PDA®
Parenteral Drug Association
D/A/CH Chapter

PDA D/A/CH Chapter Webinar:

Visual Inspection

February 26th, 2025

Your Expert Lineup for Today's Webinar

Roman Mathaes
Chief Executive Officer
Clear Solutions Laboratories

Elisabeth Wagner
Senior Lead Visual Inspection
CSL Behring

Markus Adlberger
Product Owner
Visual Inspection Software
Koerber Pharma Inspection

Antonio Burazer
Global Head Visual
Inspection & Particle LCM
Takeda

Agenda – Wednesday February 26th, 3-4.30PM CET

Intro	**Welcome & Introduction** Antonio Burazer, Takeda (Vienna)
1st presentation	**Introduction to Regulatory Framework for Visual Inspection** Roman Mathaes, Clear Solutions Laboratories (Basel)
2nd presentation	**Training and Qualification for Manual Visual Inspection (MVI)** Elisabeth Wagner, CSL Behring (Bern)
3rd presentation	**Semi-automated and Automated Visual Inspection** Markus Adlberger, Koerber Pharma Inspection (Markt Schwaben)
Q&A	**Chat and live questions answered by the panel** Panel: Roman Mathaes, Elisabeth Wagner, Markus Adlberger Moderator: Antonio Burazer

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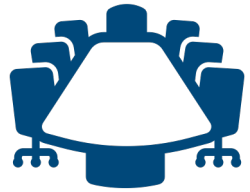

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PDA Visual Inspection Forum 2025

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2

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Visual Inspection of Parenterals IG

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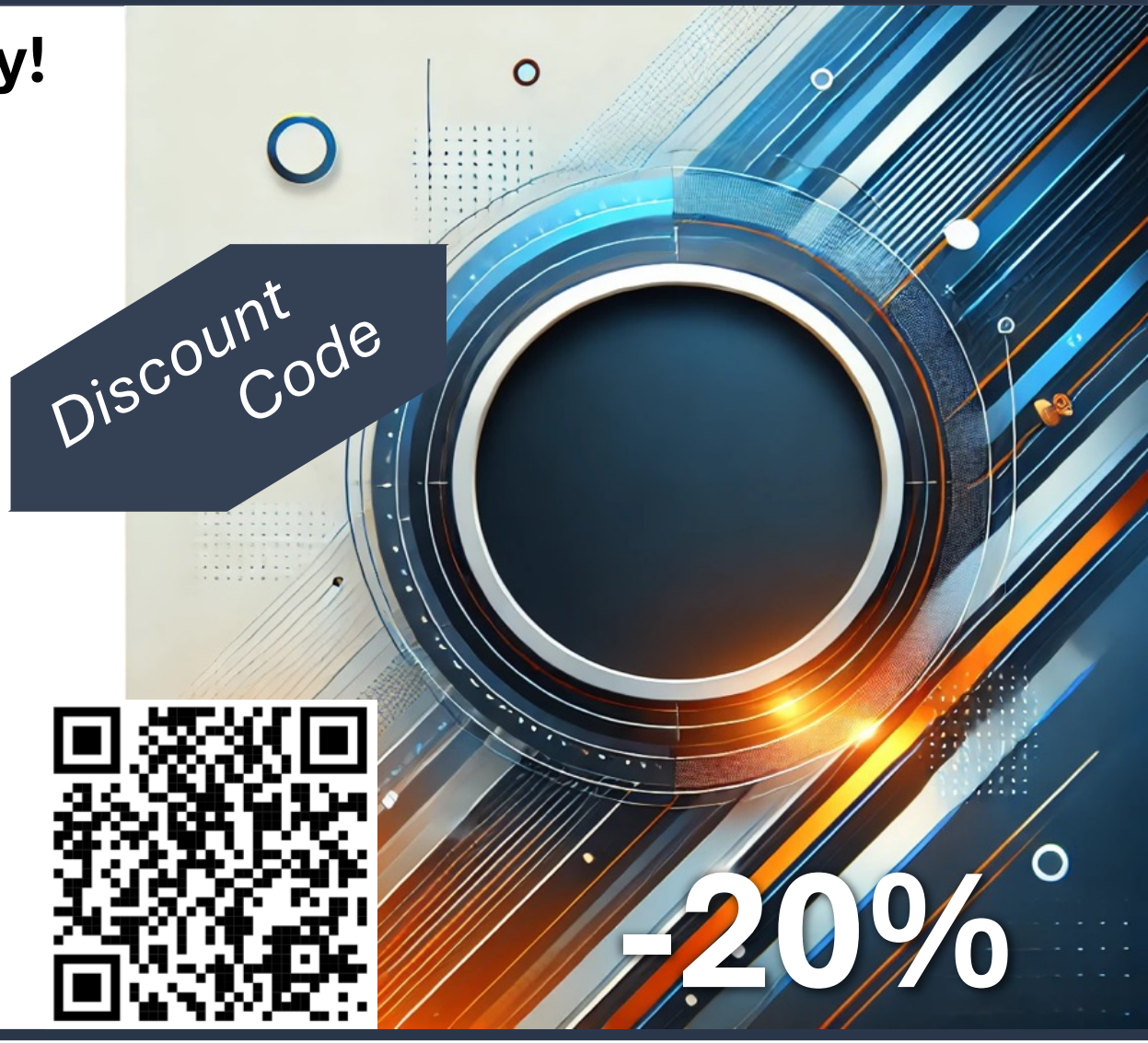

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Introduction to the Regulatory Framework for Visual Inspection

Roman Mathaes
Clear Solutions Laboratories
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Visual inspection in Parenteral Products: Why inspect?

- Main goals of VI
  - Patient Safety Risk
  - Product quality
  - GMP Process Control, CCI
- Typical focus of quality audits & inspections, often related to critical findings
- Process knowledge and improvements

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Examples of Recent Observations

FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

August 08, 2023

1. **Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)].** Specifically, your firm's sampling plan and test procedure for (b) (4) freezing bags ("Cryobags"), the primary container for [redacted], are not appropriate to assure that Cryobags are "free of…particulate matter" as required by your acceptance criteria. Between December 2018 and the date of the inspection, you identified approximately one hundred (100) batches of [redacted] contaminated with foreign particulate matter, such as wood, cellulose, brass, and steel. In November 2020, your firm concluded the Cryobags were the

(b) Your procedure for removing particulates detected in [redacted] in final product does not provide assurance that all particulates, including particulates that are not easily visible, can be identified and removed such that the final product, delivered through intravenous infusion, is free from contamination with foreign particulate matter. You have identified "sterility issue[s]" and "thrombosis issue[s]" as potential risks associated with particulate contamination.

WARNING LETTER

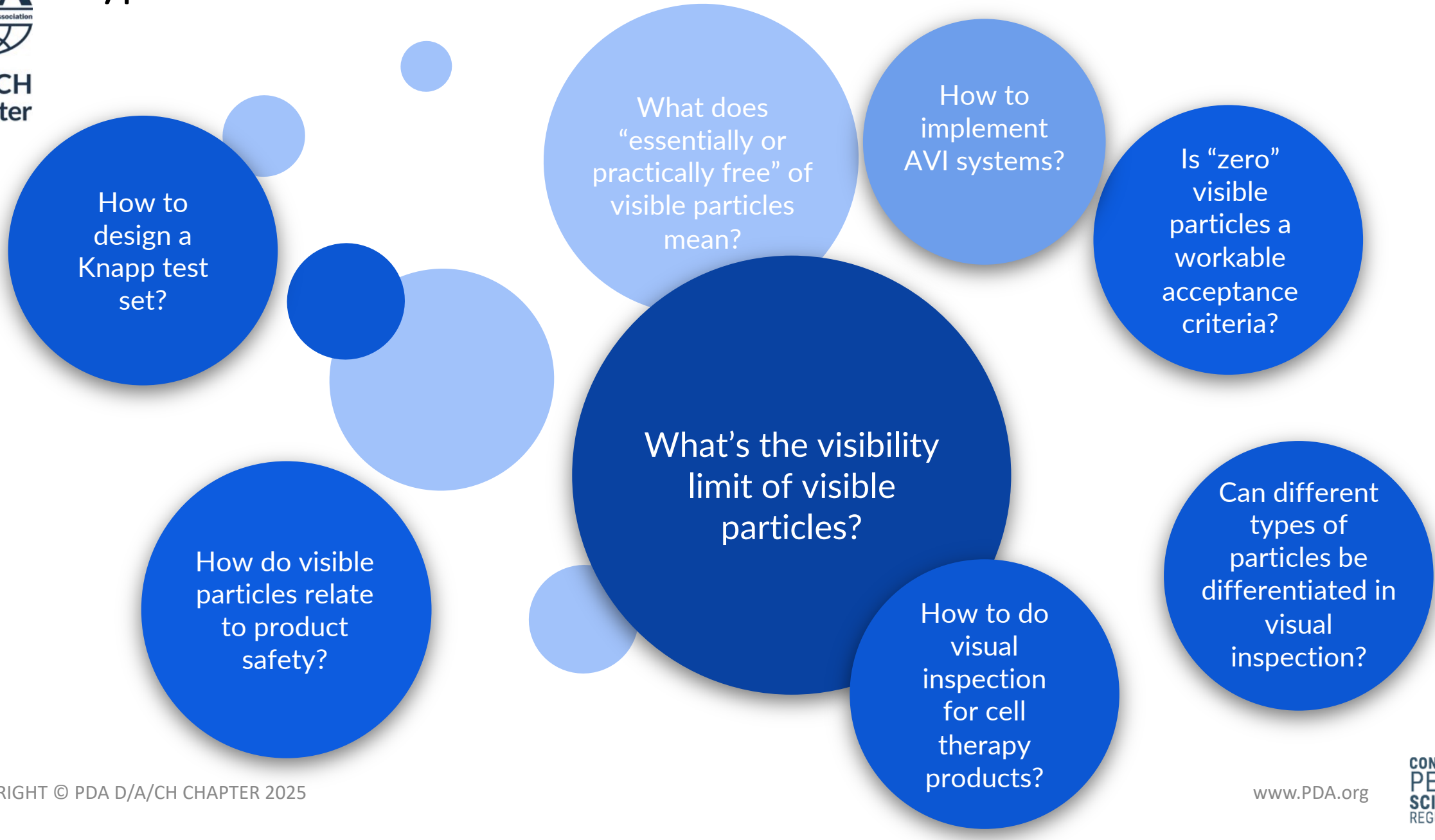
[redacted]

MARCS-CMS 6[redacted]- JANUARY 15, 2025

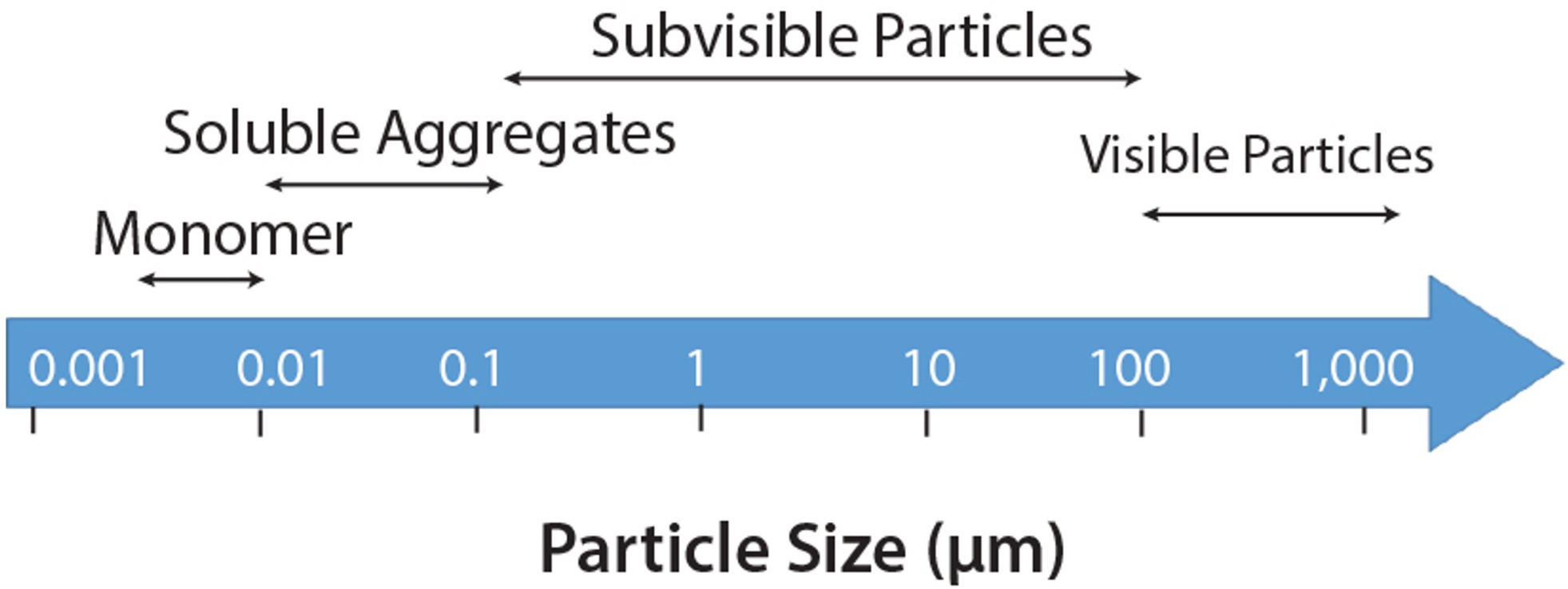
A. Two lots of **(b)(4)** and three lots of **(b)(4)** were out-of-specification (OOS) for appearance due to the presence of **(b)(4)** particles and were not adequately investigated.

• and revising your procedure governing appearance testing of APIs to ensure the observation of particles will result in an investigation that includes particle characterization.

Typical Questions Related to Visible Particles



What's the size of a visible particle? Urban Myths…



USP <1>

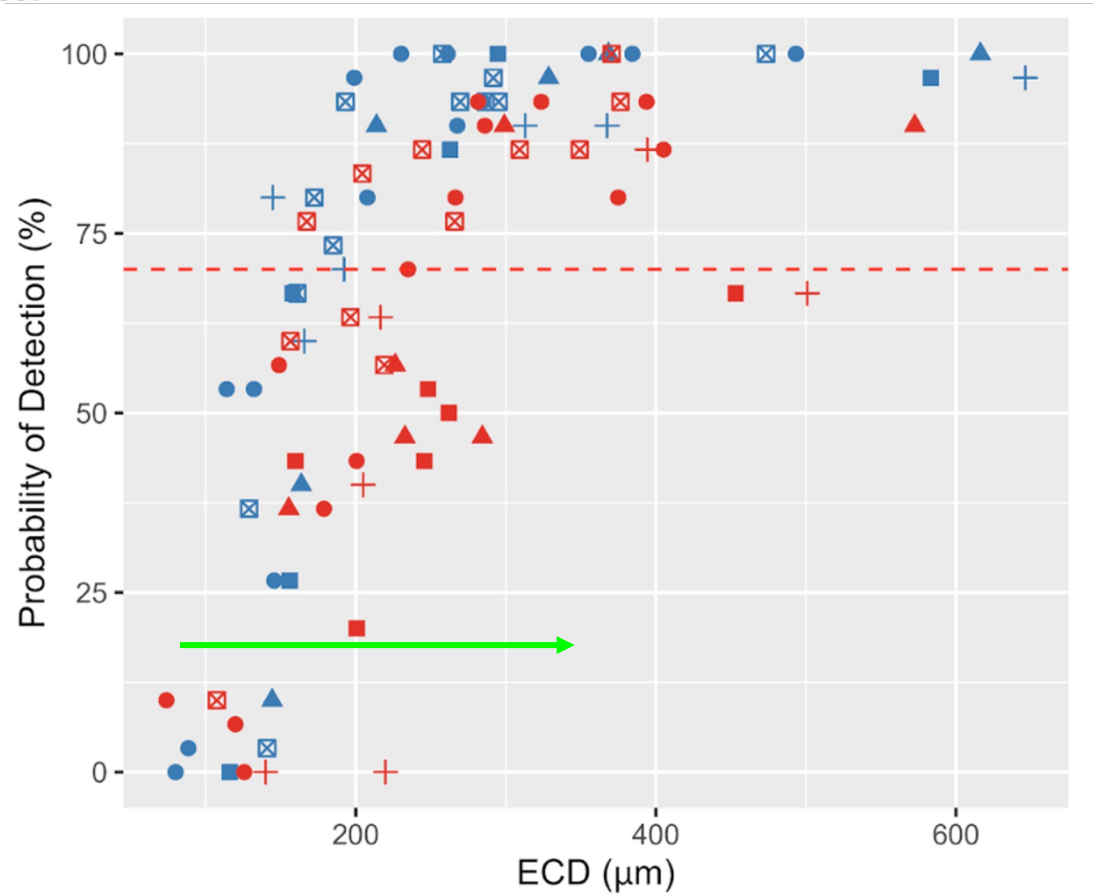
USP <1> Injections and Implanted Drug Products (Parenterals) – Product Quality Tests

Foreign and particulate matter: Articles intended for parenteral administration should be prepared in a manner designed to exclude particulate matter …

Each final container of all parenteral preparations should be inspected to the extent possible for the presence of observable foreign and particulate matter (hereafter termed visible particulates) in its contents.

The inspection process should be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates …

Visibility Limit of Particles: Knapp Study



blue 2R vial, red 20R vial

Knapp set:

- A VI test set with defective units and defect free units
- Defects in different sizes
- Inspected multiple times by a panel of VI operators
- POD can be calculated

Visibility limit for particles is impacted by

- Container size
- Product characteristics
- Operator abilities
- Inspection procedure

Inherent, Intrinsic, Extrinsic

	US FDA Guidance	USP 1790	EP 5.17.2
Extrinsic	…originate from the manufacturing environment and are foreign to the manufacturing process	…foreign to the manufacturing process	…derived from the environment, equipment, primary packaging or personnel
Intrinsic	…from the manufacturing equipment, product formulation, or container system	…from within the process	…related to the formulation
Inherent	Part of QTPP …innate product characteristic	.. designed as particle assemblies …appearance specification	**X**

Inherent, Intrinsic, Extrinsic

Extrinsic **Intrinsic** **Inherent**

Challenges with a generalized safety assessment:

- Sometimes difficult to assign categories (e.g. fiber, silicone oil)
- Product specific risk profile of inherent particles
- Qualification of visual inspection operator to discriminate visible particles categories (e.g. protein aggregates, cell clumps)

- ➢ Product specific risk assessment: possible adverse events e.g. ADAs, immunogenicity, capillary occlusion
- ➢ Dose & patient population: daily intake, patient state, exposure, in vivo behaviour, route of administration

Safety Risk of Visible Particles - Categorization

Animal studies with large doses of particles provide limited guidance for humans with small / very small doses of (foreign) particles

IV patients in Intensive care may receive large (~ 10^7/day) am… …d use of in-line filters suggests a reduction in infusion site phlebitis (Bac…

No controlled human studies

Anecdotal evidence fr…

Risk for Pu…

Rout…

…volume

P…

Do…

…gh risk category

V… …oncentration (LVP > SVP)

Frequency

Chronic > Single

Bottom line:

No clear clinical thresholds for criticality

Safety assessments can be poorly generalized to yield specific thresholds, given that safety relevance depends on the specific particle, dose and patient characteristics.

Doessegger et al., JPS, 2012
Bukofzer et al., PDA JPST, 2014
Langille, PDA JPST, 2013

Global Regulatory Framework: VI is a Requirement!

USA

- Sterile Drug Products Produced by Aseptic Processing - Current GMPs
- US FDA Compliance Program Guidance Manual 7356.002A
- Inspection of Injectable products for Visible Particles
- 21CFR 211.94 DP Containers and Closures / 21CFR 211.165 Testing and Release…
- USP <1> <1790>
- …

Europe

- Parenteral preparations (0520)
- Recommendations on Testing of Particulate Contamination: Visible Particles (5.17.2)
- Monoclonal Antibodies for Human Use (2031)
- EU GMP Annex 1
- …

Japan

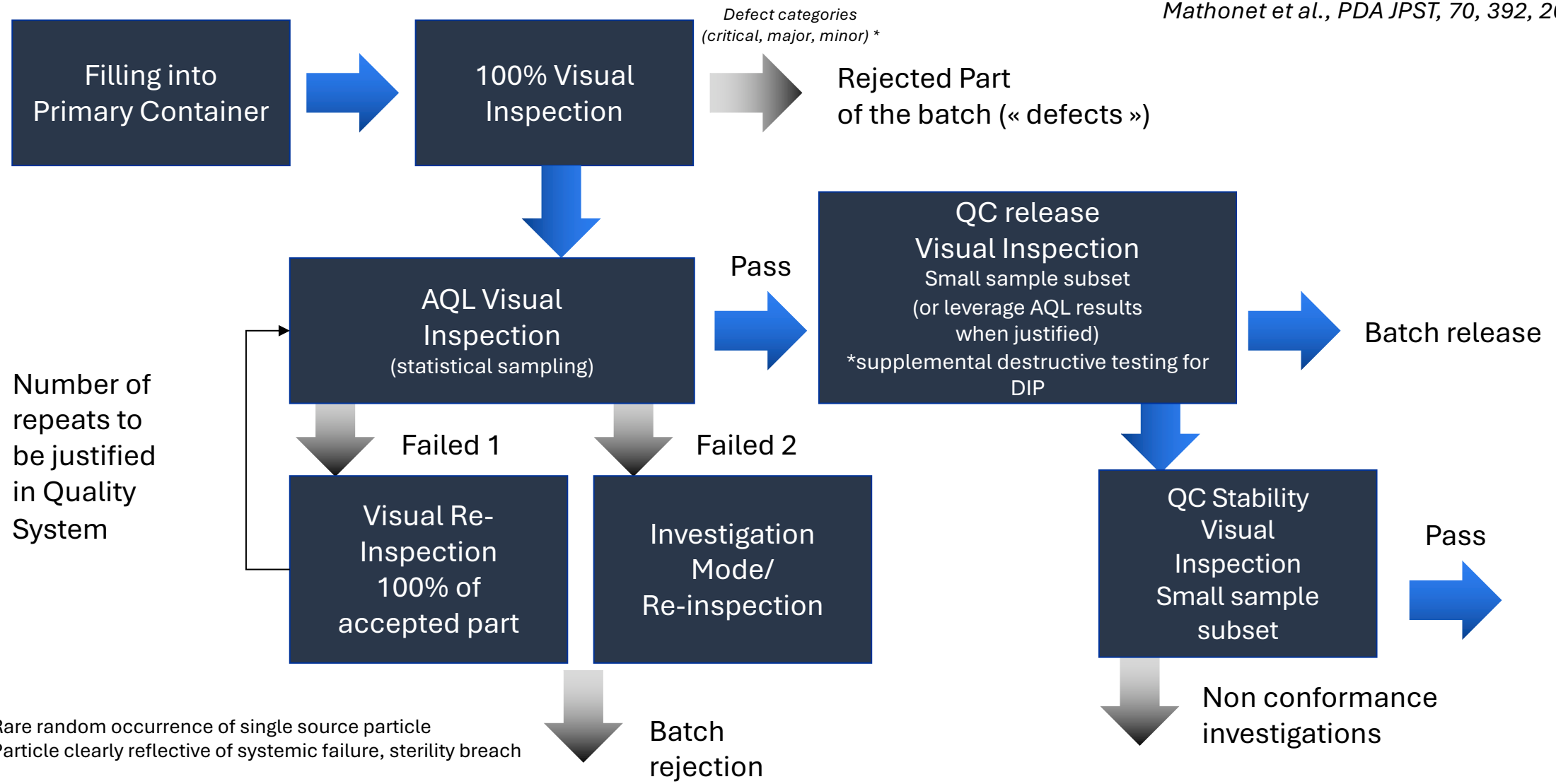
- Preparations for injection (JP 3)
- Prohibition of sale and manufacturing (Article 56)
- …

Pharmacopoeial Chapters

Visual Inspection	EP 2.9.20	USP <790>	JP 6.06	ChP 0904
Illumination Intensity (lux)	2,000 – 3,750	2,000 – 3,750	2,000 – 3,750 *8,000 – 10,000* *(plastic)*	1000-1500 *(colourless)* 2000-3000 *(brown, coloured glass or plastic)*
Duration	(5s black, 5s white)	(5s black, 5s white)	(5s black, 5s white)	(10s black, 10s white)
Backgrounds	black & white	black & white	black & white	black & white
Acceptance Criteria	“practically free of particles”	“essentially free from visible particulates” ANSI/ASQ Z1.4 AQL=0.65%	“free of readily detectable foreign insoluble matter”	No protein particles >1mm No obviously visible foreign matters (e.g. fiber or glass) >2mm No precipitate or turbidity etc.

Visual Inspection Process

Mathonet et al., PDA JPST, 70, 392, 2016



1 Rare random occurrence of single source particle
2 Particle clearly reflective of systemic failure, sterility breach

Holistic Strategy: Roadmap to a compliant visual inspection process

- **Product and Process knowhow**, build quality into the product (not by testing)
  - Formulation, CCS, Facility, equipment, SUS components, process unit operations, operational excellence
- **Product specific safety risk assessment** of visible defects (e.g. particles, container defects)
- **Inspection process**
  - Harmonization across global network, VI training/qualification kits, VI method dev, product specific VI performance, facility material reference libraries
- **Implementation of VI in routine manufacturing operations**
  - **100% VI**, trending, pre-established alert/action limits, predefined procedures for 100% re-inspection
  - **AQL** sampling strategy, QC release sampling strategy and VI QC acc. Crit (translation table)
  - **Investigation**: Harmonized strategy, staged approach for defect investigations, risk assessment and evaluation tools linked to toxicological inputs, reference libraries, trending

Summary

- All injectable drug products must be visually inspected for defects (particulate matter and container defects)
- Visual inspection is a probabilistic process (concepts introduced by Knapp and co-workers, 1980)
- Visual inspection is a critical component of the quality system for injectable products (process and product).
- A robust holistic strategy needs to be implemented including training and qualification program ensures that inspectors are capable of reliably detecting defects and helps to protect patient safety.

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Training & Qualification

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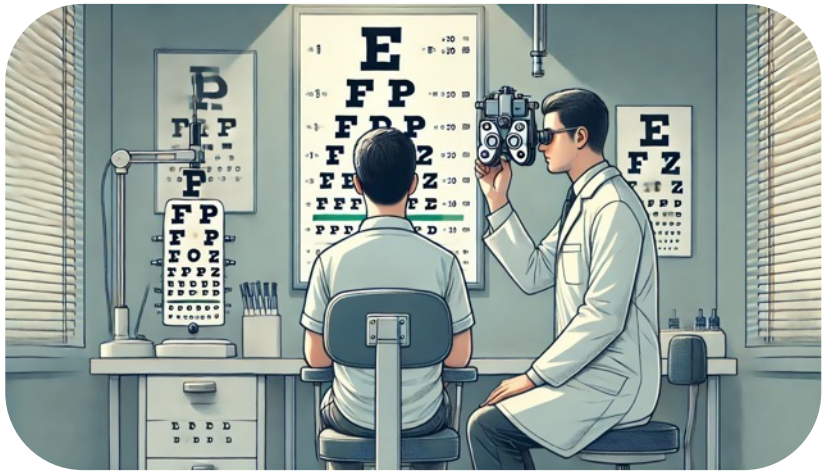
Training & Qualification: Manual Inspection Process Flow

- Pre-Requisites
  - What are the requirements for an operator in visual inspection?
- Theoretical Training Period
  - Introduction to the inspection procedures, method
- Practical Training Period
  - Training of proper inspection sequence
  - Practice inspection of different products
- Qualification for Product Inspection
  - Product specific test sets
  - Bracketing approach

Pre-Requisites

- Passed Visual Acuity (Eye) Test
  - Must have 20/20 vision, pass color perception test
  - If trainee does not have 20/20 vision, prescription glasses must be worn during inspection
  - Pass/Fail results are stored in individual's medical folder
  - Annual re-assessment of vision
  - ➢ For products distributed to China: Each 6 months



- Note: If vision cannot be corrected with prescription lenses, the individual cannot proceed to manual inspection training and qualification

Theoretical Training Period

- To be considered:
  - Specific Curricula with procedures related to Visual Inspection (Learning Management System)
  - Gowning, safety, housekeeping, container handling
  - GMP documentation principles, Line Clearance
  - Defect library (real defect samples and/or pictures of defects)
  - Introduction to defect criticalities and related defects
  - Familiarize with a manual inspection training set
  - Train Inspection Sequence (Manual Inspection Booth)

Practical Training Period

- Before operator is admitted to the initial MVI qualification for a product / format
- Practicing either with training material or routine product
- If routine product, always under supervision and verification of inspected units
  (Inspected units are verified and discussed with trainee)

- Proceed with Practical Qualification
  - ✓ If theoretical and practical part passed

Manual Inspection Sequence

- Developed specifically for the products inspected (2mL vs. 500mL vials, syringes, liquid/lyo product)
- Against black and white background but not constantly switching between the backgrounds
- Focus on a logic sequence and flowing motion (important for the operator)
- Inspect for:
  - Container defects (glass, closure, stopper)
  - Product defects (e.g. fill volume, discoloration, turbidity)
  - Particles and fibers
- Static inspection, swirling and inverting to ensure proper detection
- Operators are trained to follow the sequence for inspection against both backgrounds
- Multi-unit vs. single-unit inspection (multi-unit inspection needs method qualification)

Threshold Studies

- Required according to USP<1790>
- Determination of process capability
- No focused inspection of particles only (= Knapp Test)!
- Amount of inspection runs 30-50 (less possible, if justified)
- Executed according to routine production conditions
  - Defect distribution: critical, major, minor defects
  - Not more than 10% defect rate
  - Defined evaluation criteria
  - Routine and worst-case conditions to consider
  - Without magnifiers
  - Following standard method

Threshold Test Sets

- Considerations
  - Origin of the defective units (artificially made or collected from routine)
  - Using real product
  - Contains all types of defects
  - Sufficient samples
    - E.g. Particles 50 – 5000 microns
    - Enough samples for qualification test sets plus spare samples

Manual Qualification Test Sets

- Considerations
  - The test set must be qualified for use and approved by QA
  - Threshold study (threshold test set) as origin
    - Containers in the set: based on results of the threshold studies performed upfront
  - Chicken and egg problem: Qualified operators vs. qualified test set?
  - Defect distribution: critical, major, minor defects
  - 10% defect rate
  - Must be blinded (no identification of defects by other means)
  - Must be verified prior and after use

Qualification/Requalification requirements

- Qualification
  - Successful completion of representative test set (3 runs)
    - False Reject Rate ≤5%
    - Detection rate according to acceptance criteria
  - Considering the site products range (bracketing, e.g. small & large)
  - Consider volume, product characteristics and primary packaging material
  - Cover all operational shifts (consider fatigue)
- Requalification
  - Annual requalification of the operators with respective test sets
  - If defect catalogue changes, e.g. new defects
  - One successful pass sufficient

Failed (Re-)Qualification

- Considerations
  - Procedure needed for qualification/requalification/disqualification - QA approved
  - Issue deviation for failed re-qualification
  - May be repeated up to 2 times
  - Test is repeated earliest next working day
  - In case of second failure, operator must undergo re-training
  - If third attempt is failed, operator is disqualified from performing visual inspection activities

Conclusion

- Operator qualification for MVI is:
  - The foundation for the inspection of containers at each site
  - Important and expected to know your process capability (threshold/baseline studies)
  - A standard to qualify semi-automated & automated inspection

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Semi-automated and Automated Visual Inspection

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Agenda

1. Semi-Automated Inspection System
2. Automated Inspection System
3. Typical Qualification Approach
4. Choosing the right Method
5. Two Stage Inspection
6. AI-based Inspection

Semi Automated Visual Inspection System (SAVI)

Key Features

- Automated material handling with Operator judgment of containers
- Transport rotate containers in the inspection zone
- High speed spin station to set particles in motion for liquid inspection
- Mirror for top and bottom view of containers

Benefits

- Advanced controlled environment (e.g. light options)
- Comparable detection rates to manual visual inspection (MVI)

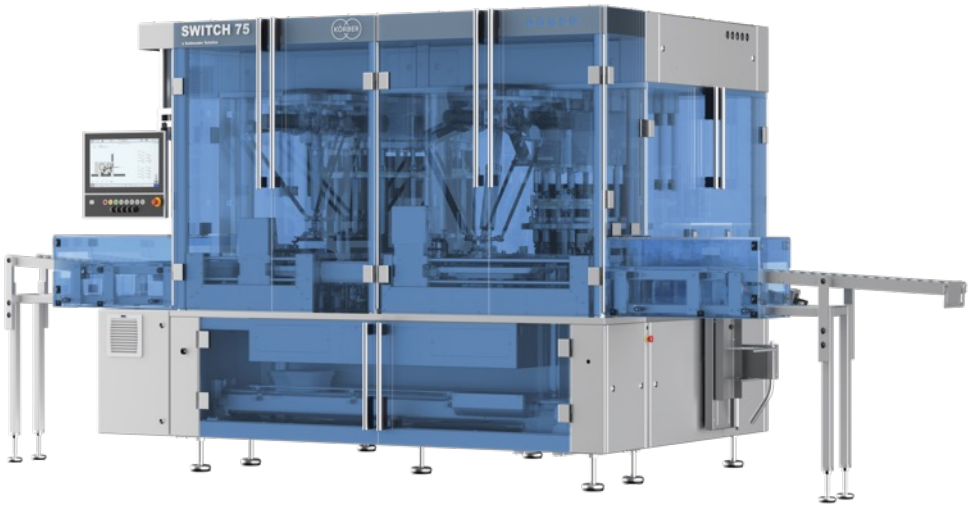
Challenges

- Human Dependency
- Detection Limitations
- Throughput Constraints

Automated Visual Inspection System (AVI)

Key Features

- Combines automated material handling and 100% inspection of containers
- Multiple cameras for detailed imaging of specific regions
- Unique lighting techniques for enhanced defect detection
- Spinning containers to set particles in motion for better visibility



Benefits

- Higher throughput and consistency compared to MVI
- Enhanced defect sensitivity for certain types of defect
- Detailed defect reporting for production lots

Challenges

- Potential risk for higher false rejection rates during the ramp up phase due to low amount of production data (e.g. primary packaging variations)
- Validation Requirements

Typical Qualification Approach AVI vs. SAVI

Vision Recipe Development

Vision Recipe Qualification

Process Qualification

Key Success Factors

AVI SME and Test kit

AVI ≥ MVI

3 Batches with extended Sampling

Operator Training

Operator Qualification

Key Success Factors

Operator and Test kit

SAVI ≥ MVI

Choosing the right system depends on different factors

Up to 1000 units / min

- High speed
- High performance
- High reliability

≈ 25 units / min

- More efficiency than MVI
- Small footprint
- Flexibility through human decision

≈ 4 units / min

- Flexibility to adapt
- Decision based on experience
- Classification of defects

A detailed analysis of **production needs** and **economic factors** should guide the choice

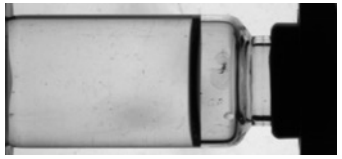
★ Production volume

★ Product diversity

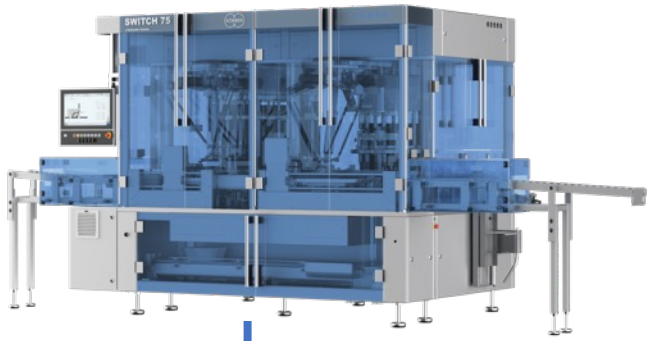
★ Cost considerations

* Typical speed in production

Two Stage Inspection



Rejects



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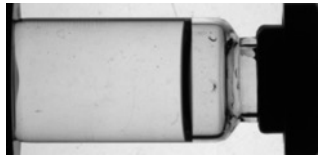


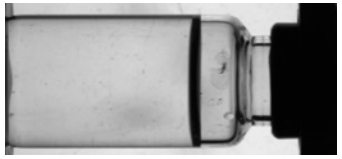
SAVI

AQL

Separate AQL

Good units

Two Stage Inspection



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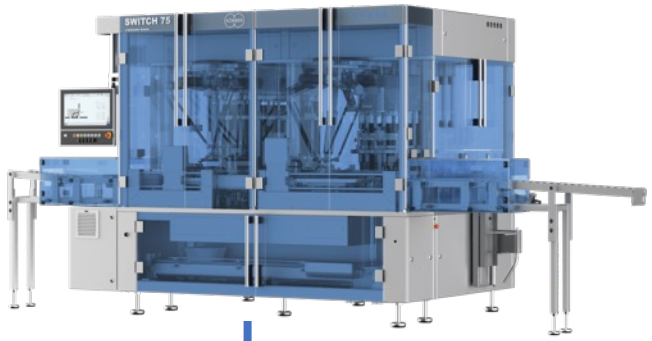

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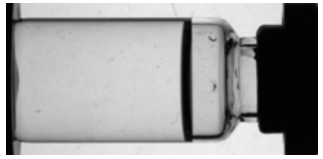


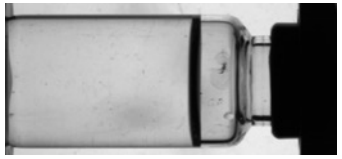
MVI

AQL

Separate AQL

Good units

Two Stage Inspection



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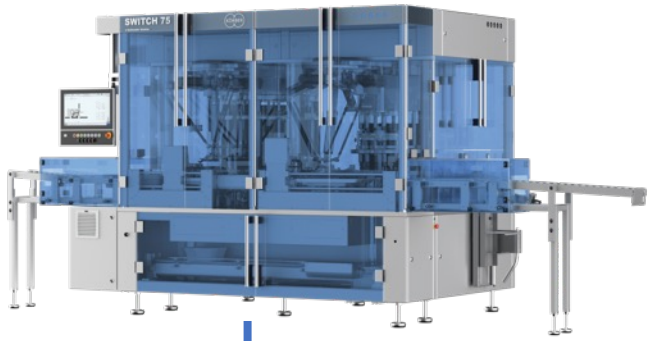

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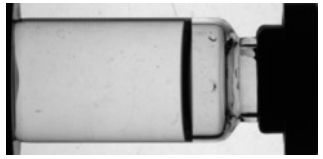


AVI

Strong Justification needed !!!

AQL

Separate AQL

Good units

Two Stage Inspection Process Qualification

Vision Recipe Development

Operator Training

Vision Recipe Qualification

Operator Qualification

AND

Process Qualification

Key Success Factors

PoD Stage1 x PoD Stage2

=

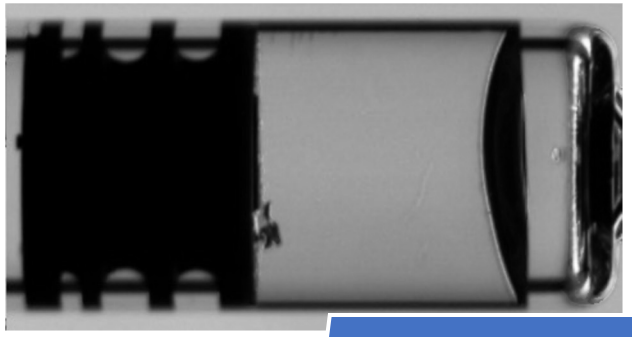
Overall PoD ≥ **MVI**

3 Batches with extended Sampling

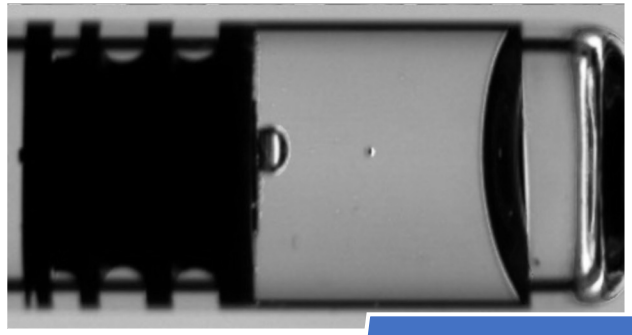
Key Take aways for introducing a Two Stage inspection

- The **limitations of the first inspection** and the **purpose of the second stage** must be **clearly defined and documented**
- Using the **same Method in Stage 2** is **not recommended**
- Since the **Probability of Detection (PoD) decreases at each stage**, it should be assessed after both to ensure acceptable sensitivity
- Dedicated **extended AQL for Stage 2** is recommended

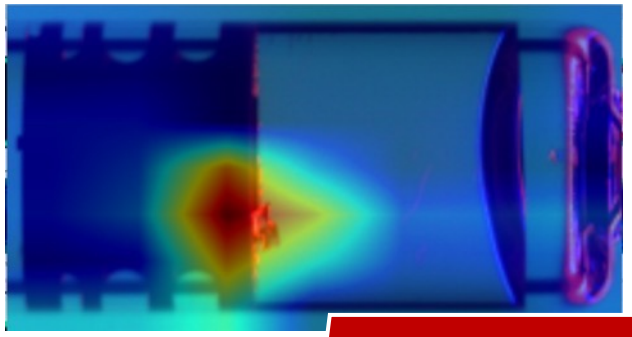
What's next? Advantage of AI-based inspection



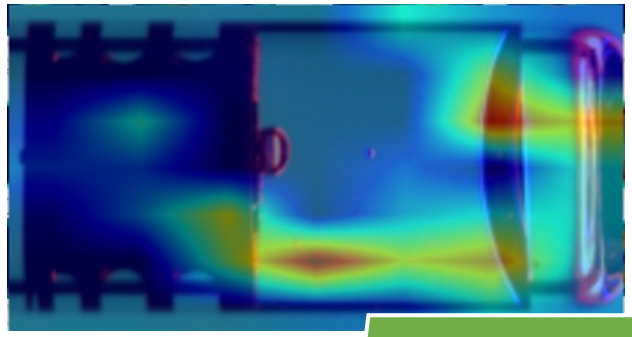
Particle



Air Bubble

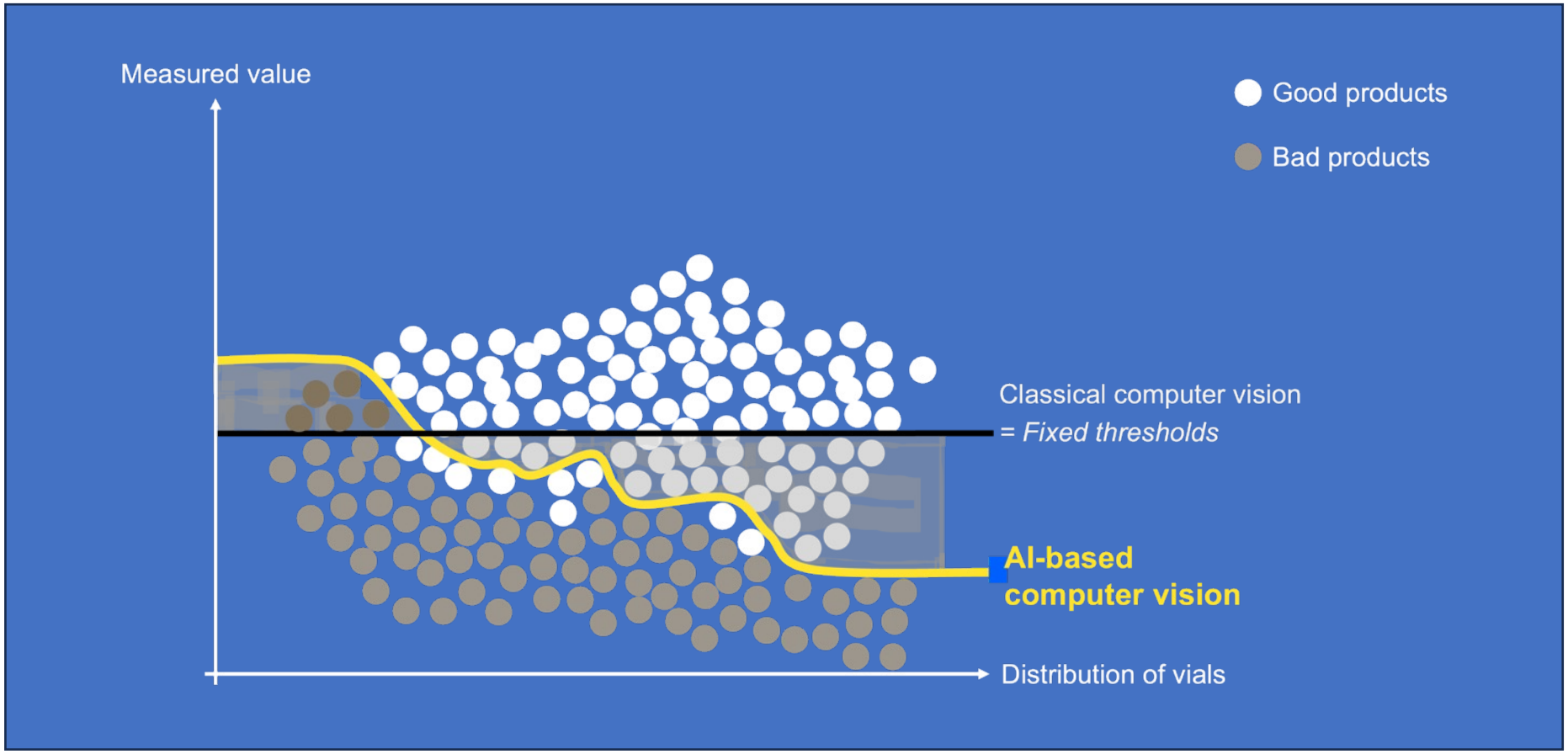


AI: Defect

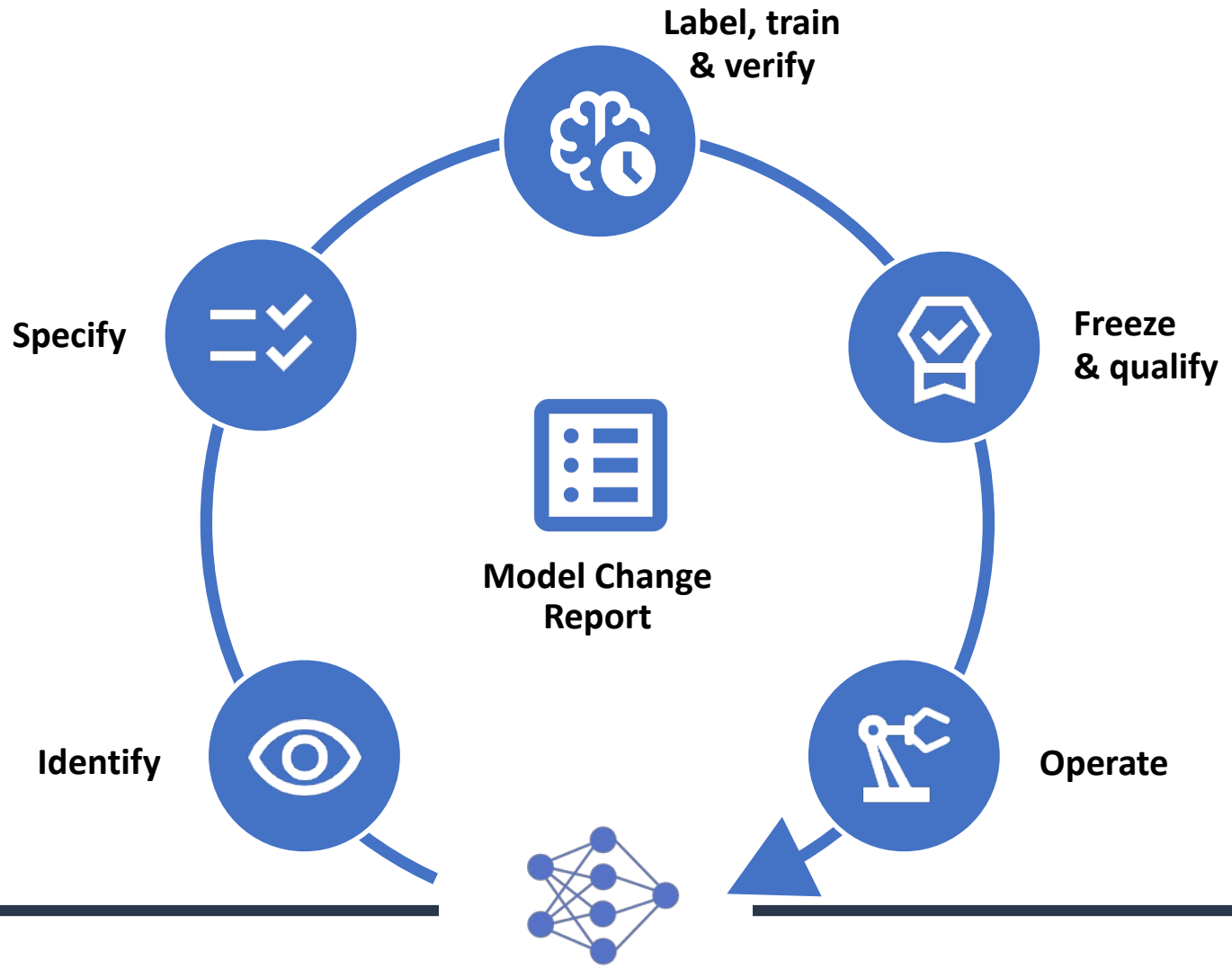


AI: Good

Advantage of AI-based inspection



AI Model implementation Process



Conclusion

- SAVI is **flexible** but **slower** and relies on **human judgment**.
- AVI is **faster**, **consistent**, but requires more **effort in qualification**.
- A **two-stage approach** can **enhance inspection reliability** if properly **justified**.
- **AI** brings new possibilities by **improving defect classification** and **reducing false rejects**.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What's next?

- We will share the webinar slides on our DACH chapter website https://www.pda.org/chapter-detail/pda-dach-chapter
- We will collect and analyze your questions.
- We will schedule a follow-up event with an even wider expert panel to answer all your questions – stay tuned for updates by email and LinkedIn!

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Thank you for attending the webinar!