- Theory 6:
- Qualification Test Set and Routine Test Set

- **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**

Theory 6:
Qualification Test Set and Routine Test

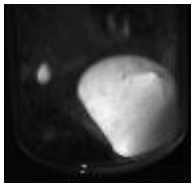
1. Prior study of particle/defect occurrence in real prod => control charting / number lots sampling
   - What type of particles/fibers, occurrence
   - This will also identify where introduced for process improvement
     - Removing the cause versus solving the problem
   - Necessary for selecting machine/supplier
     - 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

Theory 6:
Qualification Test Set and Routine Test

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
   - Building a library of defect images and good units
   - The more the merrier
5. Virtual machine test
   - Having these images one can do offline configuration of machine recipes.
   - The automatic inspection machine stays in production for already validated configurations

Theory 6:
Qualification Test Set and Routine Test

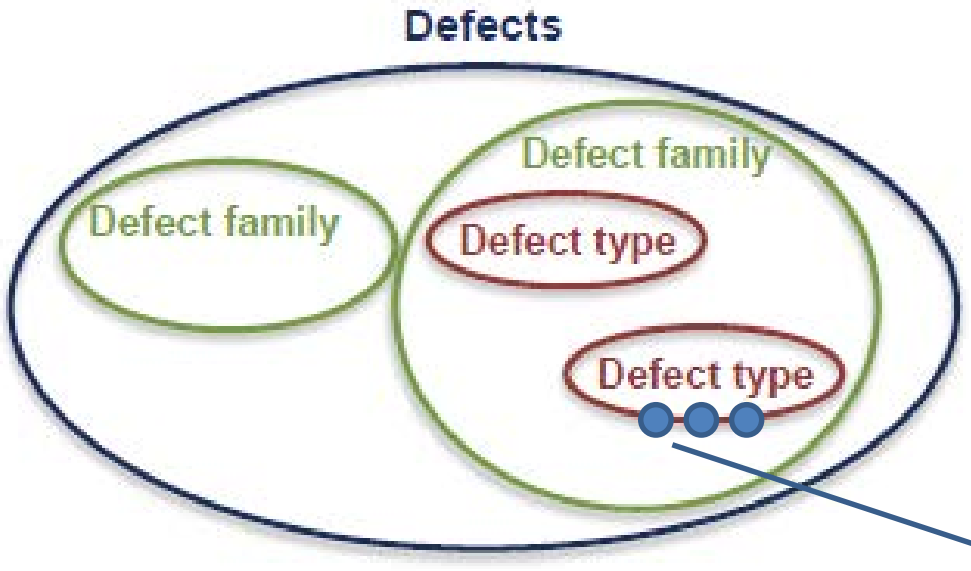
What do? Whatever dosage form (liq or lyo),100% visual inspection required for each parenteral product for following defects:



- 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*

Theory 6:
Qualification Test Set and Routine Test

Need some defintions:



Defect replicates for the same defect type

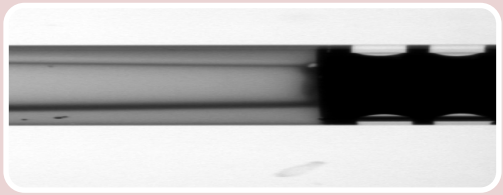
Theory 6:
Qualification Test Set and Routine Test

Points to consider:

Defect standard should:

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

Theory 6:
Qualification Test Set and Routine Test



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**

Theory 6:
Qualification Test Set and Routine Test

- 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	• Polymorphism coverage can also be difficult • Costs • For some defects difficult to reproduce (lyo color changes..) • Possible, avoid cold storage • Risk of departing from actual defects • Contamination (undesired particles or microbio

Visual Inspection Defect Master Library

Process rejects

Complaints

Vaccines Creation

Defects catalog

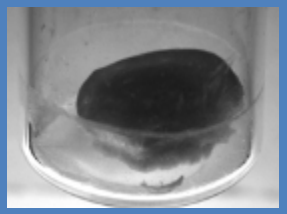
Basis for kits

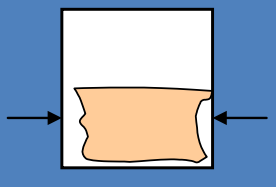
Operators certification

Machine validation

<Name>

<Root cause if known>





Description:

- Color
- Shape
- …

Instruction for defect evaluation:

- Instruction 1
- Instruction 2

Criticality level:

Crticial – Major - Minor

- Justification 1
- Justification 2

Product knowledge

Visual Inspection Defect Master Library 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.)

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

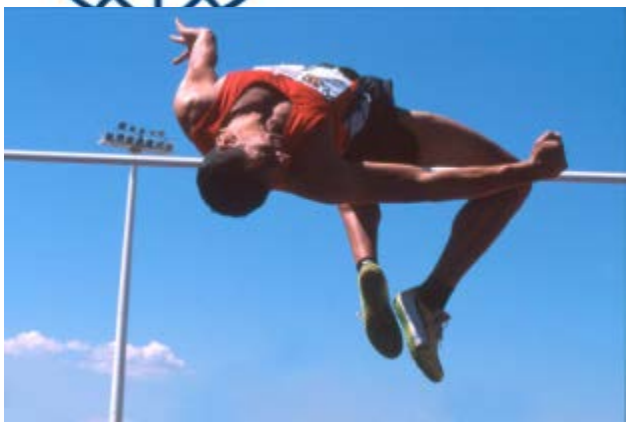
Hoshin matrix visualization for particles

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

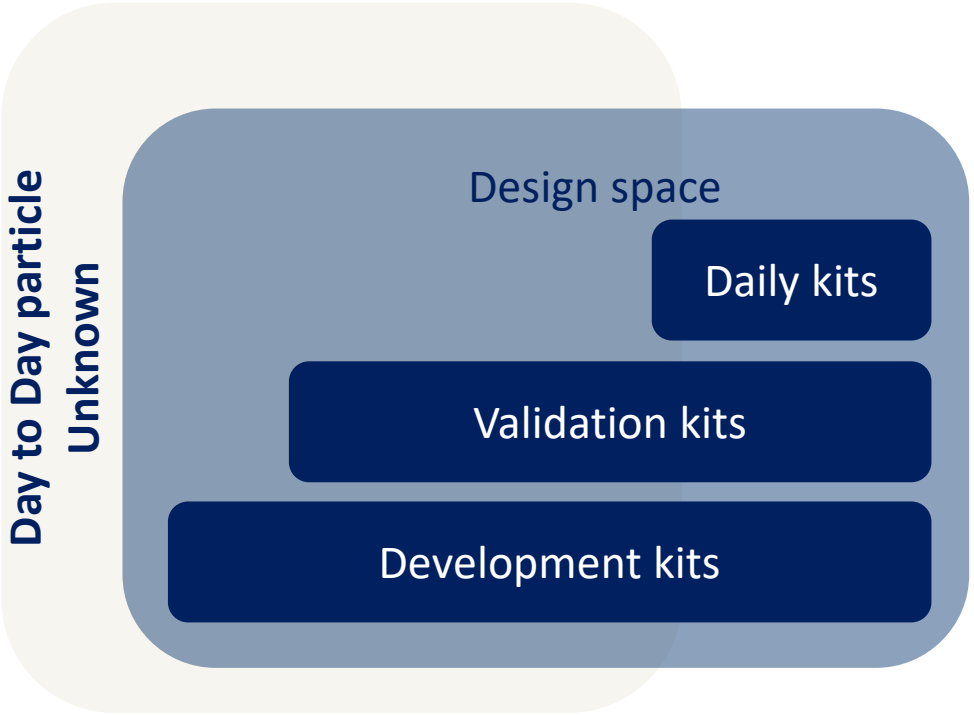
The purpose is to cover a pertinent polymorphism based on manufacturing data, not to cover all possible polymorphism

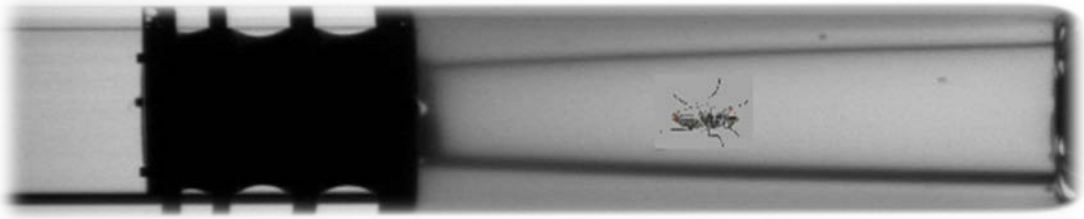
Can AVI detect unknown particles ?



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



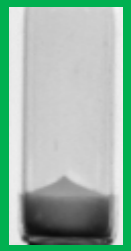


!Fake image!

Lyophilized Parenteral defects

NO Grey zone is Acceptable => define the limit

Conform

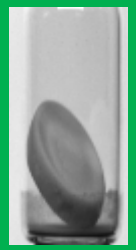


Acceptable Imperfections


broken


Lifted


Debris


Bent

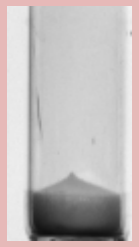

Flipped


Powder

. . . . . .

Defect


crack


crack


X2 dose


liquid


half

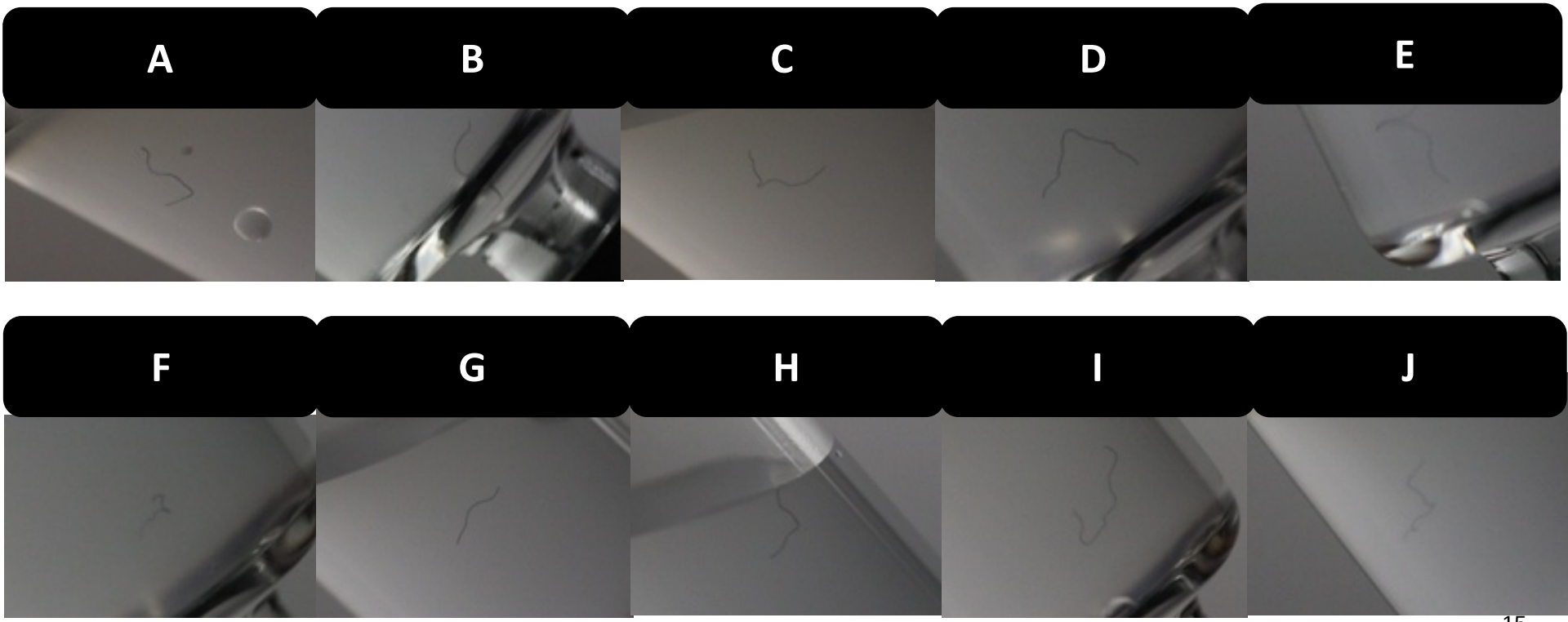

Moon

. . .

Theory 6: Qualification Test Set and Routine Test Set Number of Replicate ?

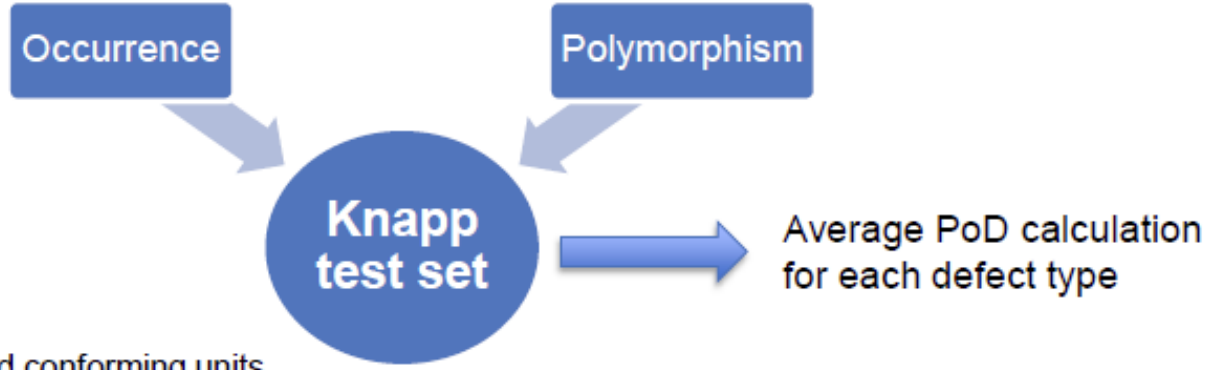
Precipitating particle:
- black
- lengenthed, type fiber
- big : 0.6 mm²

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



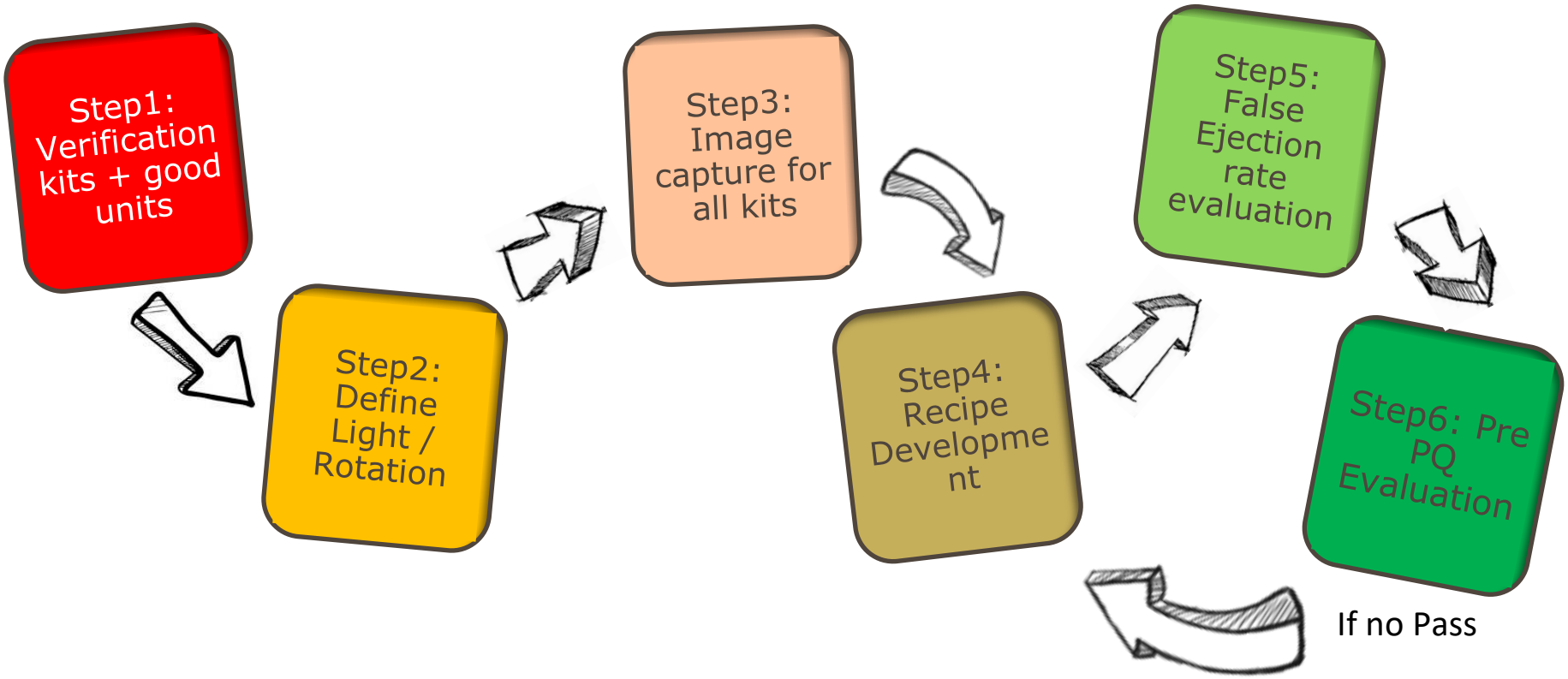
Theory 6: Qualification Test Set and Routine Test Set PoD Studies to establish MVI Baseline?

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.)

Vision Recipe development



Reference defect Kit

+ consistent defects
+ no degradation
+ stable years
+ Fixed Detection rate

- Artificial
- Gross defects

Real Defect Kit

+ Real defects

- Degrade fast
- Variability between defects
- No Detection rate limit

Theory 6: Qualification Test Set and Routine Test Set

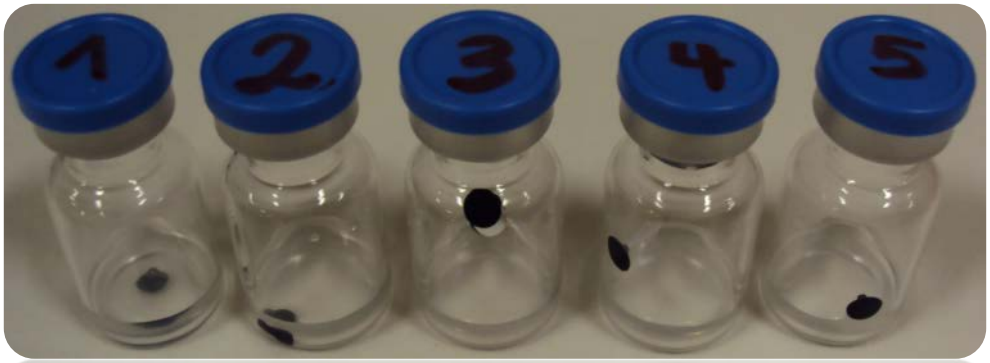
Supply of kits / Life cycle

- 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 kits ?

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



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