Visual Inspection of Sterile Drugs

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Agenda

1. Regulations and Guidelines
2. Overview of Visual Inspection Elements
    - Visual Methods
    - Equipment
    - Standards
    - Training and certifications
    - Process controls
    - Defect libraries
3. Key Takeaways

Regulations and Guidelines

Regulations/Requirements

- US: FDA – CFR 21, 211.82
- US: USP ⟨790⟩
- Europe: Ph. Eur. 2.9.20
- Europe: EU GMP Annex 1

Guidelines

- FDA Draft Guidance – Dec 2021
- USP⟨1790⟩
- Europe Ph. Eur. 5.17.2
- Others - PDA (Parenteral Drug Association)

Regulations and guidelines require 100% of parenteral products to be inspected for particles and container defects

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Particles and Container Closure Integrity

- Zero defects / Zero particles…
- Monitoring defects…
- When to investigate…

Industry-wide limitations prevent achieving zero defect product

Continuous improvement is expected

For Defect Control… Prevention is better than detection.

Holistic Approach:

- Raw materials
- Facility Design
- Equipment design and function
- Operational Procedures
- Personnel Training
- Component Prep
- Formulation process

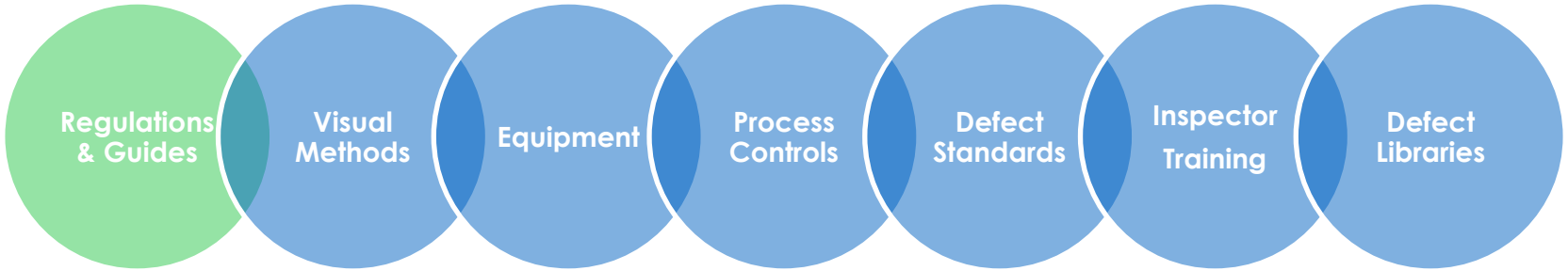
Visual Inspection Elements

- Regulations & Guides
- Visual Methods
- Equipment
- Process Controls
- Defect Standards
- Inspector Training
- Defect Libraries

All the elements work together to deliver products that are in compliance and are essentially or practically free of particles

Visual Inspection Elements

Regulation requirements	USP <790>	Ph. Eur. 2.9.20
Product requirement	Inspect 100% of units	Inspect 100% of units (guide EP 5.17.2)
Illumination Intensity (lux)	Minimum between 2,000-3,750	2,000-3,750
Inspection Time (sec)	10 sec	10 sec
Background	Black/White	Black/White
Technique	Be gently swirled and/or inverted	Gently swirl or invert the container
Acceptance Criteria	Sampling per ANSI Z1.4 is acceptable. The batch is considered **essentially free of visible particulates**	A successful AQL inspection indicates that the batch complies with the requirement **practically free from visible particles**



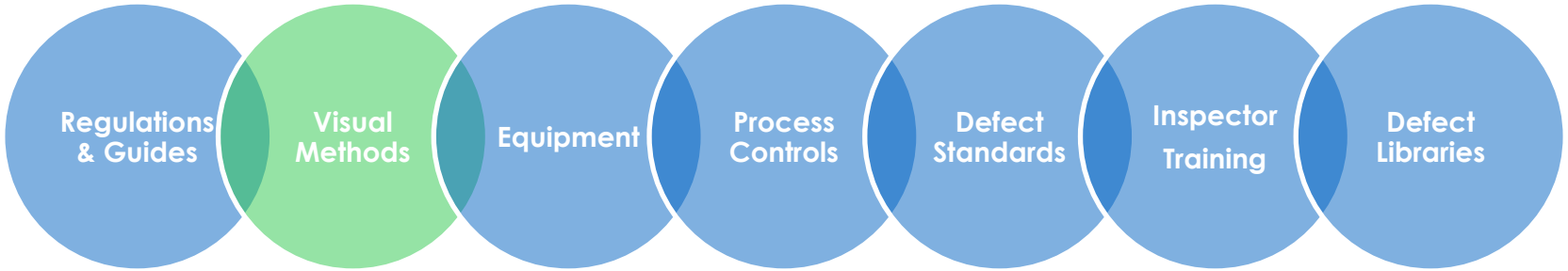
Visual Inspection Elements

TYPES OF VISUAL INSPECTION

There are three types of visual inspection:

- **Manual visual inspection** (MVI): reference inspection method described in all the major pharmacopeias. It consists of viewing filled and sealed containers under controlled conditions. The quality decision to either accept or reject the container is made by a trained inspector.
- **Semi-automated visual inspection** (SAVI): combines automated material handling of the containers to be inspected with human vision and judgment to make the decision to accept or reject.
- **Automated visual inspection** (AVI): combines automated material handling of the containers with electronic sensing of product appearance. Containers that meet the criteria are accepted by the machine. Containers that do not, go to a second stage inspection or are rejected.

More companies are adopting the use of AVI systems. Typically dictated by large batch sizes.

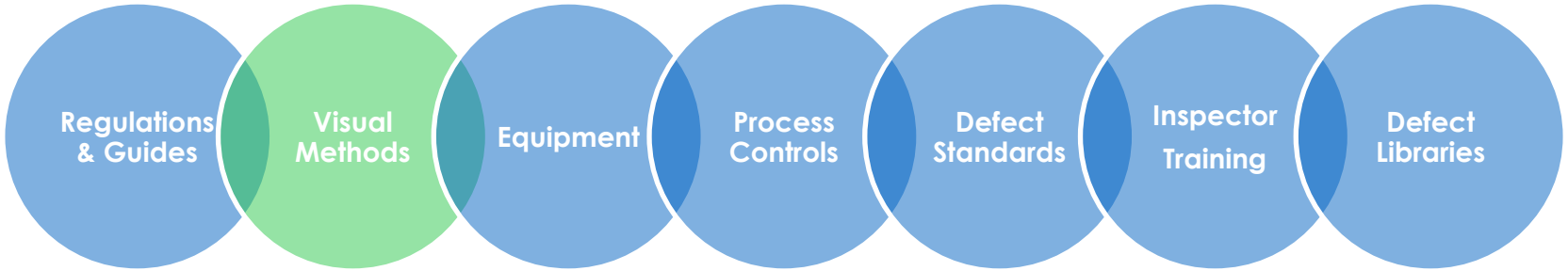


Visual Inspection Elements

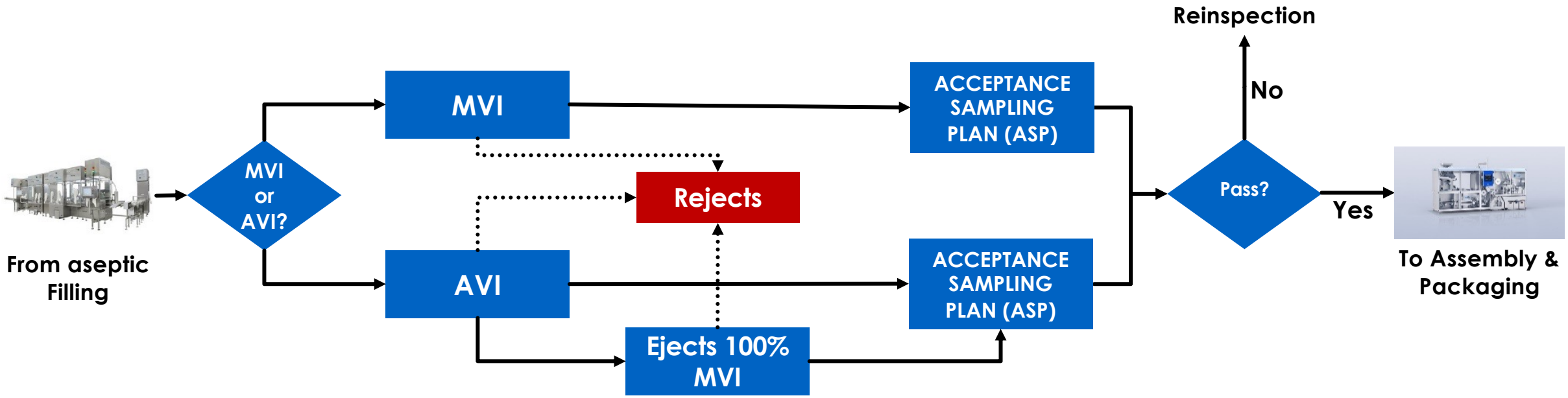
The industry is seeing an increased emphasis by regulators on having a well-characterized and robust inspection process, especially regarding **particulates.**

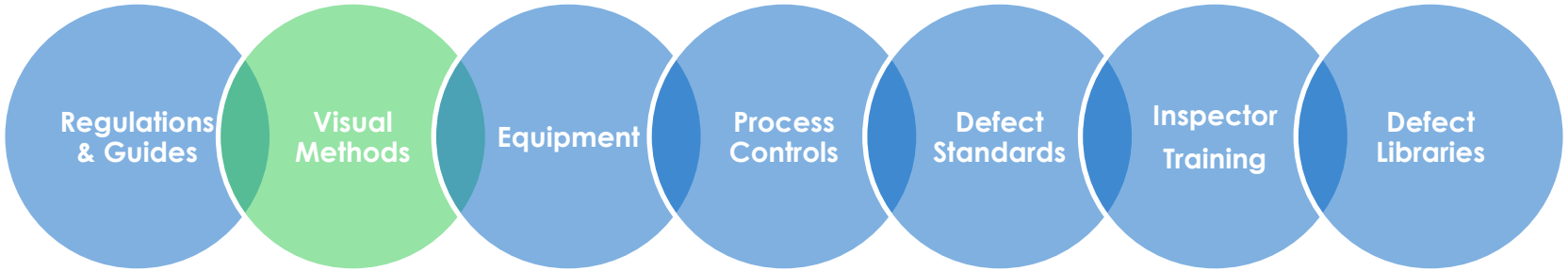
PARTICLE DETECTION & KNAPP METHODOLOGY

- The Knapp study intends to quantify the efficiency of the established MVI process and document the capability of the inspectors to detect defects
- According to USP: Secure probabilistic data for particulate standards can be achieved with 30-50 inspections per container
- The studies are typically executed using defect standards with a single seeded particle
- Size ranges of 100-500 µm and fibers ranging up to 2,500 µm are used
- Study proportion of approximately 90% good units and 10% units with particles is typical
- The performance of the automatic visual inspection (AVI) system is required to be equal to or better than the performance of the MVI process
- Knapp studies are becoming an expectation by auditors during inspections



Visual Inspection Elements





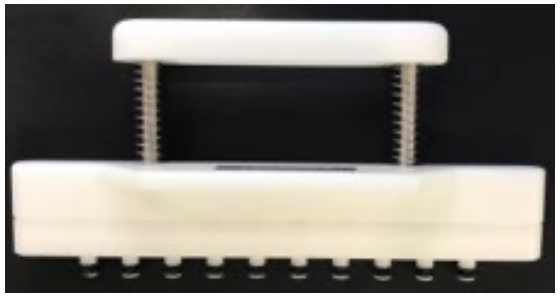
Visual Inspection Elements

Image from Syntegon web page catalog

https://www.syntegon.com/solutions/pharma/semi-automated-and-manual-visual-inspection/

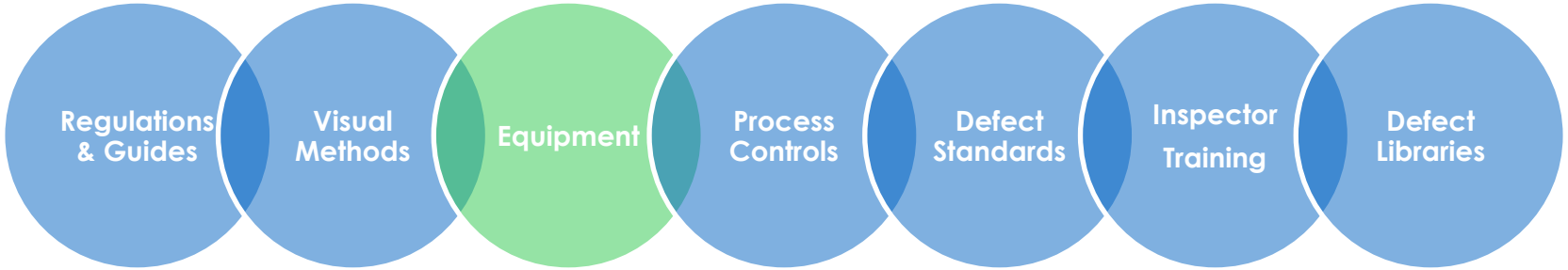
Manual Inspection Booth

- Both white and black backgrounds are used to aid inspection of various defects
- Used for both syringe and vial inspection
- Illumination at the inspection point is maintained at a minimum intensity between 2000 and 3750 lux
- Additional controls may be added to the booth to assist in time keeping and sequence



The inspection may require use of a holding tool

Inspectors wear corrective glasses if needed

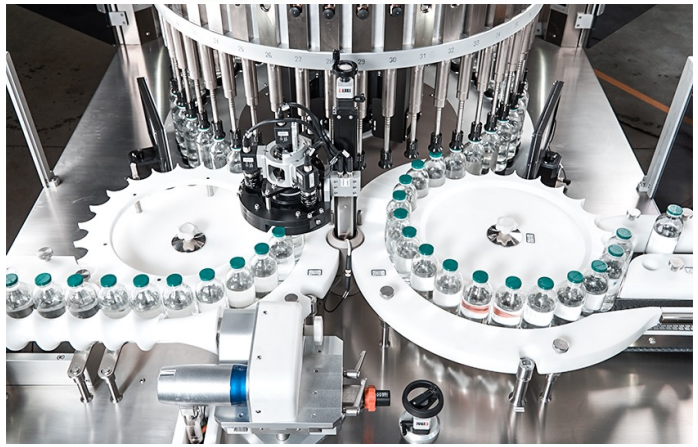


Visual Inspection Elements

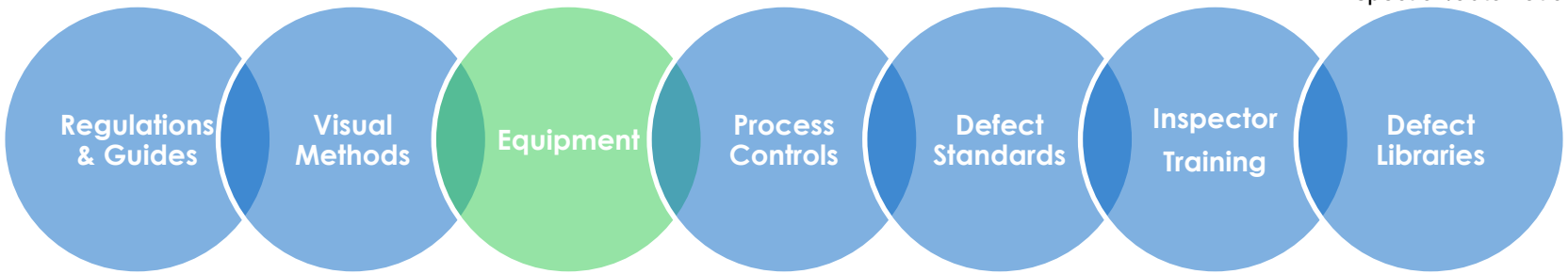
Automatic Visual Inspection (AVI) Machines

- Several manufactures provide AVI solutions for vials, syringes, ampoules and cartridges.
- AVI is typically used **to support high-volume** product inspections
- Per USP – The qualification acceptance criteria for an AVI system must be **equal to or better than MVI** in terms of detection
- From USP ⟨1790⟩ "AVI may also offer enhanced sensitivity for some defects, compared with MVI, but may **suffer from higher false rejection rates** due to the inability to tolerate normal variation in containers or product.

https://www.koerber-pharma.com/en/solutions/refurbished-machinery/automatic-inspection-seidenader-cs30



https://www.stevanatogroup.com/en/offering/visual-inspection/automatic-inspection-equipment/plus-lvp/



Visual Inspection Elements

Automatic Visual Inspection (AVI)

- Most AVI processes are really a **two-stage process** where ejects (units with uncertain disposition) are manually inspected (flow chart from USP ⟨1790⟩ page 6/20)

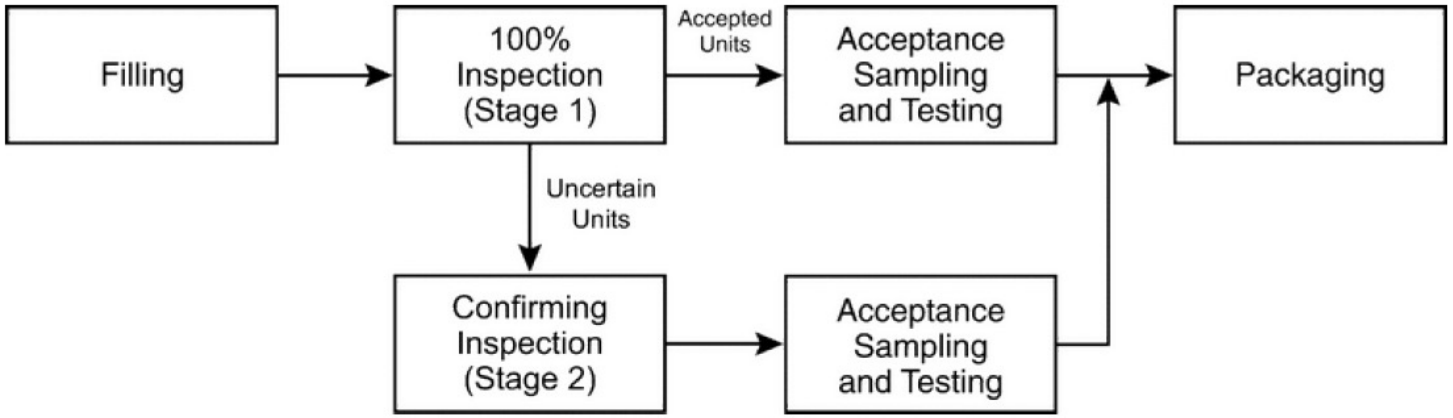
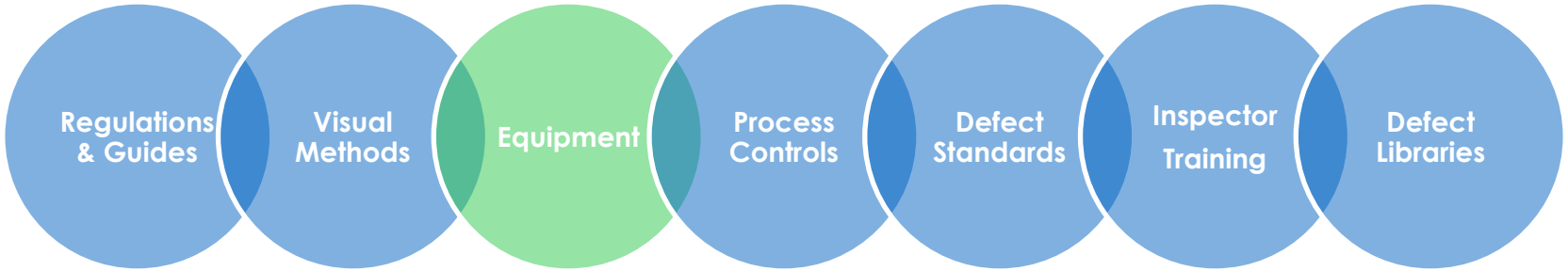


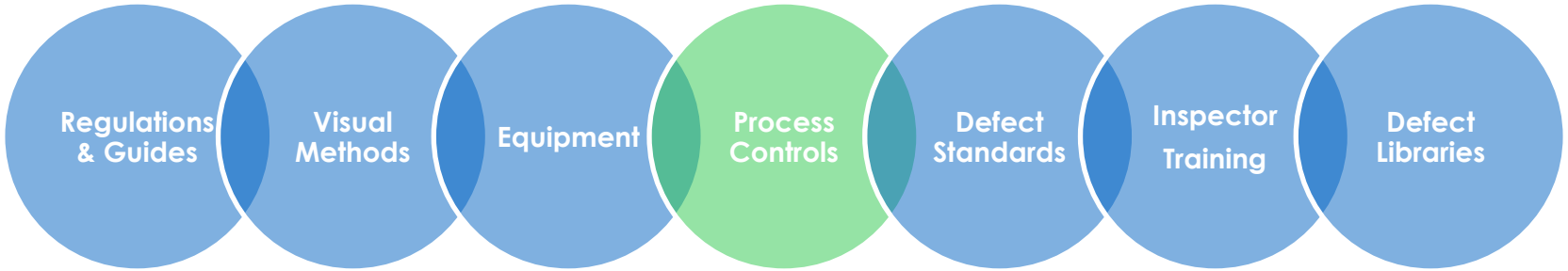
Figure 2. Two-stage inspection process flow chart.



Visual Inspection Elements

Inspection Process Controls

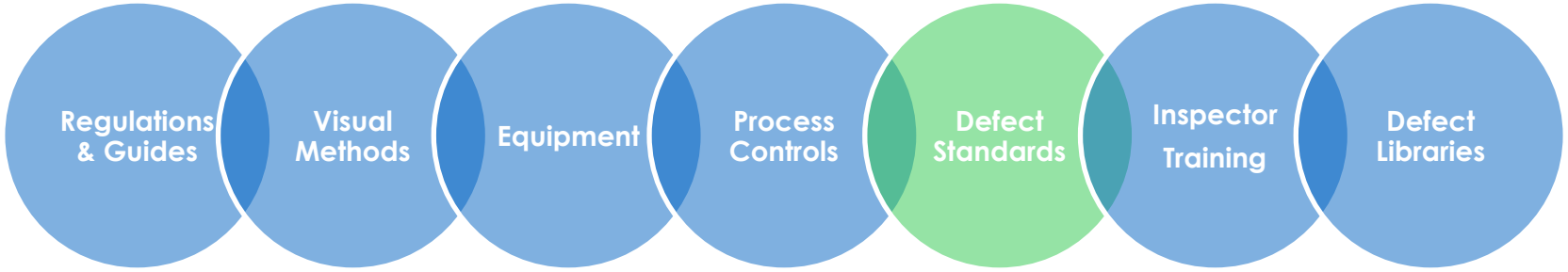
- Sampling Plans
  - Per USP & EP – ANSI/ASQ Z1.4 or equivalent is acceptable
  - If no particles are observed in sampling, the batch may be deemed essentially free of particles
- Established defect rate action alerts (limits)
  - Per USP - Defect rate limits are established using statistical principles to determine if the batches behave within current process capability
- Continuous Improvement - Adverse results or trends are investigated as part of the quality system and acted upon to continuously improve the process (defect prevention)



Visual Inspection Elements

- Defect standards are lab or process-generated units that are representative of product with selected defects (particles & container)
- Per guidelines: Use single particle seeded containers
- Defect Standards are used in both, the MVI and AVI method development and qualifications.
- Certified defect standards are placed in sets (panels) for the training/certification of inspectors (typically 10% defectives)
- Standard generation and certification follows SOPs. Unit traceability is highly recommended

https://www.syntegon.com/solutions/pharma/semi-automated-and-manual-visual-inspection/



Visual Inspection Elements

Training

Visual Acuity Tests: Certified by a physician or an optometrist examiner based on the following criteria:

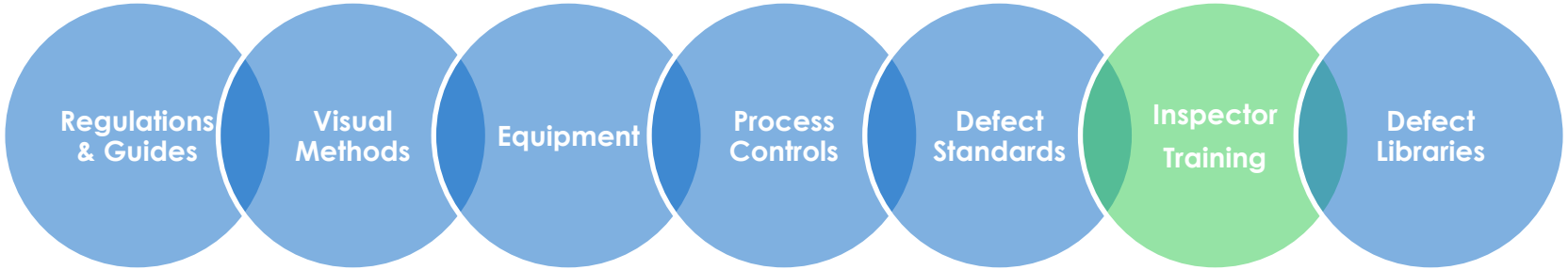
- 20/20 visual acuity (near vision)
- Color perception (Ishihara) test
- Depth perception
- Annual Re-Certification

On the Job Training: Procedural and skill development training

- Practice defect identification and technique mastery using blind defect panel sets to an acceptable fluency level.

Performance Criteria: Initial and yearly examinations are provided

https://www.pda.org/pda-letter-portal/home/full-article/qualification-of-manual-visual-inspection-still-critical



Visual Inspection Elements

Sampling plans (AQLs) are based on defect criticality

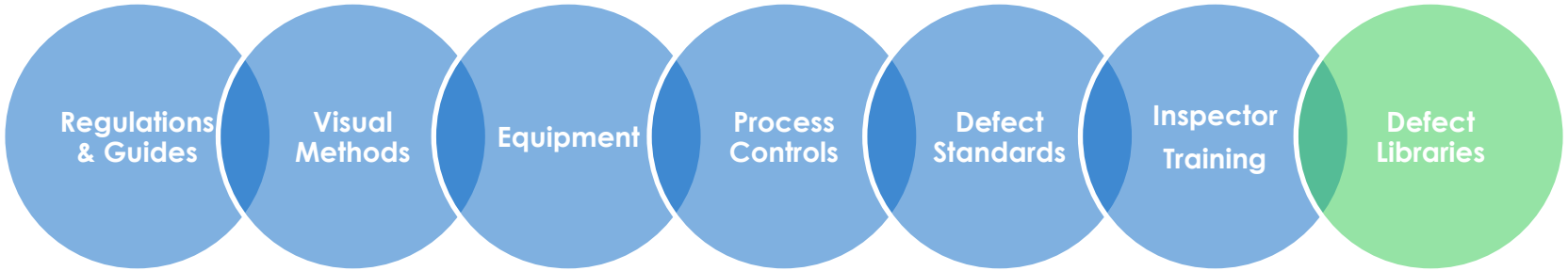
Table 1. Typical AQL Values for Visual Inspection Processes.

Defect Category	AQL Range (%)
Critical	0.010–0.10
Major	0.10–0.65
Minor	1.0–4.0
[NOTE—When selecting a sampling plan for AQL testing after 100% inspection using ANSI/ASQ Z1.4, ISO 2859, or JIS Z9015, choose the sample size to satisfy the AQL value for the most critical category (e.g., critical) of defects being evaluated. Then use the accept numbers for this sample size for the AQL values chosen for the other defect categories (e.g., major and minor). This assures that the sample size will produce a statistically valid result for all defect categories examined. The defect categories shown here represent a common basic approach to grouping defects by risk; however, additional categories may be added to these for more detailed analysis.]	

Table from page 4/20 USP <1790>

Define Defect Categories

Defects must be catalogued into categories based on risk to patient or product quality

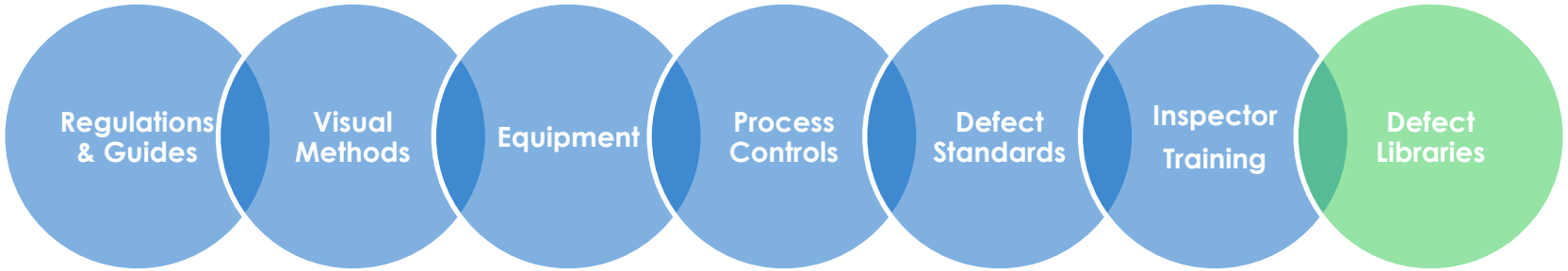


Visual Inspection Elements

Defect Libraries

- Defect library creation is an expectation per USP & Annex 1
- Contains Images and descriptions of defects including defect category (e.g. critical, major, minor)
- Defects represent container supplier's and manufacturing generated defects
- Should be used for training of manufacturing and QA
- May contain studied conditions that are deemed acceptable

Defect Library
Defect1
Description
Classification
Example Pictures
References/Sources



Key Takeaways

- Regulator expectations as well as **cGMP are always evolving**
- Guidelines for the visual inspection process are limited – **practices vary across the industry**
- There is a **growing expectation of products free of defects and particles**
- **Inspection is probabilistic & part of a holistic effort** to control and minimize particles, contamination and container defects
- Methods and practices **must be developed and validated** to ensure detectability
- All visual inspection elements described here work together, interacting as a system
- **The Importance of data**: Supports studies, validations, training, certifications, trending and continuous improvements
- Inspectors expect manufacturers to self-identify areas of opportunity using data and trends, and act accordingly

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Questions?