# Mastering AVI

## Part 7: Qualification and Routine Test Sets

- Statistical considerations on number of objects containing defects
- Particle selection, particle size and size uniformity
- Labeling of test set objects
- Supply/purchase of test sets
- Maintaining and lifecycle of test sets
- Sampling from rejects
- Defect master library
- Types of defects
- Quality requirements

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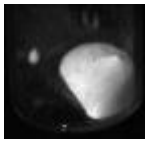
# What to include ?

**What do?** Whatever dosage form (liq or lyo),100% visual inspection required for each parenteral product for following defects (type or family):



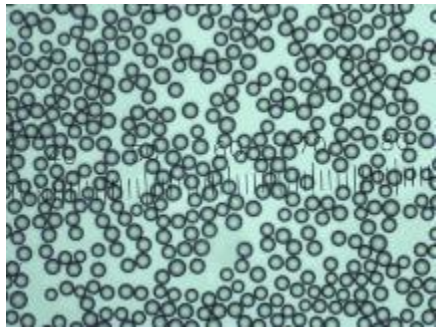
- Glass defects
- Closure defects (caps & crimp inspection)
- Particulate matter (lyo only external)
- Fill volume *specific for liquid products*
- Cake defects *specific for freeze-dried products*
- *Cosmetics defects*

Extrinsic particles are very difficult to anticipate in defect kits

# Qualification Test Set and Routine Test Set

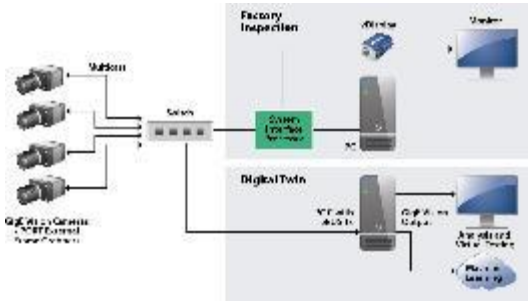
1. Prior study of particle/defect occurrence in real prod => control charting / number lots sampling
   - What type of particles/fibers, occurrence
   - This will also identify where introduced for process improvement
     - Removing the cause versus solving the problem
   - Necessary for selecting machine/supplier
     - URS and defined test sets make it possible to compare offers
2. Choosing how to build test sets and good units for testing and validation
   - Real defects versus manufactured defects
     - They should not fall apart during usage
     - They should represent the process defects found
     - They have a limit lifespan, so they should be reproducible for building new sets for later revalidation which will be far easier with manufactured defects

3. Artificial beds particles
   - They are completely reproducible, for 100%
   - They have exact dimensions like spheres, triangles, rectangles etc.
   - Detection limits can exactly being set
   - But their behavior in liquid motion do not resemble movement of real particles/fibers

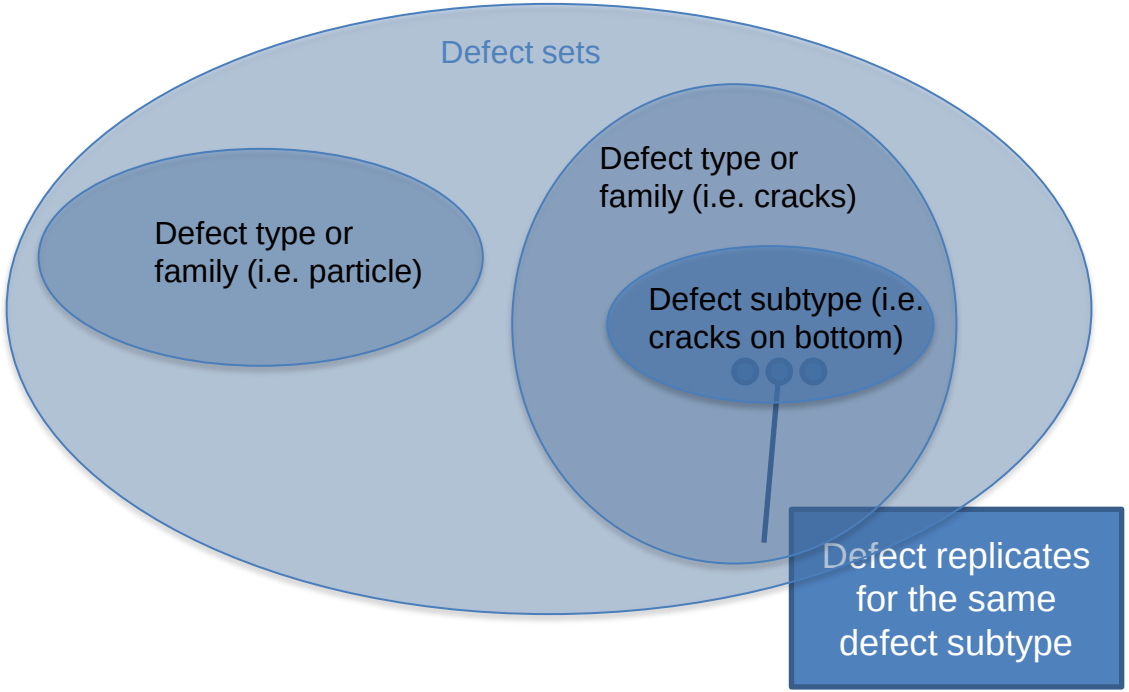



4. Virtual defect library = digitalization of test sets
   - Building a library of defect images and good units
   - The more the better

5. Virtual machine test = digital twins
   - Having these images one can do offline configuration of machine recipes.
   - The automatic inspection machine stays in production for already validated configurations



# Some terms to define:

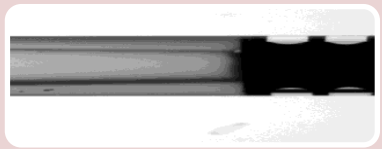



# Points to consider:

Defect standard should:

- Demonstrative of real defects occurring in production
- Cover the polymorphism of defects
- Include defects with MVI PoD ≥ 70%*

# Defect type by presentation (non exhaustive)

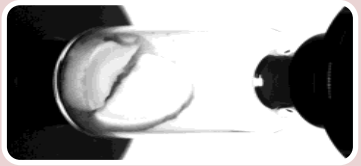


## Syr.

- Cracks
- Particles
- Fill Level
- Stopper
- Closure
- Flange/gripper
- Stain
- scratches

## Vial Liq.

- Cracks
- Particles
- Fill Level
- Closure
- Cap Color
- Stain
- scratches



## Lyo

- Cracks
- Particles
- Lyo defects
- Closure
- Cap Color
- Leaks
- Stain
- scratches

# Test sets

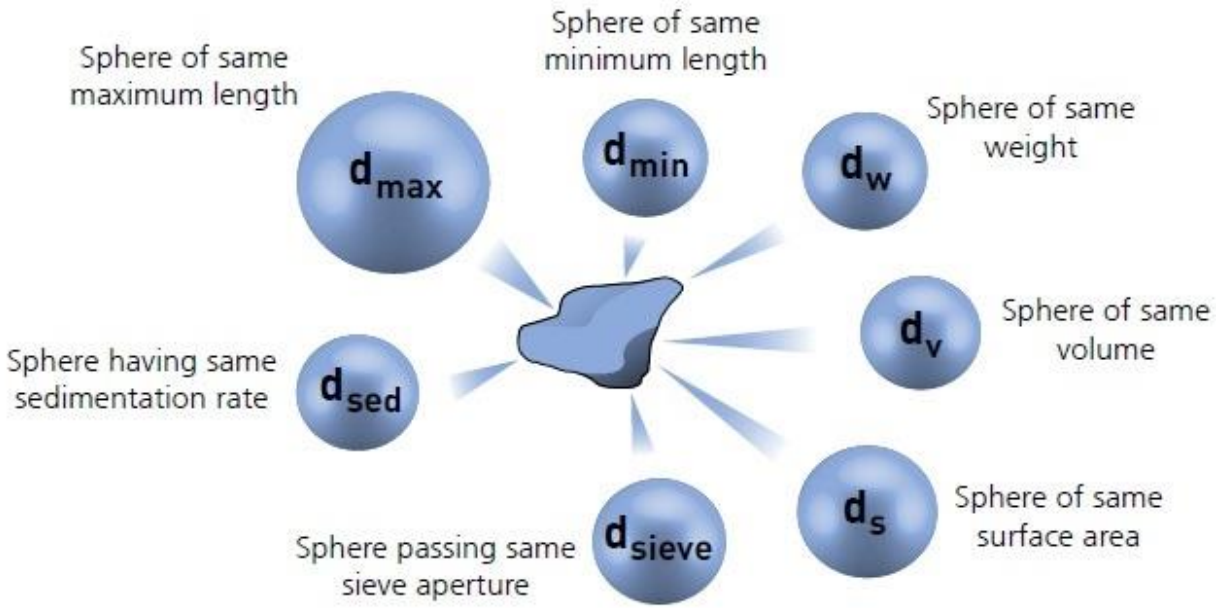
## 2 possibilities to create test sets:

- Select defects from production
  *"selection from naturally occurring particulate and physical or cosmetic production rejects removed from product lots"*
- Identify defect types and recreate defects in a controlled laboratory environment
  *"re-creation of equivalent defect types in a controlled laboratory environment"*

*The 2 possibilities can be mixed*

| | From production | Recreated defects |
|---|---|---|
| + | • Cost<br>• Production sites ownership | • Ensured polymorphism<br>• Controlled defects<br>• Dedicated team (experts)<br>• Harmonization across sites<br>• Lifecycle |
| − | • Polymorphism coverage<br>• Defect characterization (particles)<br>• Defect evolution (e.g. cracks)<br>• Lifecycle<br>• Side activity | • Cost<br>• For some defects, difficult to reproduce (lyo, color changes…)<br>• Risk of departing from actual defects<br>• Contamination (undesired particles or microbio) |

# Why not using commercial particle beads?




See Stimuli article USP 2021 where particle beads is promotted

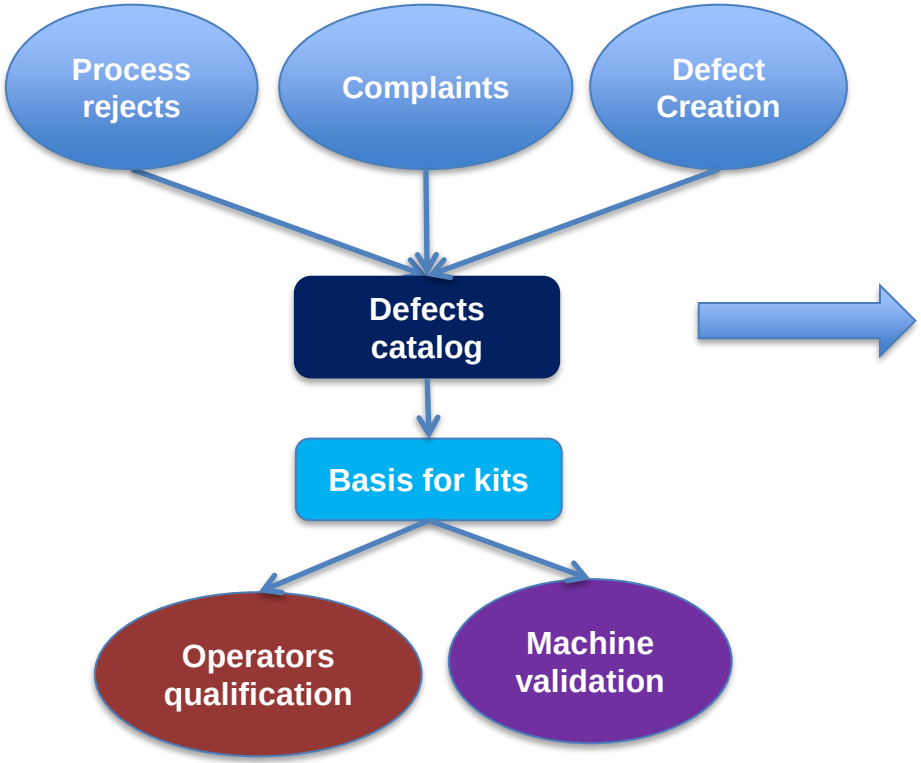
## Note

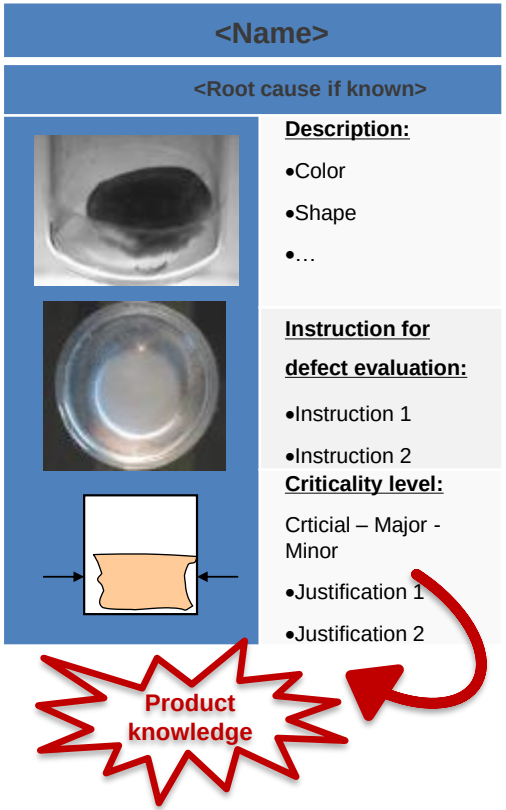
Keep in mind that real particles will behave differently.

Your machine supplier has chosen rotational speeds based on container size and viscosities.

Study should be done under the same conditions

# Why a defect catalogue ?

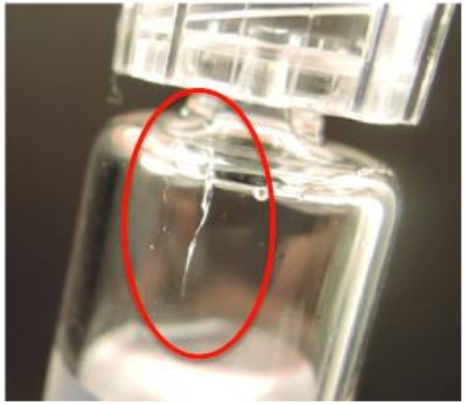


# Defect Catalogue example

## Master Defect Library version XX

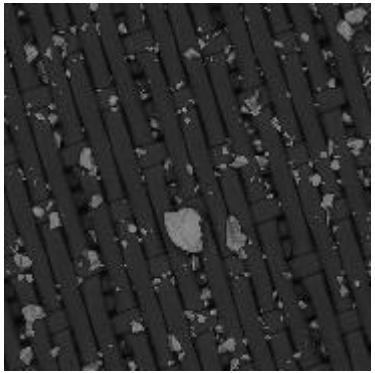
**Critical – Glass Defect – Crack – At shoulder level**



| | |
|---|---|
| Category | Glass Defect – Crack |
| Location | Shoulder |
| Size | Medium |
| Orientation | Vertical |
| Color | N/A |
| Shape | N/A |
| Description | Mirror effect, syringe is not empty. Can be felt by passing nail on |
| Ref VICOC | CS20 |

Physical attributes

# How to collect defects?

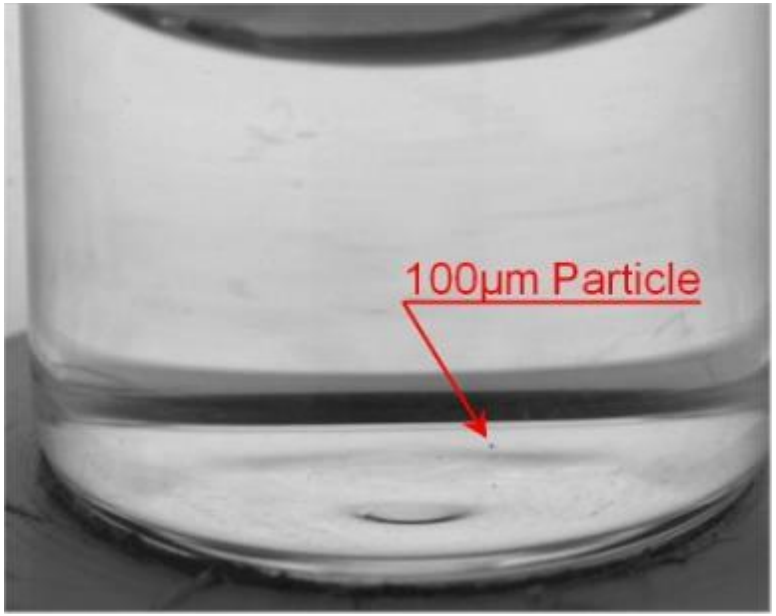


- For established products and facilities:
  - Collect data from rejects trending in production (Control Charting, AQL)
  - Select the most occurring defect types in typical batches (more than X ppm, Pareto, etc.)

- For new product/container/closure system or new facility:
  - Evaluate the most occurring defect types based on available information (from R&D, Clinical, expertise, engineering runs, etc.)
  - Select defect types based on risk approach
  - Re-evaluate the defect standard after a certain time

In both cases, defect standard must encompass all defect families (particles, cracks, closure defects, etc.)

# What is smaller size ?




Threshold study of various particle sizes will orientate you in selection of particle size in your true defect zone.
Take into consideration:

- Standard work
- Fatigue effect
- Defect concentration in goods
- Opacity / viscosity / volume

# How to adress defect polymorphism?

- **Not only white particle!** → different kinds of:
  - Shape (spherical, elongated, fiber…)
  - Color (transparent, white, black…)
  - Material (glass, rubber, steel…)
  - Behavior (fixed, floating…)
  - Size (small, medium, big…)
- *One particle per container (USP<1790> requirement)*

- **Not only big vertical crack!** → different kinds of:
  - Orientation (vertical, horizontal,)
  - Position (bottom, neck, shoulder…)
  - Size (small, medium, big…)

- For **other defects** (closure defects, etc.) → same logic

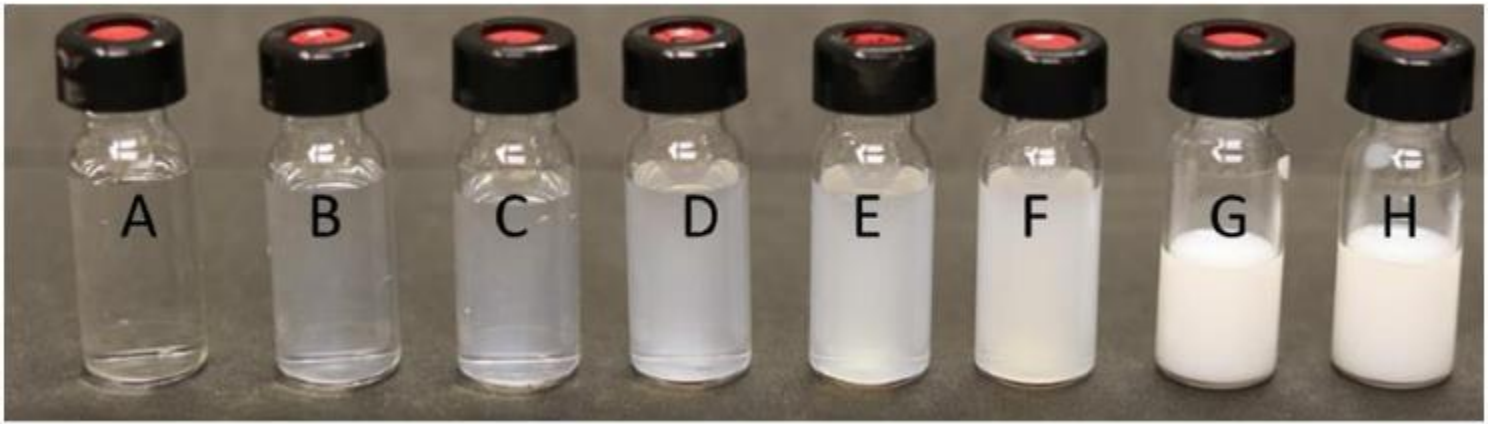
*Hoshin matrix visualization for particles*

| *occurrence [ppm]* | | | | Other | . | . | . | . |
|---|---|---|---|---|---|---|---|---|
| | | | | Steel | . | . | . | . |
| | | | | Rubber | . | . | . | . |
| | | | | Glass | . | . | . | . |
| Other | Fiber | Spherical | Elongated | MATERIAL / SHAPE / BEHAVIOR / COLOR | Clogged | Fixed | Floating | Precipitating |
| . | . | . | . | Transparent | . | . | . | . |
| . | . | . | . | White | . | . | . | . |
| . | . | . | . | Black | . | . | . | . |
| . | . | . | . | Other | . | . | . | . |

***Risk to over-represent polymorphism***

***The purpose is to cover a pertinent polymorphism based on manufacturing data, not to cover all possible polymorphism***

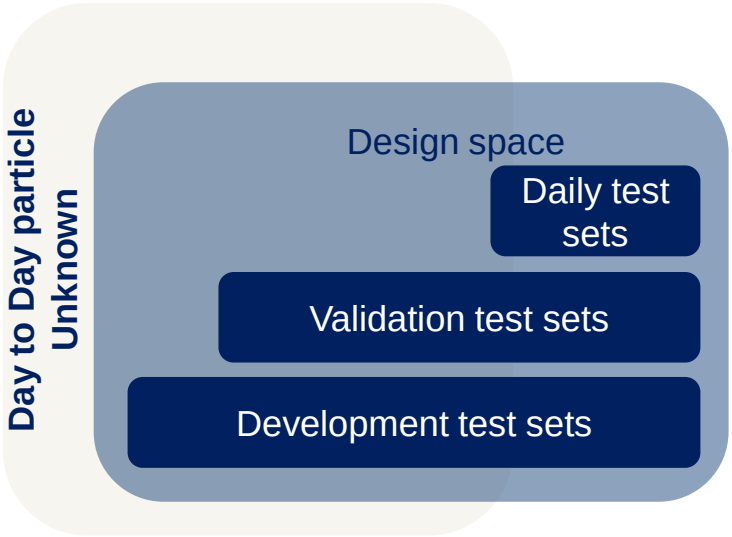
# Bracketing approach?

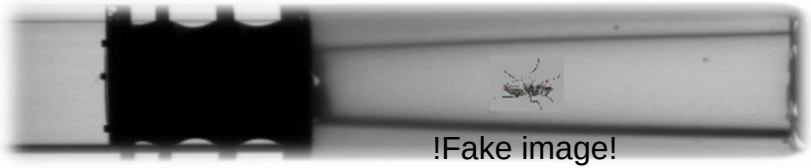


# Design Space: How to anticipate unknown defects?

**Key learning:**

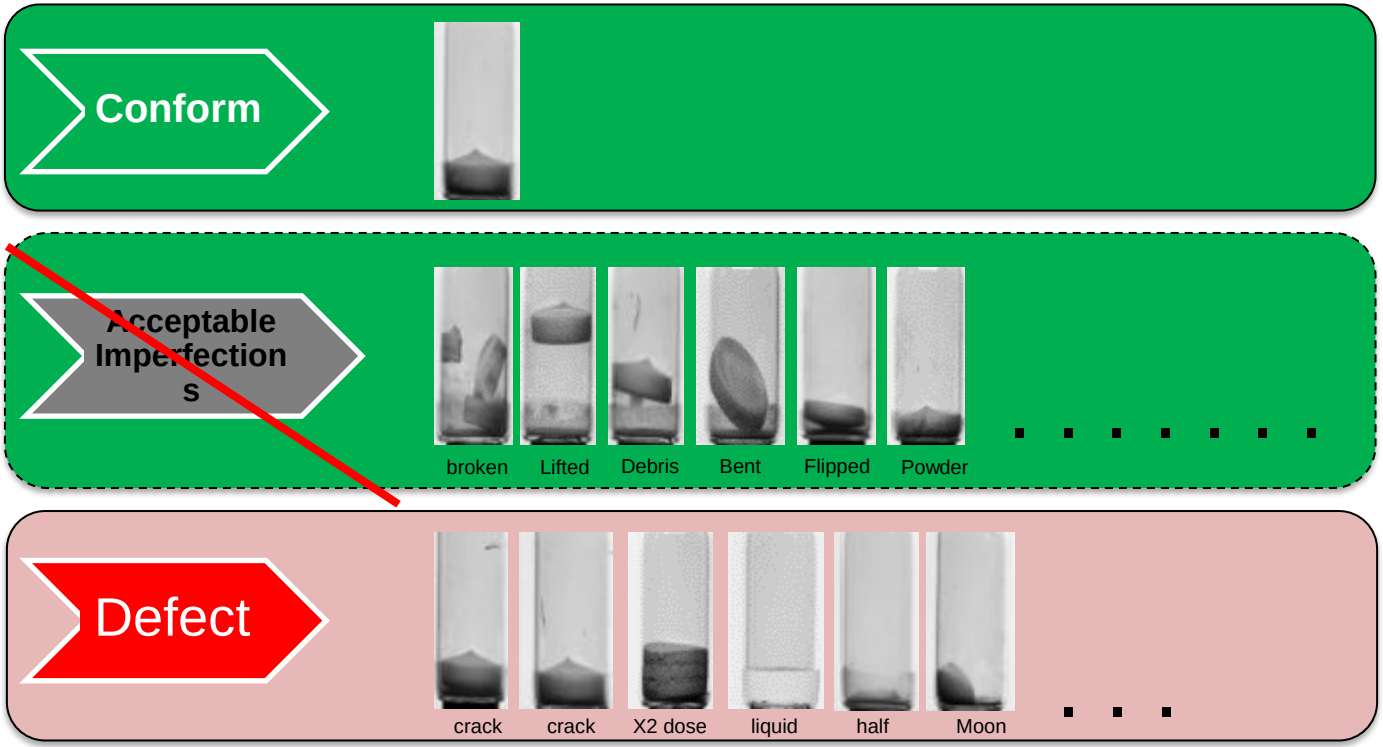
- Machine vision is designed with minimum threshold, may be compared to high jump.
- Machine vision is designed to detect defect that are outside the design space to anticipate some new defects (unknown)
- With artificial image library we can demonstrate capability of unknown detection



!Fake image!

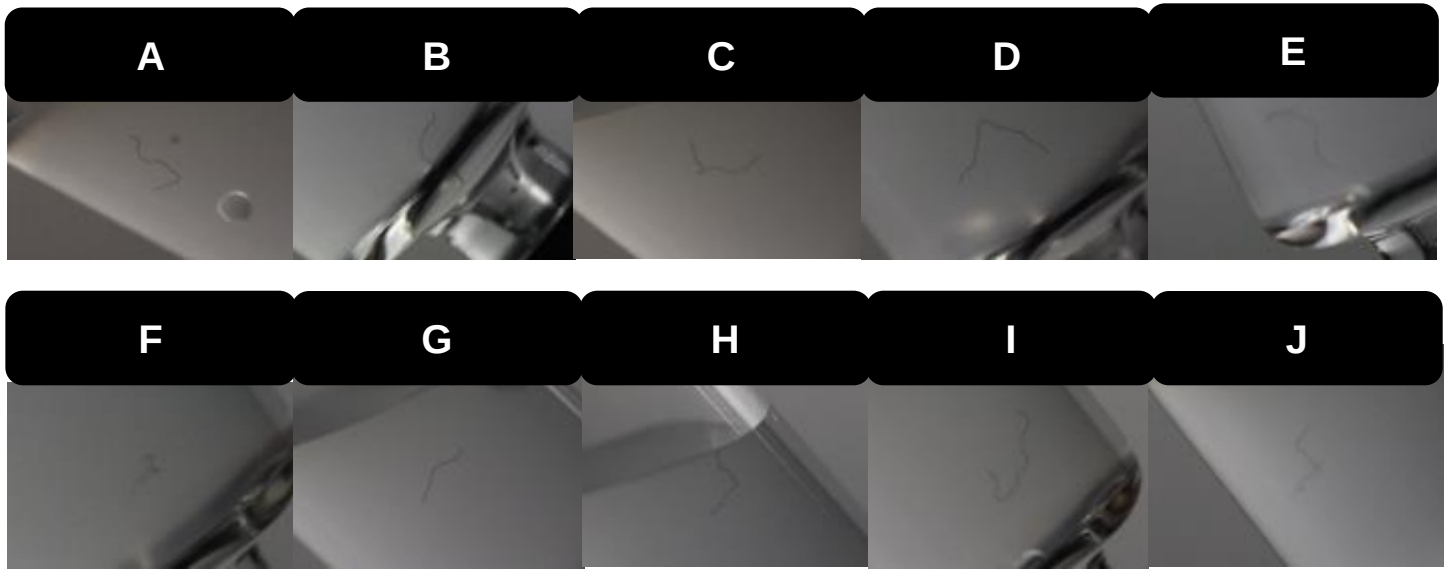
# NO Grey zone is Acceptable => define the limit



# Need for replicates

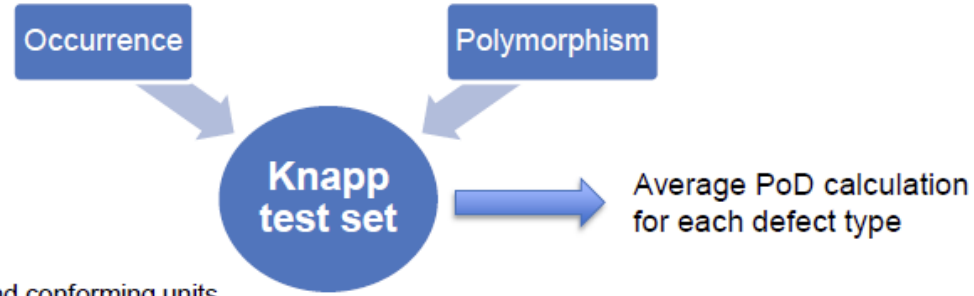
**Precipitating particle:**
- black
- lengenthed, type fiber
- big : 0.6 mm²

**Location definition**
**Defect family (particle/Crack/closure)**
**Defect types (attributes)**



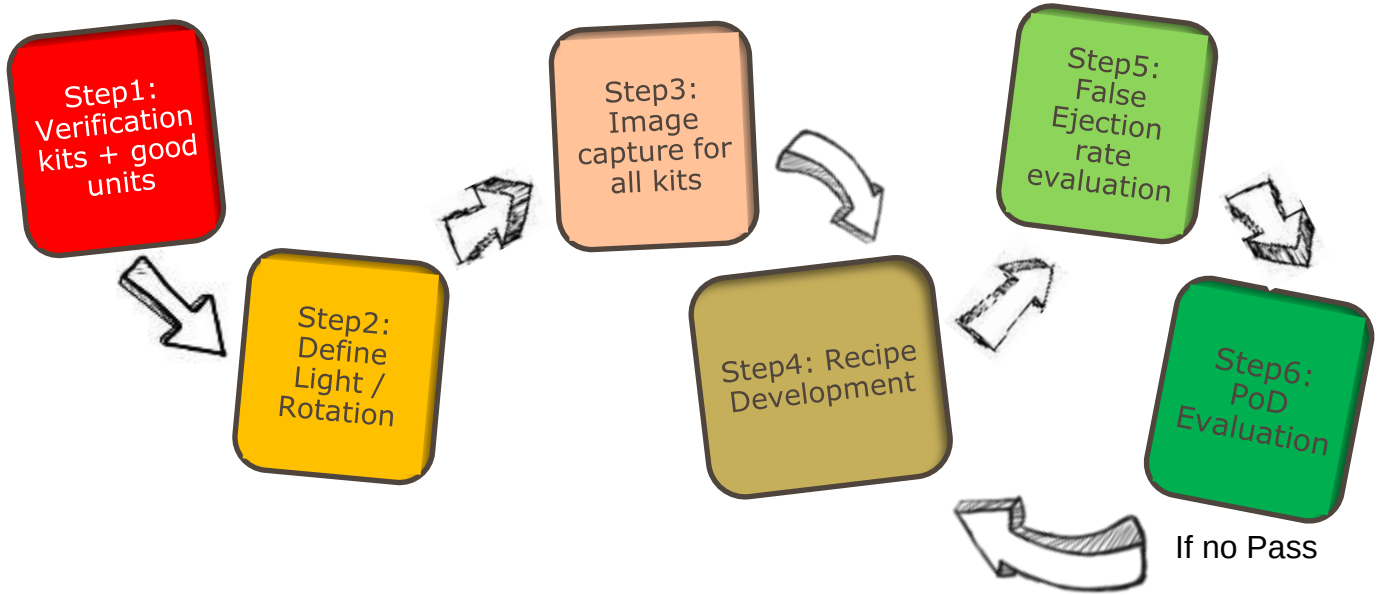
# Define MVI Baseline PoD

## Perform a Rejection Probability Determination study according to USP<1790>




- Test set:
  - Mix of selected defect types and conforming units
  - At least 3 replicates per defect type
  - Maximum rate of defect (e.g. 10%)
  - Integrate inspector fatigue effect (cover one standard MVI shift)
- Average PoD calculation must be statistically robust *(USP<1790>: at least "30–50 inspections of each container")*:
  - Define the number of runs
  - Define the number of inspector (e.g. 10)
  - Perform MVI runs in production conditions (method, light, people, pacing, etc.)

# How to work with defect sets?




Document test set life cycle in a logbook

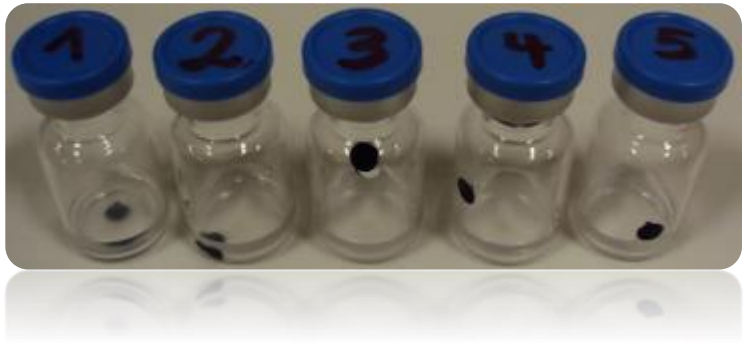
# QA oversight on Test Sets

- Collection in production
- Manufacturing
  - Subcontracting : working instruction / DML /
  - Internal group: working instruction / DML /
  - Labelling units / UV printing➔ anti mix-up
  - Back up units when broken
- Logbooks of kits
- Supply for sites
- Storage condition
- Documentation of use / line clearance
- Verification / change units
- Expiry date

SOPs
+
QA Oversight

# Daily test sets

- Daily kit test for machine functionality
- = gross defect to simulate ejection
- Not a performance evaluation only for vision system functionality of detection and rejection => need to control absence of critical alarms



# RECAP


**You have learnt**
**KITS**

- Statistical considerations on number of objects containing defects
- Particle selection, particle size and size uniformity
- Labeling of test set objects
- Supply/purchase of test sets
- Maintaining and lifecycle of test sets
- Sampling from rejects
- Defect master library
- Types of defects
- Quality requirements

**KITS**

- Which defect families should be present
- Which basic steps, prior to the creation of test sets, should be mandatory
- What is meant with digital twins
- Which steps, prior to creating a test kit, are mandatory
- A defect standard should consist of?
- Why not use commercial particle beds
- Why do we need a defect catalog and is it static?
- What is a daily test kit and why