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

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 ≥ 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 to1.0 (>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

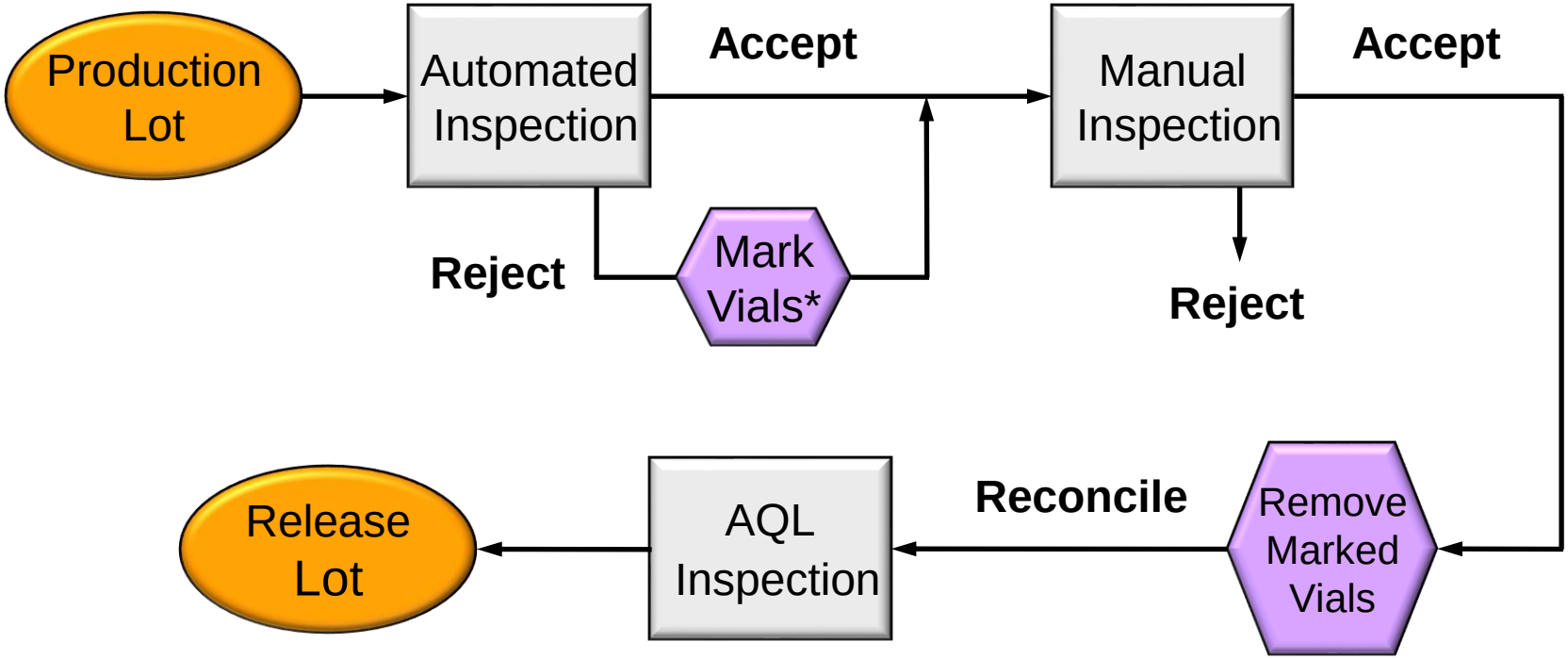
- 100% validate automated inspection equipment.
- Validation Criteria:
  - Equivalent or better than manual: 77%
  - Other, Not compared to manual: 19%
  - Hybrid, Particles and/or Critical and Major defects equivalent or better than human and Minor defects compared to a fixed criterion: 4%

From 2023 PDA Visual Inspection Survey

Performance/Process Qualification

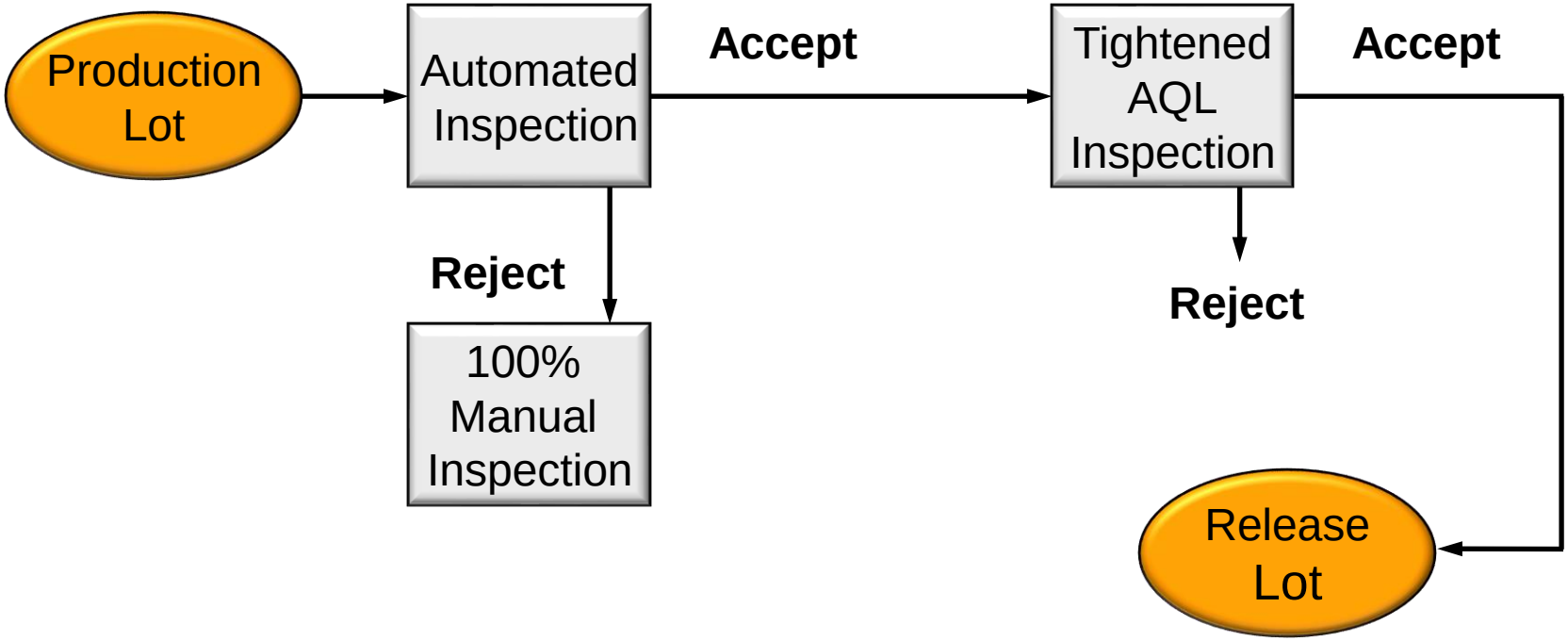
- Performance / Process Qualification (PQ) confirms expected performance with full production lots
  - Method 1
    - Inspect three production lots by both manual and automated methods
    - Compare defect detection rates
    - Determine false reject rate
  - Method 2
    - Inspect three production lots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

Remember, everyone is an inspector!