



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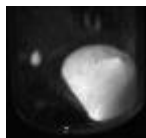
What do? Whatever dosage form (liq or lyo), 100% visual inspection required for each parenteral product for following defects (type or family):



- 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*

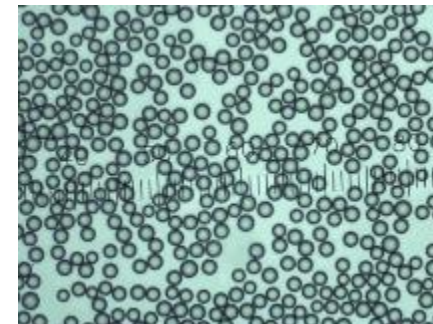
Extrinsic particles are very difficult to anticipate in defect kits

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

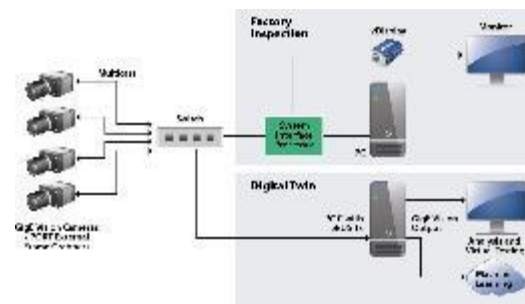


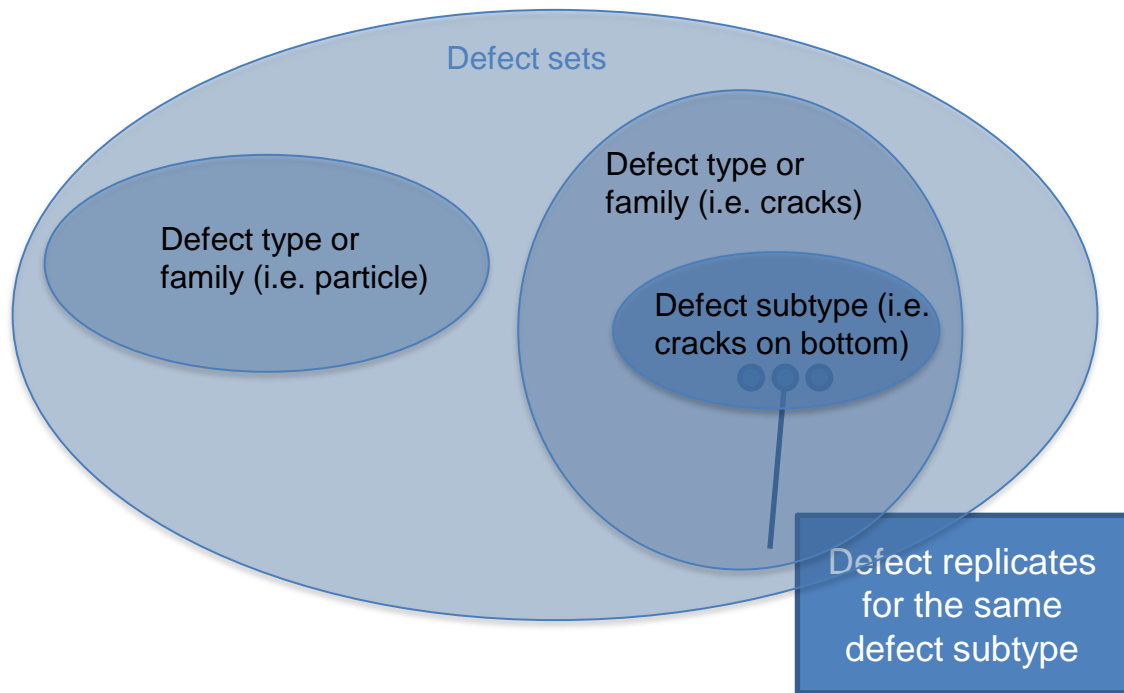
4. Virtual defect library = digitalization of test sets

- 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



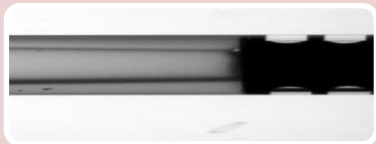


Defect standard should:

Demonstrative of real defects occurring
in production

Cover the polymorphism of defects

Include defects with MVI PoD $\geq 70\%^*$



Syr.

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



Vial Liq.

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





Lyo

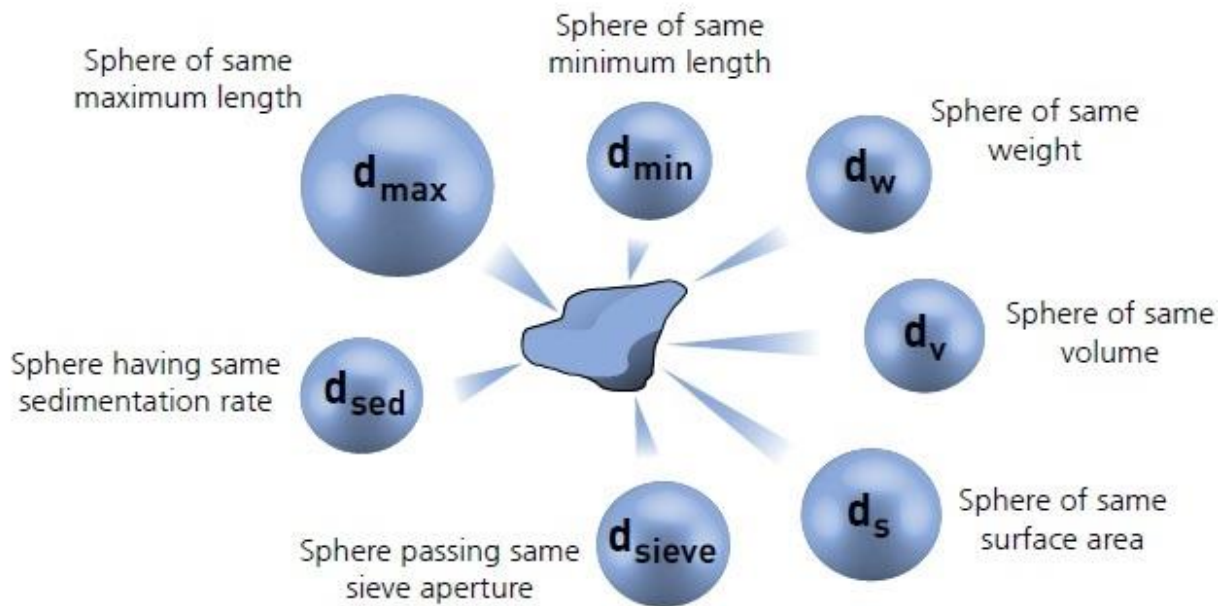
- Cracks
- Particles
- Lyo defects
- Closure
- Cap Color
- Leaks
- Stain
- scratches

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
	<ul style="list-style-type: none"> • Cost • Production sites ownership 	<ul style="list-style-type: none"> • Ensured polymorphism • Controlled defects • Dedicated team (experts) • Harmonization across sites • Lifecycle
	<ul style="list-style-type: none"> • Polymorphism coverage • Defect characterization (particles) • Defect evolution (e.g. cracks) • Lifecycle • Side activity 	<ul style="list-style-type: none"> • Cost • For some defects, difficult to reproduce (lyo, color changes...) • Risk of departing from actual defects • Contamination (undesired particles or microbio)



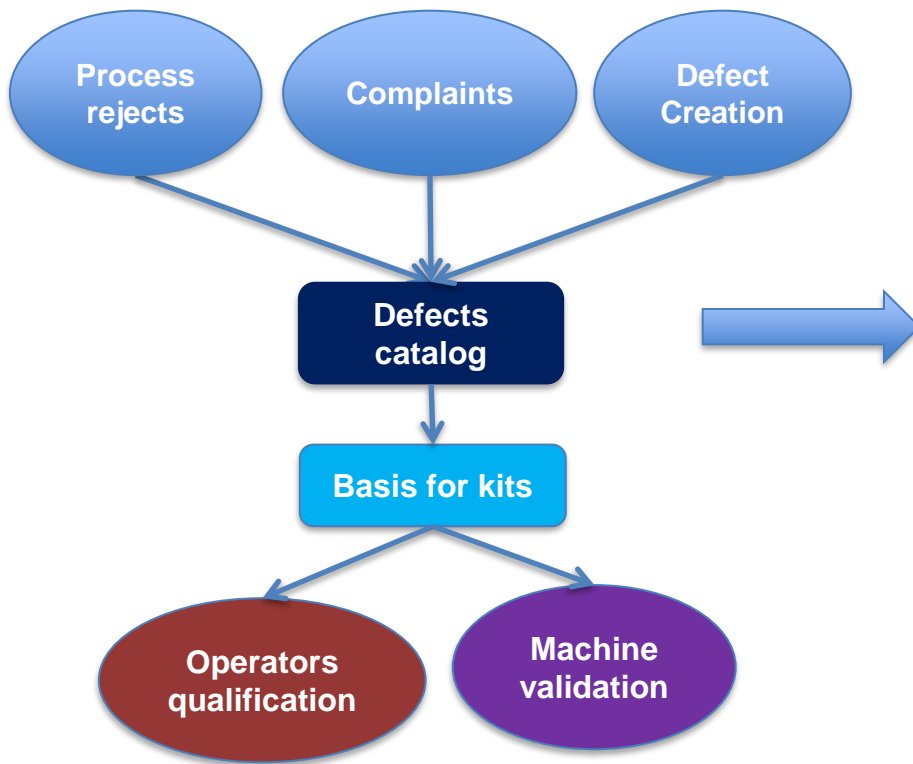
See Stimuli article USP 2021 where particle beads is promoted

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



<Name>	
<Root cause if known>	
 	<p>Description:</p> <ul style="list-style-type: none"> •Color •Shape •... <p>Instruction for defect evaluation:</p> <ul style="list-style-type: none"> •Instruction 1 •Instruction 2 <p>Criticality level:</p> <p>Critical – Major - Minor</p> <ul style="list-style-type: none"> •Justification 1 •Justification 2

Product knowledge

Master Defect Library version XX



Critical – Glass Defect – Crack – At shoulder level

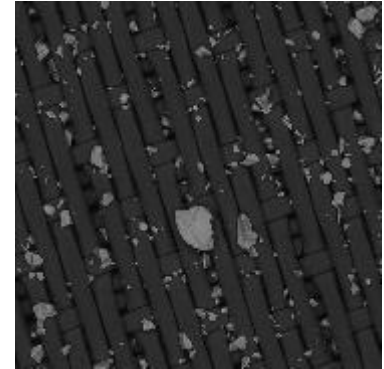


Category	Glass Defect – Crack
Location	Shoulder
Size	Medium
Orientation	Vertical
Color	N/A
Shape	N/A
Description	Mirror effect, syringe is not empty. Can be felt by passing nail on
Ref VICOC	CS20

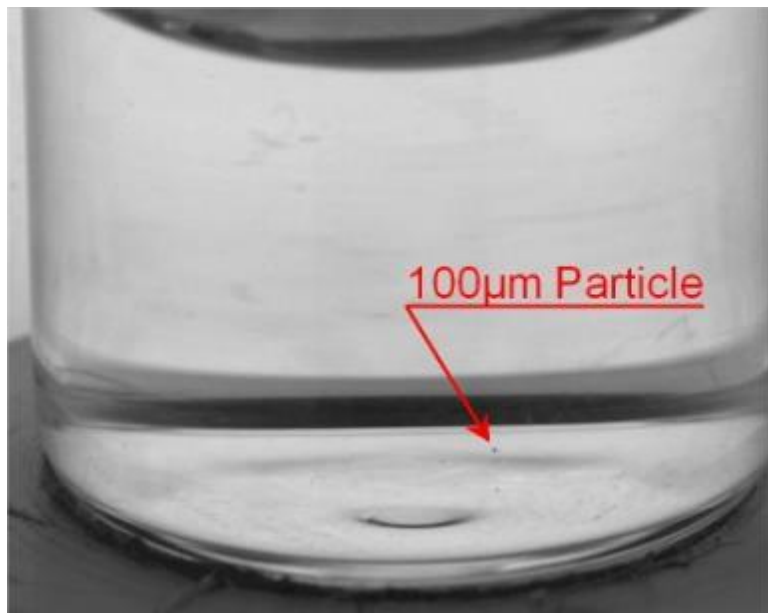
Physical attributes

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.)



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

Take into consideration:

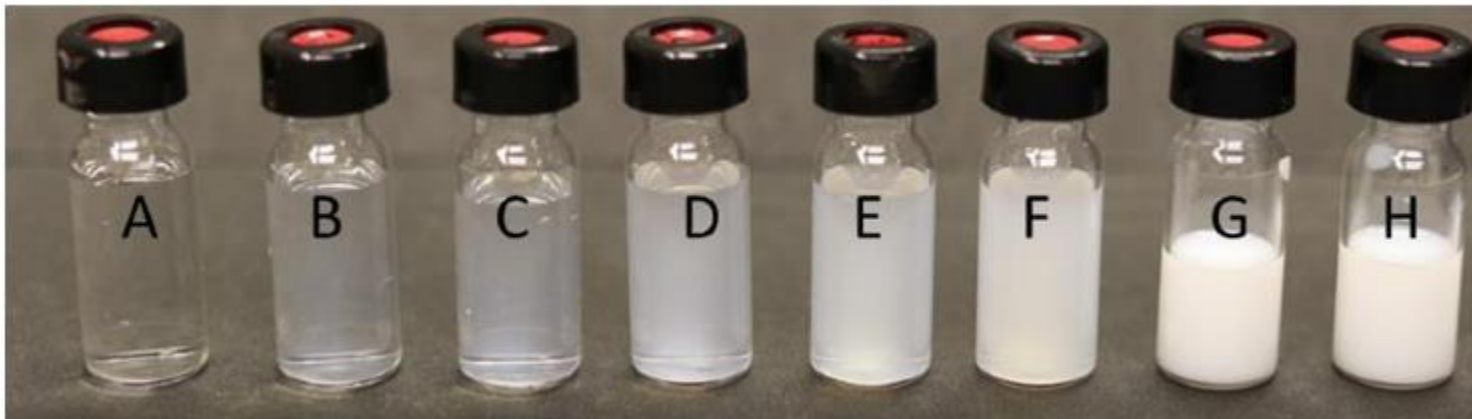
- Standard work
- Fatigue effect
- Defect concentration in goods
- Opacity / viscosity / volume

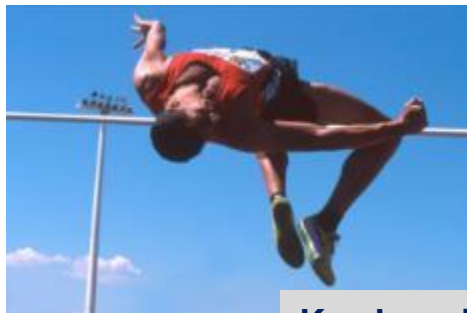
- **Not only white particle!** → different kinds of:
 - Shape (spherical, elongated, fiber...)
 - Color (transparent, white, black...)
 - Material (glass, rubber, steel...)
 - Behavior (fixed, floating...)
 - Size (small, medium, big...)
- *One particle per container (USP<1790> requirement)*
- **Not 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	Clogged	Fixed	Floating	Precipitating
				COLOR						
.	.	.	.	Transparent	
.	.	.	.	White	
.	.	.	.	Black	
.	.	.	.	Other	

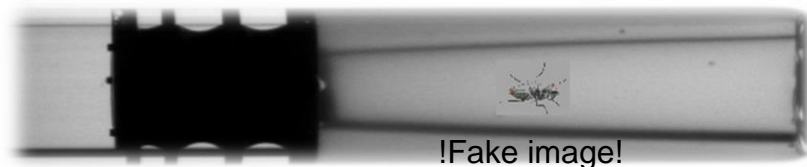
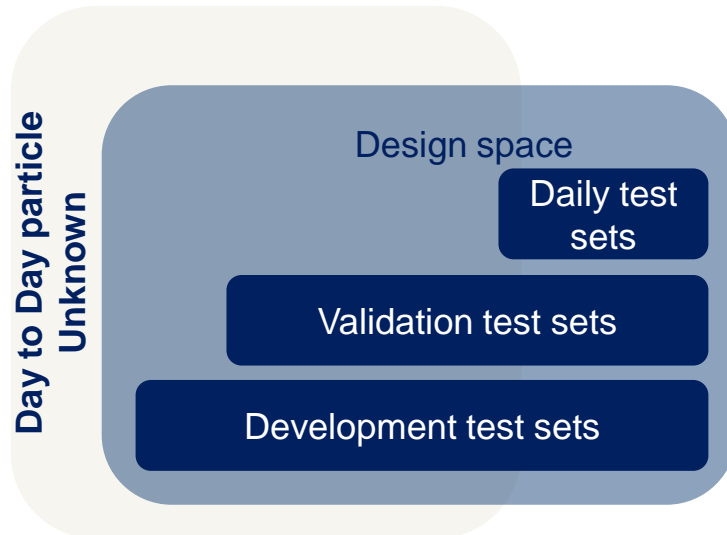
Risk to over-represent polymorphism
The purpose is to cover a pertinent polymorphism based on manufacturing data, not to cover all possible polymorphism





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



Conform

~~**Acceptable Imperfections**~~

Defect

broken Lifted Debris Bent Flipped Powder

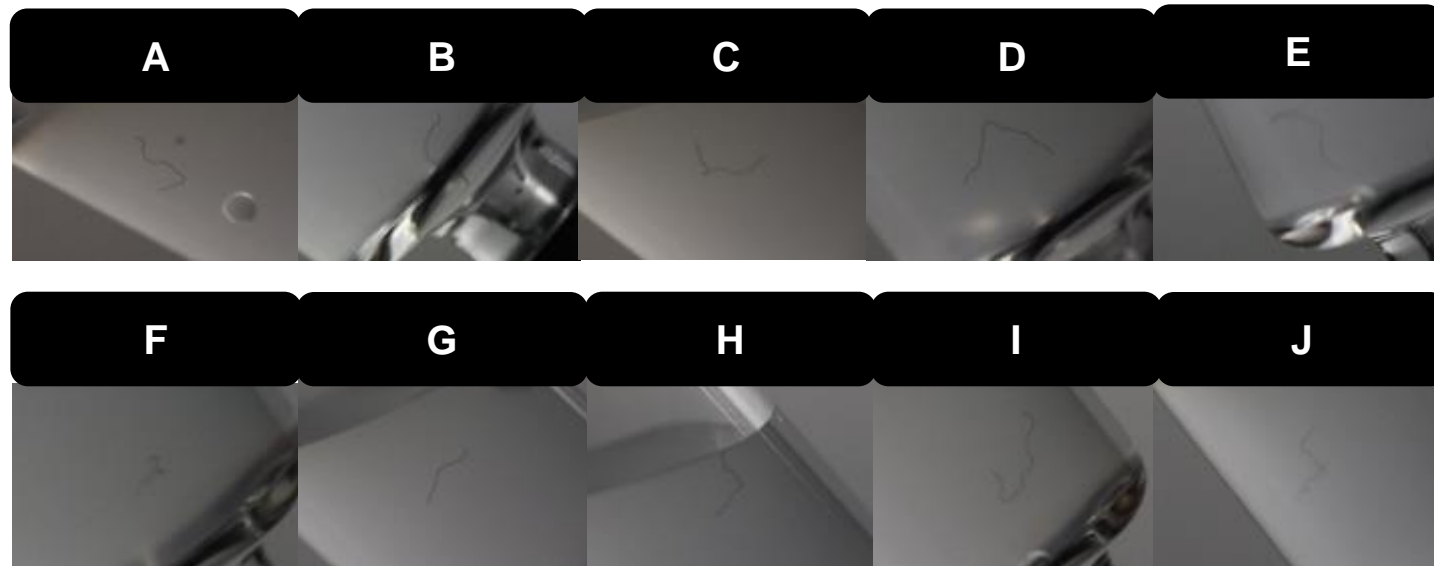
crack crack X2 dose liquid half Moon

Precipitating particle:

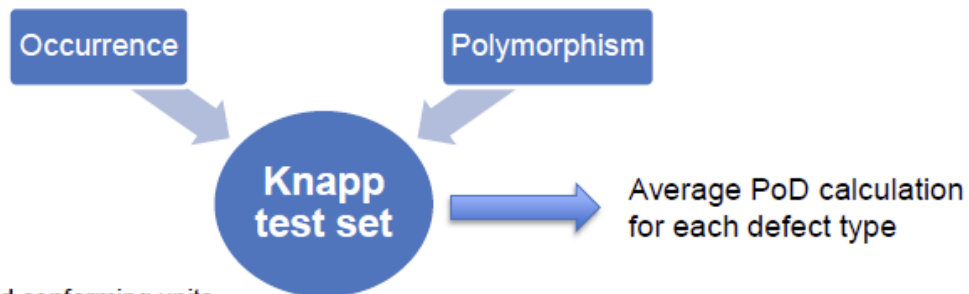
- black
- lengthened, type fiber
- big : 0.6 mm²

Location definition

- Defect family (particle/Crack/closure)
- Defect types (attributes)

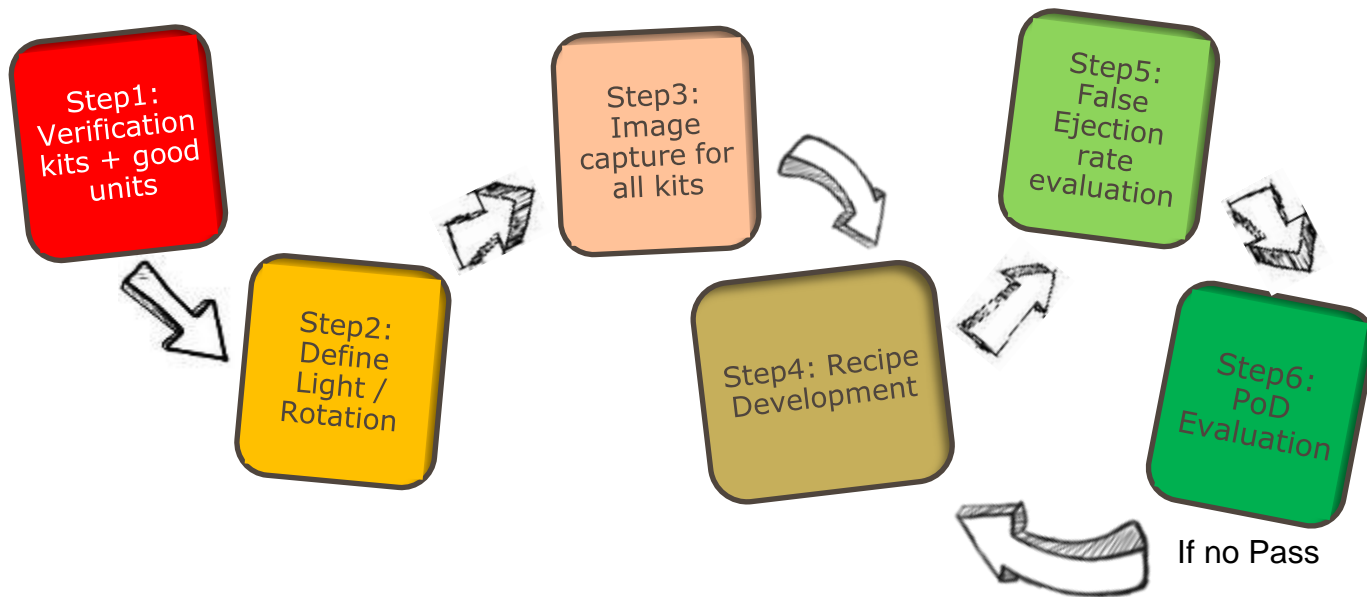


Perform a Rejection Probability Determination study according to USP<1790>



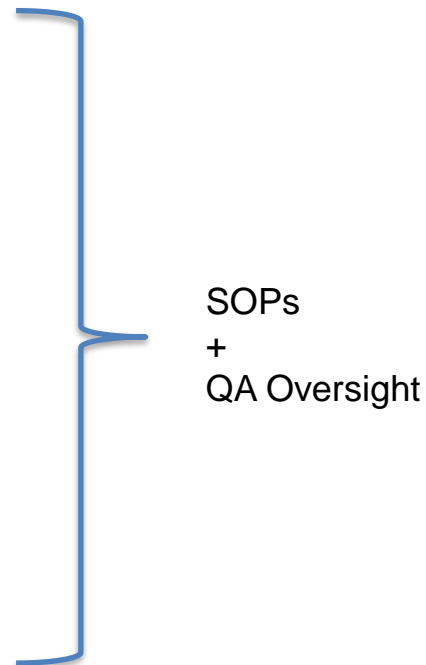
- **Test set:**
 - Mix of selected defect types and conforming units
 - At least 3 replicates per defect type
 - Maximum rate of defect (e.g. 10%)
 - Integrate inspector fatigue effect (cover one standard MVI shift)

- **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.)

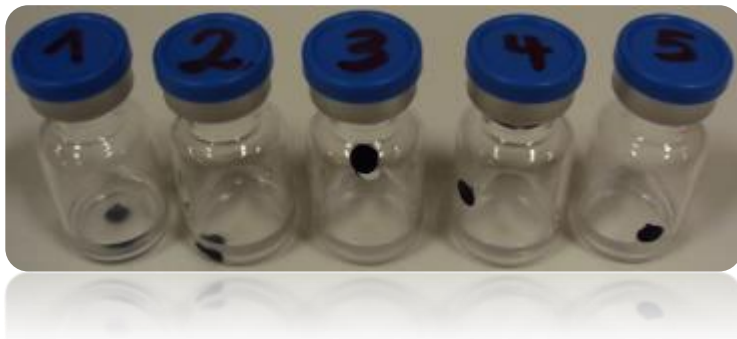


Document test set life cycle in a logbook

- 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



- 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
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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
- 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