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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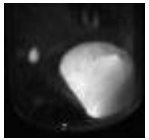
What to include ?

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*

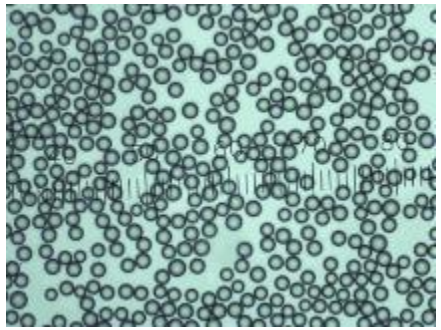
Extrinsic particles are very difficult to anticipate in defect kits

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

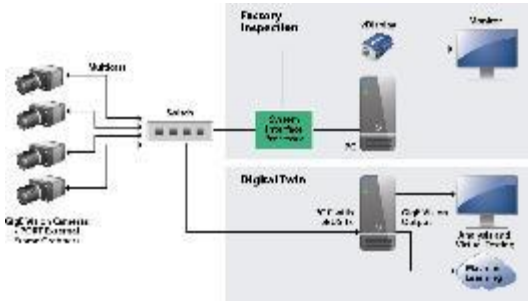
New Trends

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

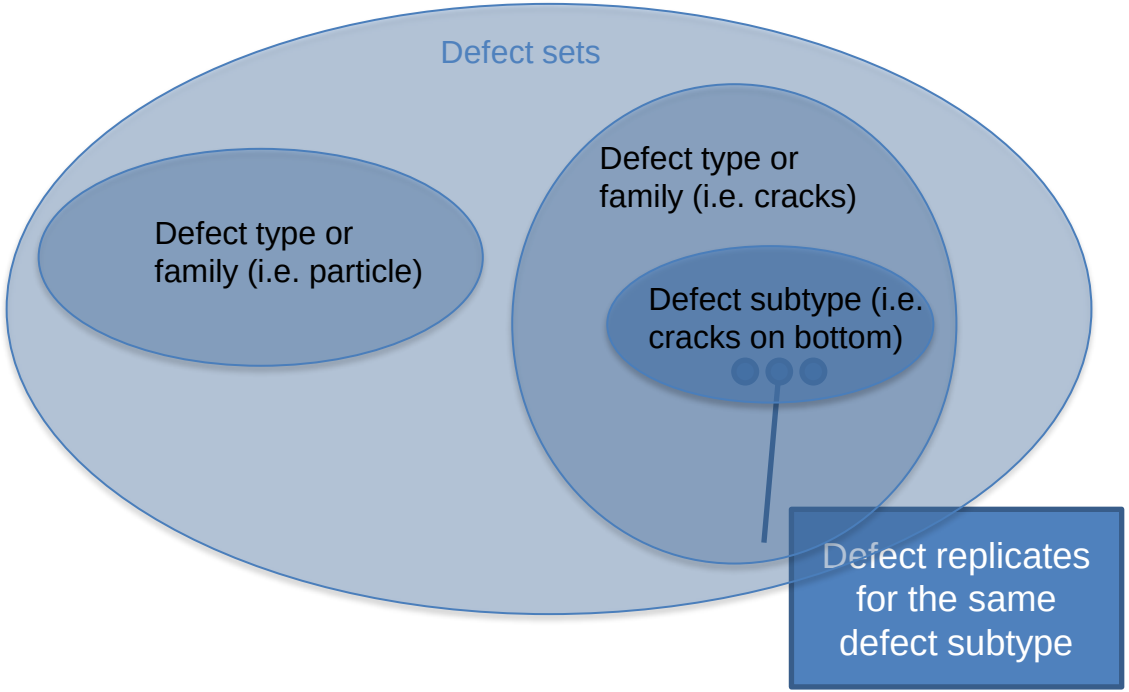


4. Virtual defect library = digitalization of test sets
   - Building a library of defect images and good units
   - The more the better

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:

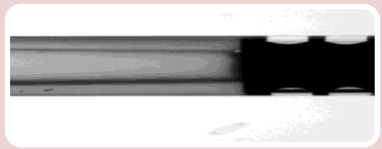


Points to consider:

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

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"

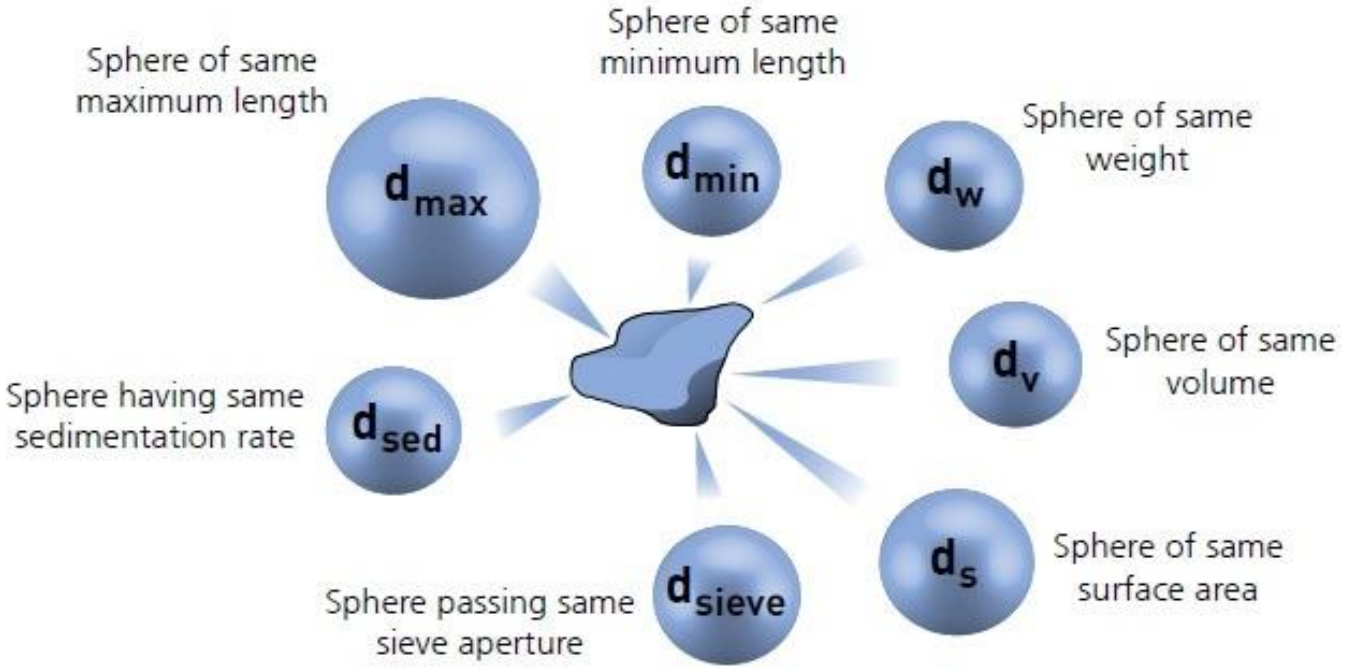
- Identify defect types and recreate defects in a controlled laboratory environment

  "re-creation of equivalent defect types in a controlled laboratory environment"

The 2 possibilities can be mixed

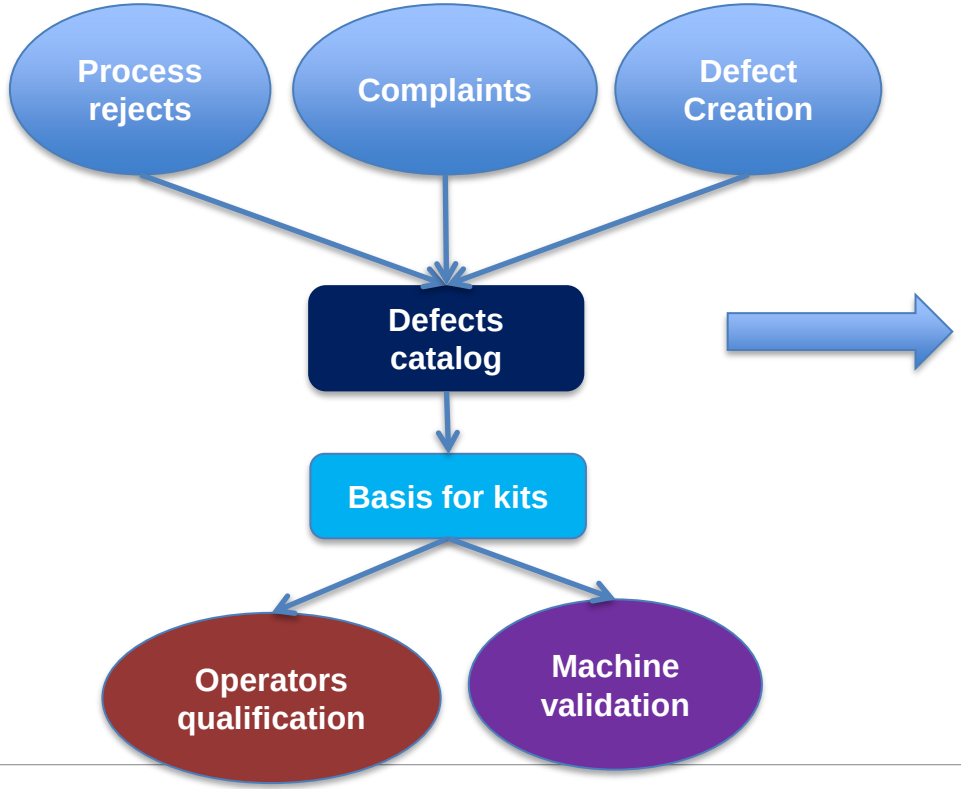
	From production	Recreated defects
+	• Cost • Production sites ownership	• Ensured polymorphism • Controlled defects • Dedicated team (experts) • Harmonization across sites • Lifecycle
−	• Polymorphism coverage • Defect characterization (particles) • Defect evolution (e.g. cracks) • Lifecycle • Side activity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

Why not using commercial particle beads?



See Stimuli article USP 2021
where particle beads is promotted

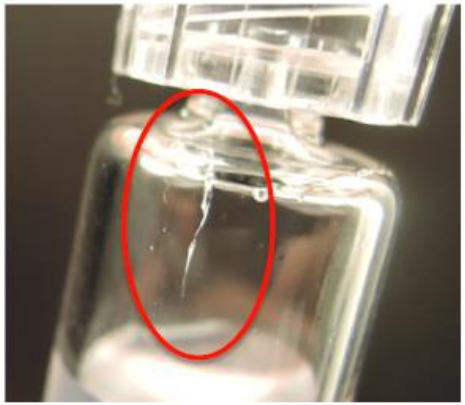
Why a defect catalogue ?



Defect Catalogue example

Master Defect Library version XX

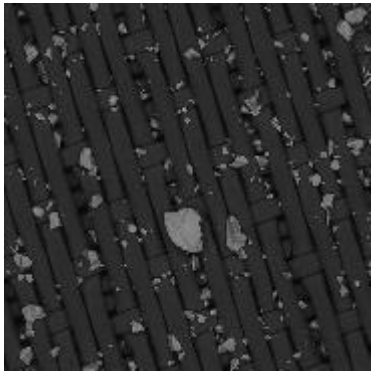
Critical – Glass Defect – Crack – At shoulder level



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?

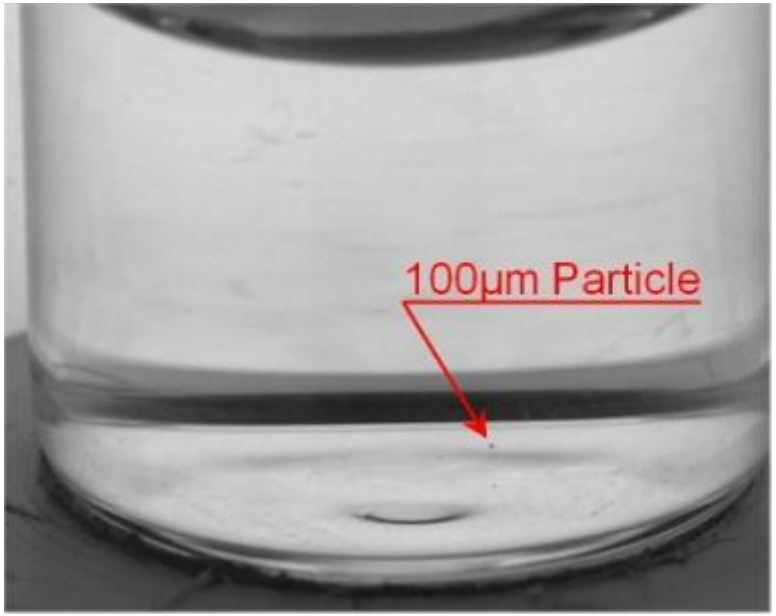


- For established products and facilities:
  - Collect data from rejects trending in production (Control Charting, AQL)
  - Select the most occurring defect types in typical batches (more than X ppm, Pareto, etc.)

- 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

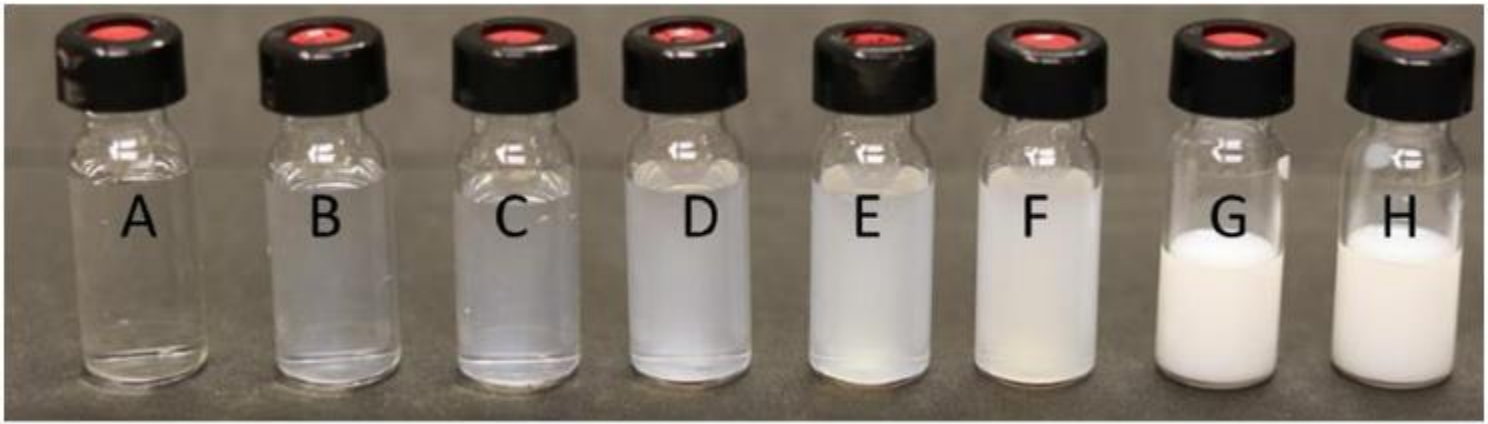
Hoshin matrix visualization for particles

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

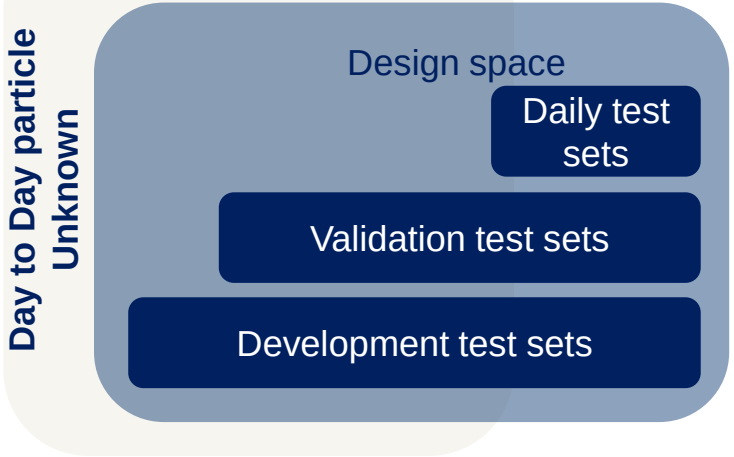
Bracketing approach?



Design Space: How to anticipate unknown defects?

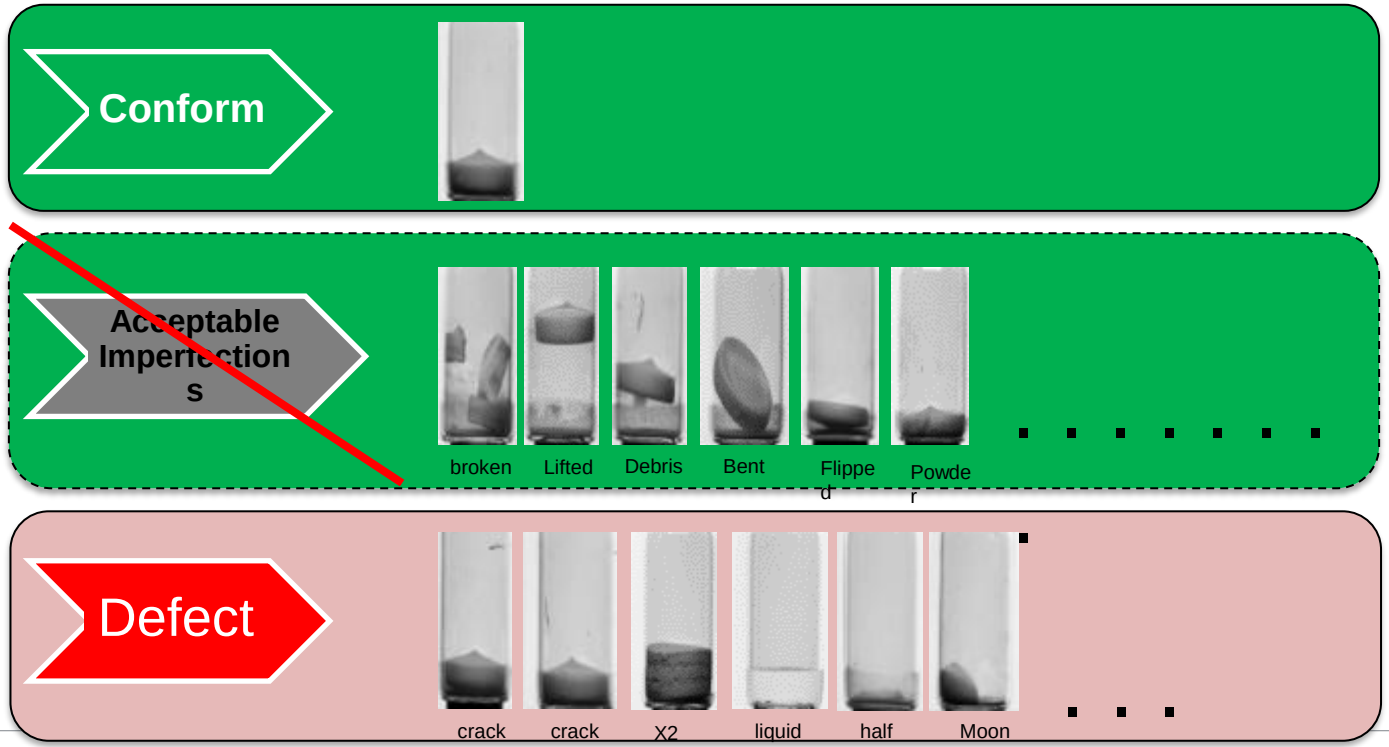
Key learning:

- 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!

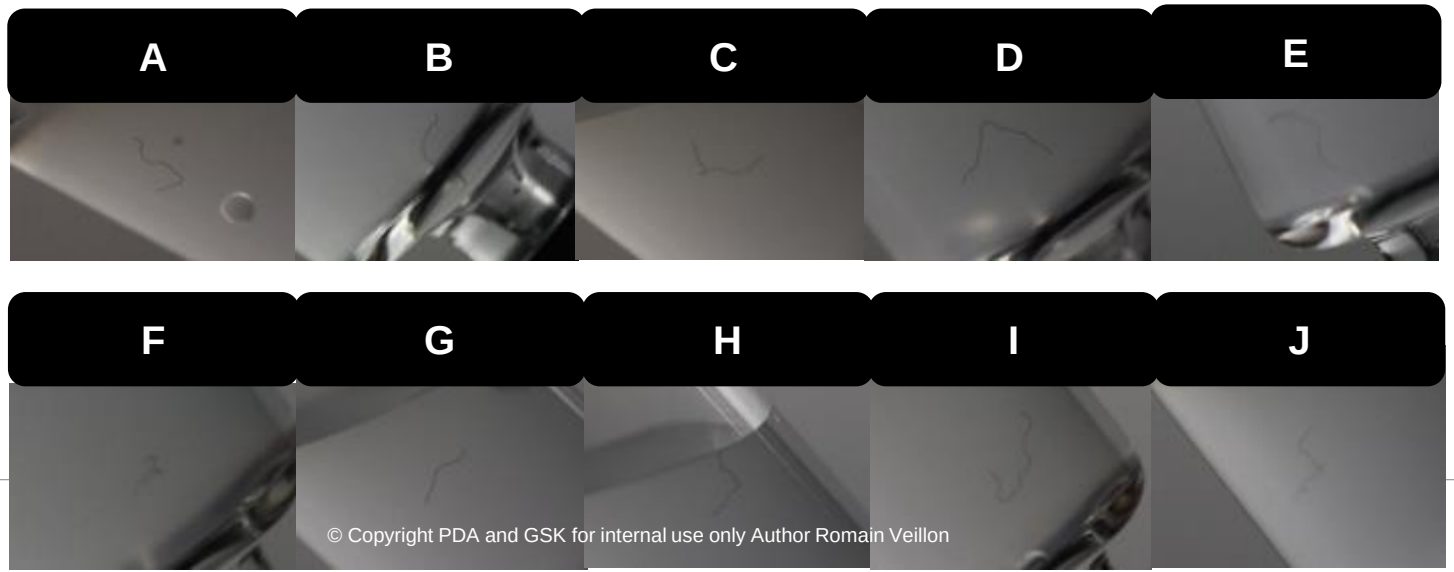
NO Grey zone is Acceptable => define the limit



Need for replicates

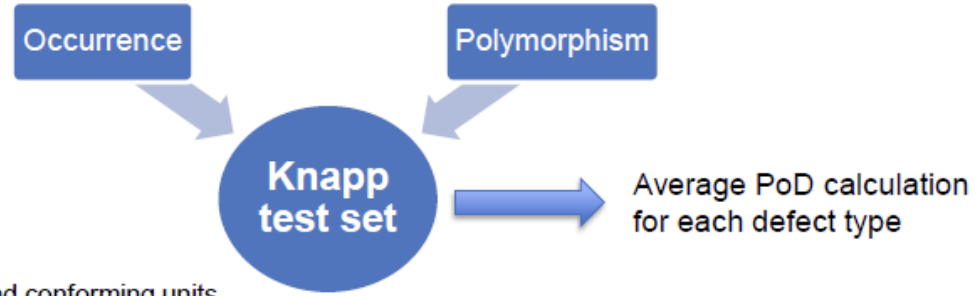
Precipitating particle:
- black
- lengenthed, type fiber
- big : 0.6 mm²

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



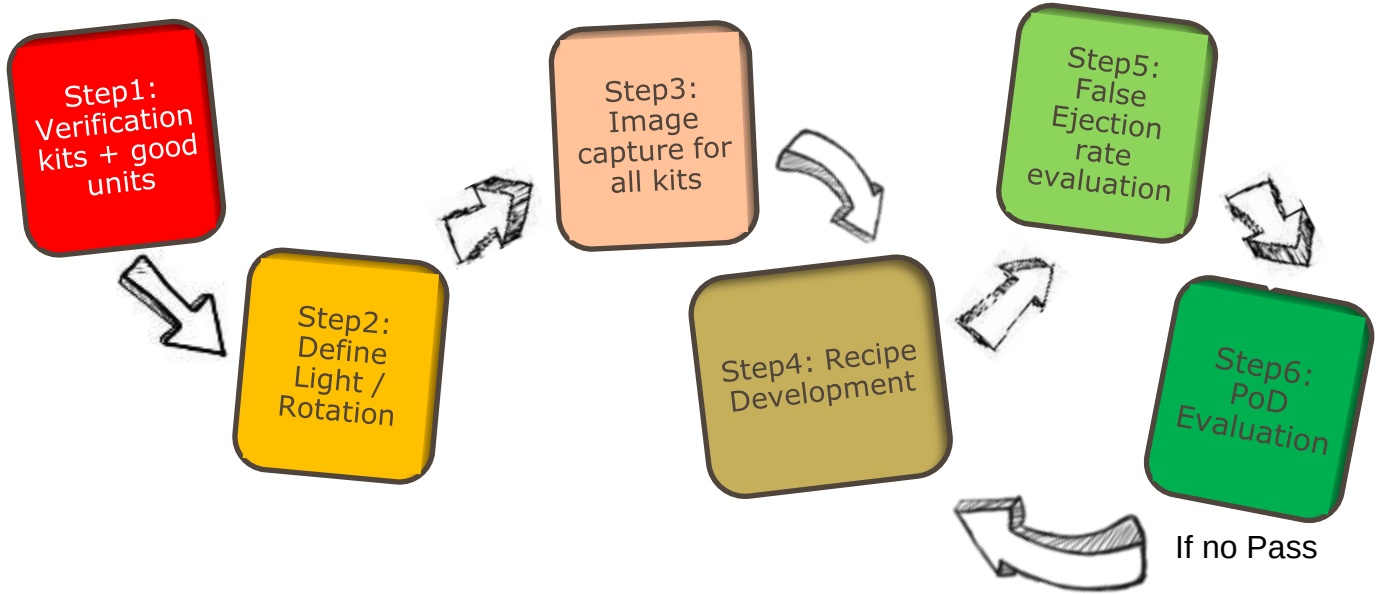
Define MVI Baseline PoD

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

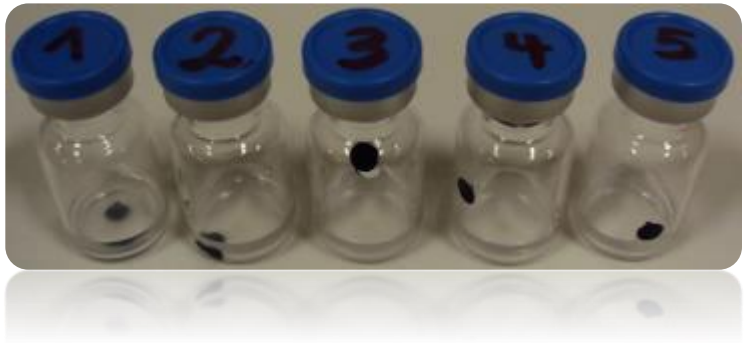
QA oversight on Test Sets

- Collection in production
- Manufacturing
  - Sub contracting : working instruction / DML /
  - Internal group: working instruction / DML /
  - Labelling units / UV printing➔ anti mixup
  - 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



Key take away:

- In this section 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