.00%	1.50%	2.50%	Statistical (+2 std. dev.)	Statistical (+3 std. dev.)

* Per EU GMP Annex 1 (§§8.30–8.33), any post-inspection finding of a Critical defect must trigger a formal investigation into inspection process failure. For rare criticals, consider adding a g-chart (units between events) alongside the p-chart.

5.0 Conclusion & Recommendation

This SPC-based method is industry standard for AVI and fully defensible. It anchors limits to validated machine performance (FRR) and process capability (TDR).

Recommendation: Implement the methodology, using robust PQ data to set initial baselines and SOP limits. Then trend and re-baseline under CPV.

6.0 Key Industry References

- **21 CFR Part 211 (Finished Pharmaceuticals)**
 - **§211.68:** Equipment must be routinely calibrated/inspected/checked per a written program to assure proper performance.
 - **§211.100(a):** Written procedures for production and process control to assure product quality.
 - **§211.110(b):** In-process specifications derived from process averages/variability and determined by application of suitable statistical procedures, where appropriate.

- **USP General Chapter <790>, *Visible Particulates in Injections***
Establishes that injectable products shall be “essentially free of visible particulates” and are subject to 100% visual inspection.
- **USP Informational Chapter <1790>, *Visual Inspection of Injections***
Primary methodology guidance: inspector qualification, representative test sets, comparative (Knapp-style) studies, and characterization of AVI performance (detection and false-reject rates).
- **FDA Guidance for Industry (Jan 2011), *Process Validation: General Principles and Practices***
Framework for modern validation; SPC-based monitoring aligns with Stage 3 – Continued Process Verification.
- **EU GMP Annex 1 (2022), *Manufacture of Sterile Medicinal Products***
 - §8.32: AVI performance should be challenged with representative defects prior to start-up and at regular intervals throughout the batch.
 - §§8.31–8.33: Defect classification, trending, statistical principles, and investigation of unusual defect levels.