



Inspection Validation Methods

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Agenda

- Requirements / Specifications
- Installation Qualification
- Human Baseline Performance
- Test Set Composition
- Operational Qualification
- Performance / Process Qualification
- Routine Performance Verification



Validation vs. Qualification

- Equipment must be validated
 - IQ/OQ/PQ
- Human inspectors are trained and qualified
 - NOT validated



Human Performance Baseline

- Establish human inspection performance with defect test set.
- Can use to make direct comparison to compendial inspection method.
 - USP and EP



Inspection Standards



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Test Set Composition

- Defects to include in Test Set
 - Multiple examples of anticipated defects
 - Weighted toward critical defects
 - Defect examples are qualified by multiple inspection by qualified inspectors. Reject zone defects (with POD \geq 70%) selected for inclusion.
- Typical Test Set Size
 - 500 to 1000 units



Test Set Composition

- Production Defects vs. Standards
 - “Real” defects necessary to validate production performance
 - Standard spheres useful to establish baseline, compare methods and settings and monitor routine performance
- Defect rate in test set
 - For human studies, 10% or less is preferred to avoid Hawthorne Effect (positive reinforcement)
 - Not relevant for machine studies



Human Qualification

- Inspector Selection
 - Visual Acuity (near-vision)
 - Color Perception
- Initial Training
 - Defect Examples
- Initial Qualification
- Periodic Requalification



Knapp Method

- Multiple inspections of test set to determine reject probabilities of individual units
- Sort results into the following ranges:
 - Accept Zone: $P = 0.0$ to 0.3 (<30%)
 - Gray Zone: $P = 0.3$ to 0.7 (30-70%)
 - Reject Zone: $P = 0.7$ to 1.0 (>70%)
- Calculate Reject Zone Efficiency (RZE)
- Calculate Accept Zone Loss (AZL)



RZE

$$RZE = RZR/RZN$$

Where:

RZR = Reject Zone Rejects, the number of vials rejected in the Reject Zone

RZN = Reject Zone Number, the total number of vials in the Reject Zone



Knapp Method

- Calculate comparable terms for the Gray and Accept Zones.
- Accept Zone Loss (AZL) is a measure of the false reject rate.
- The RZE for an alternative method should be the same or better than the reference method.
- Gray Zone vials may be “sacrificed” to achieve higher RZE.



Knapp Method

- Remember, as originally published, this method was designed to assess inspection for particles only.
- To apply the method to the full range of visible defects normally addressed, it is necessary to categorize defects by risk and determine an RZE for each risk category.
- As published, defect test sets have a ~30% defect rate. This is very high and likely to bias the results. A defect rate of 10% or less is recommended.



How often are inspectors requalified?

| | 2023 | 2014 | 2008 | 2003 | 1996 |
|----------------------|------------|------|------|------|------|
| Never | 0% | 5% | 21% | 8% | 35% |
| Monthly | 0% | 1% | 5% | 0% | 8% |
| Quarterly | 1% | 4% | 0% | 0% | 8% |
| Semi-Annually | 11% | 10% | 11% | 8% | 16% |
| Annually | 87% | 79% | 63% | 75% | 69% |
| Biennially | 1% | ND | ND | ND | ND |

ND = No Data, Question not asked in these survey years

From 2023 PDA Visual Inspection Survey



Equipment Validation (Manual and Semi-Auto Inspection)

- Equipment Specifications
- Installation Qualification (IQ)
 - Utilities
- Operational Qualification (OQ)
 - Light Intensity
 - Inspection Rate (Semi-Auto)
 - Rotation (Semi-Auto)
 - Rejection (Semi-Auto)
- Process Qualification (PQ)
 - Operator Training and Qualification



Specification / Requirements

- User Requirements and Specifications (URS)
 - Good validation starts with clear documentation of the performance expectations for the new equipment.



Factory Acceptance Test (FAT)

- Equipment performance should be confirmed before acceptance for shipment.
 - Check against URS
 - Inspection performance should be tested with samples defects.
 - The false reject rate should also be determined.



Installation Qualification (IQ)

- Installation Qualification (IQ) should document receipt and installation of equipment
 - Model and serial number
 - Features / operating ranges
 - Version numbers of software / firmware
 - Verify utility connection(s)
 - Calibration
 - Spare parts
 - Change parts



Operational Qualification (OQ)

- Operational Qualification (OQ) should document proper function of equipment component systems
 - Emergency stop(s)
 - Eject system(s)
 - Man/Machine Interface (MMI)
 - Reports
 - Other features?
 - e.g., lamp failure detection
 - Establish appropriate operating ranges



Operational Qualification (OQ)

- Detection probability for each defect type
 - Compare with human baseline
 - Establish reference for routine continuous performance verification.



Validation Criteria

- 100% validate automated inspection equipment.
- Validation Criteria:
 - **Equivalent or better than manual: 77%**
 - Other, Not compared to manual: 19%
 - Hybrid, Particles and/or Critical and Major defects equivalent or better than human and Minor defects compared to a fixed criterion: 4%

From 2023 PDA Visual Inspection Survey

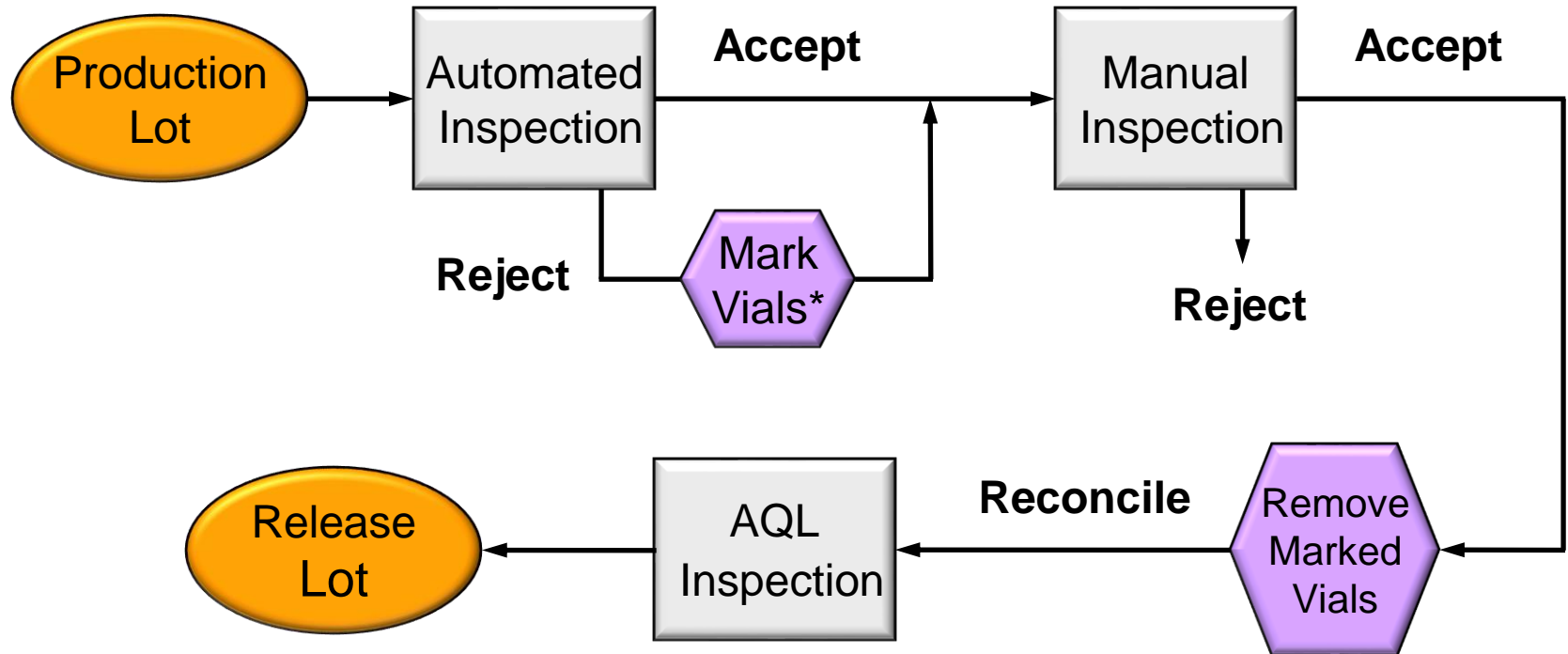


Performance/Process Qualification

- Performance / Process Qualification (PQ) confirms expected performance with full production lots
 - Method 1
 - Inspect three production lots by both manual and automated methods
 - Compare defect detection rates
 - Determine false reject rate
 - Method 2
 - Inspect three production lots by automated method and use a tightened sampling plan to assess performance
 - Determine false reject rate



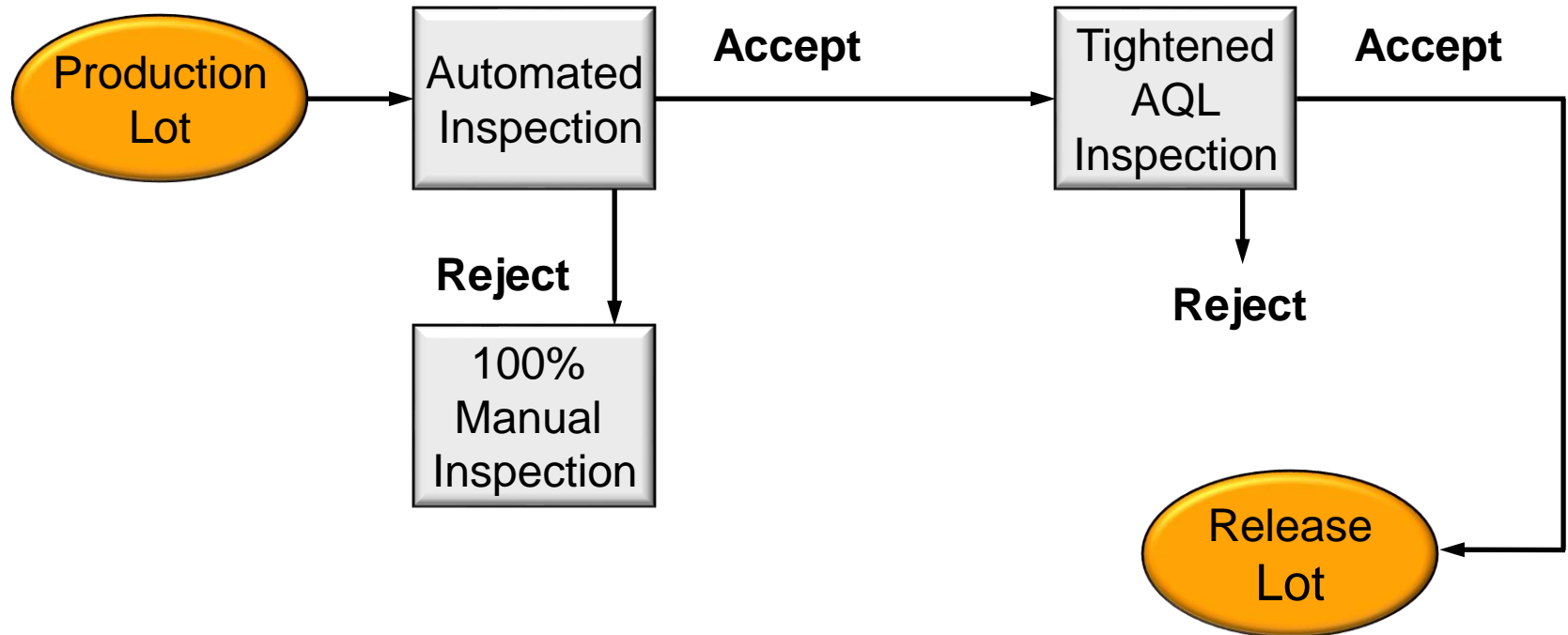
PQ Method 1



* Vials marked with UV ink; not visible during Manual Inspection



PQ Method 2



Complete 3 lots and approve validation report before releasing lots



Routine Performance Verification

- Typically run before each batch
- Small test set to challenge each sensor/camera station
- Gross examples to assure rejection, Go/No Go test
- Does not challenge sensitivity, but rather camera alignment, functionality and proper operation of reject system.



How frequently do you challenge or retest automated inspection equipment?

| | 2023 | 2014 | 2008 | 2003 | 1996 |
|-----------------------------|------------|------|------|------|------|
| Never | 4% | 1% | 0% | 0% | 15% |
| Each Shift | 7% | 1% | 8% | 13% | 8% |
| Start of Lot | 50% | 46% | 42% | 75% | 38% |
| End of Lot | 3% | ND | ND | ND | ND |
| Start and End of Lot | 1% | 8% | ND | ND | ND |
| Daily | 15% | 15% | 25% | 19% | 23% |
| Weekly | 2% | 2% | 0% | 0% | 8% |
| Monthly | 0% | 2% | ND | ND | ND |
| Quarterly | 4% | 1% | ND | ND | ND |
| Annually | 25% | 19% | ND | ND | ND |
| Other | 3% | ND | ND | ND | ND |

ND = No Data, Question not asked in survey from this year

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Remember, everyone is an inspector!

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