

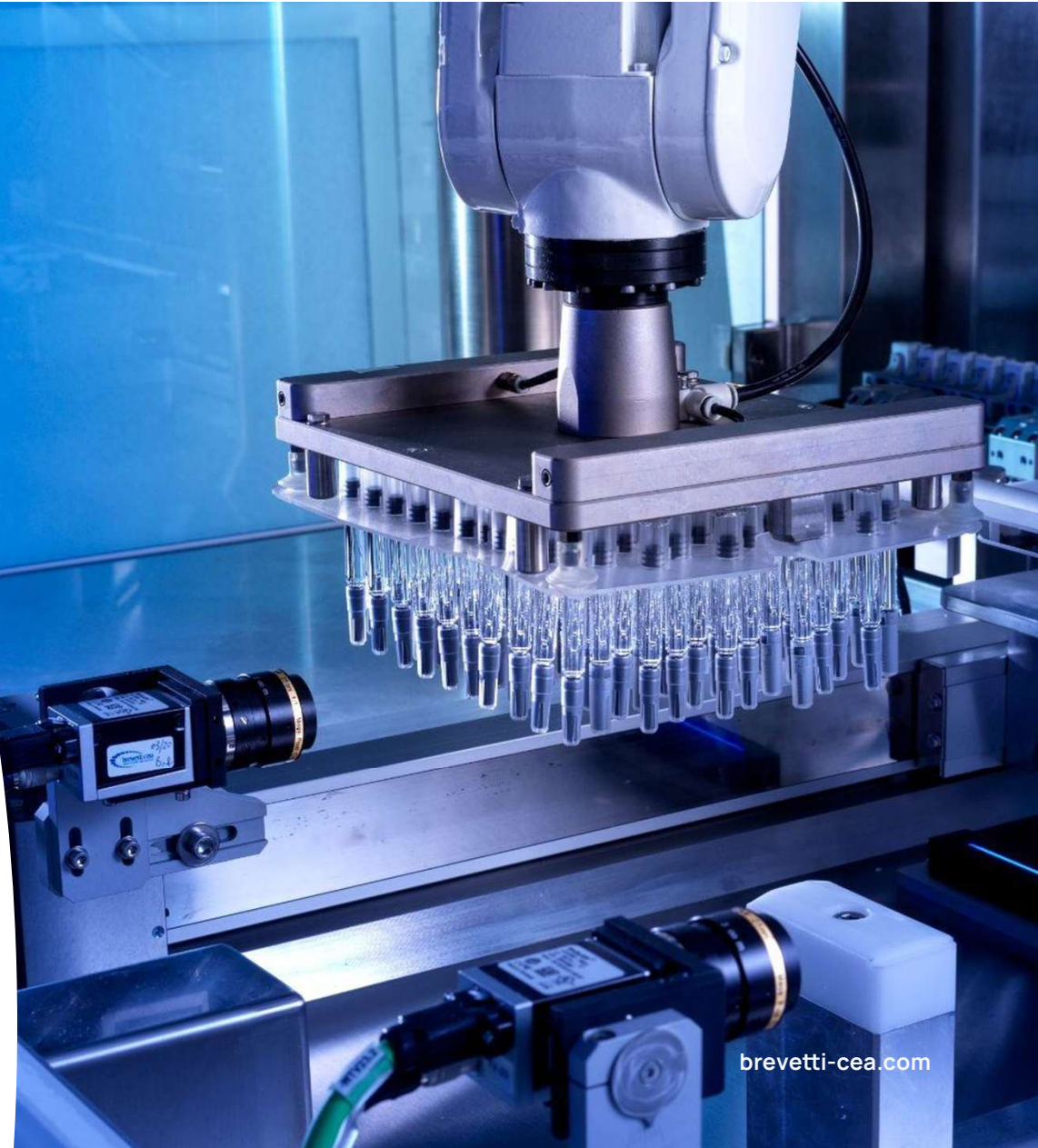


Digital Wokshop **SIMPOSIO EFT**

# From Manual to Automated

**Massimo Frasson** – CEO & General Manager  
**Andrea Sardella** – Customer Success Manager

June 2026



[brevetti-cea.com](http://brevetti-cea.com)

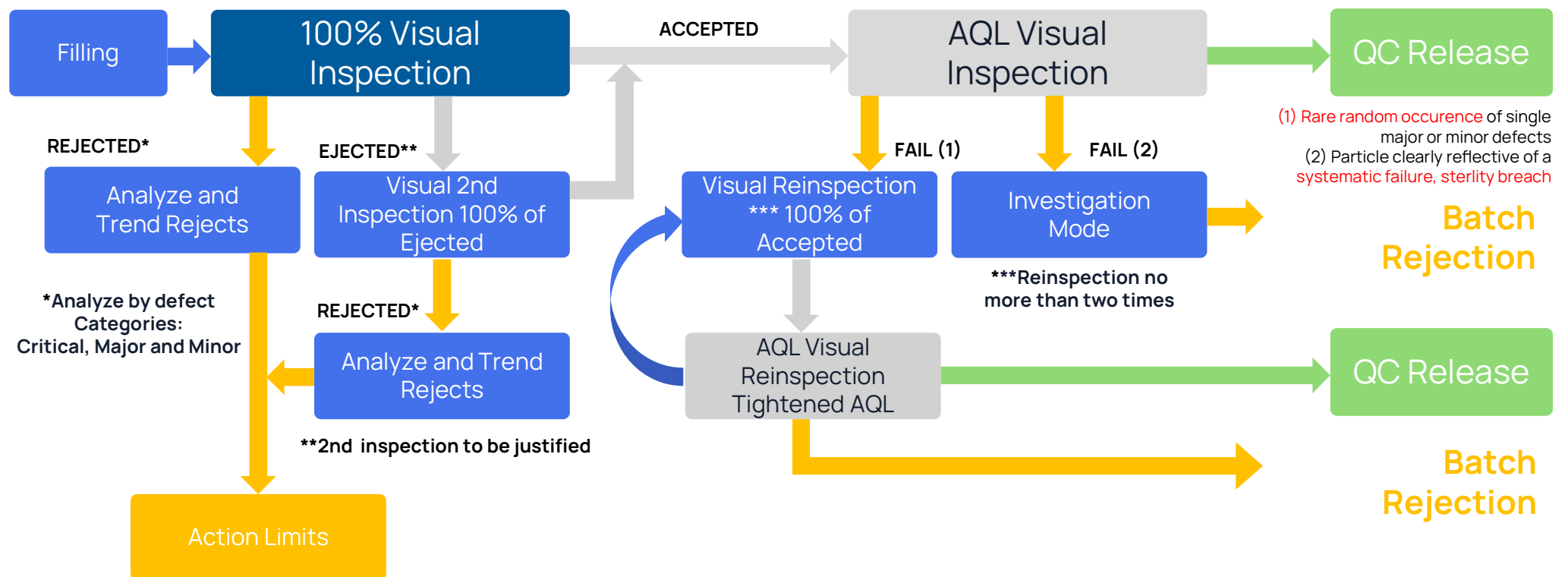


**Master manual visual inspection  
before implementing automated  
visual inspection!**

**Test sets are the language that we  
use to translate MVI in AVI.**

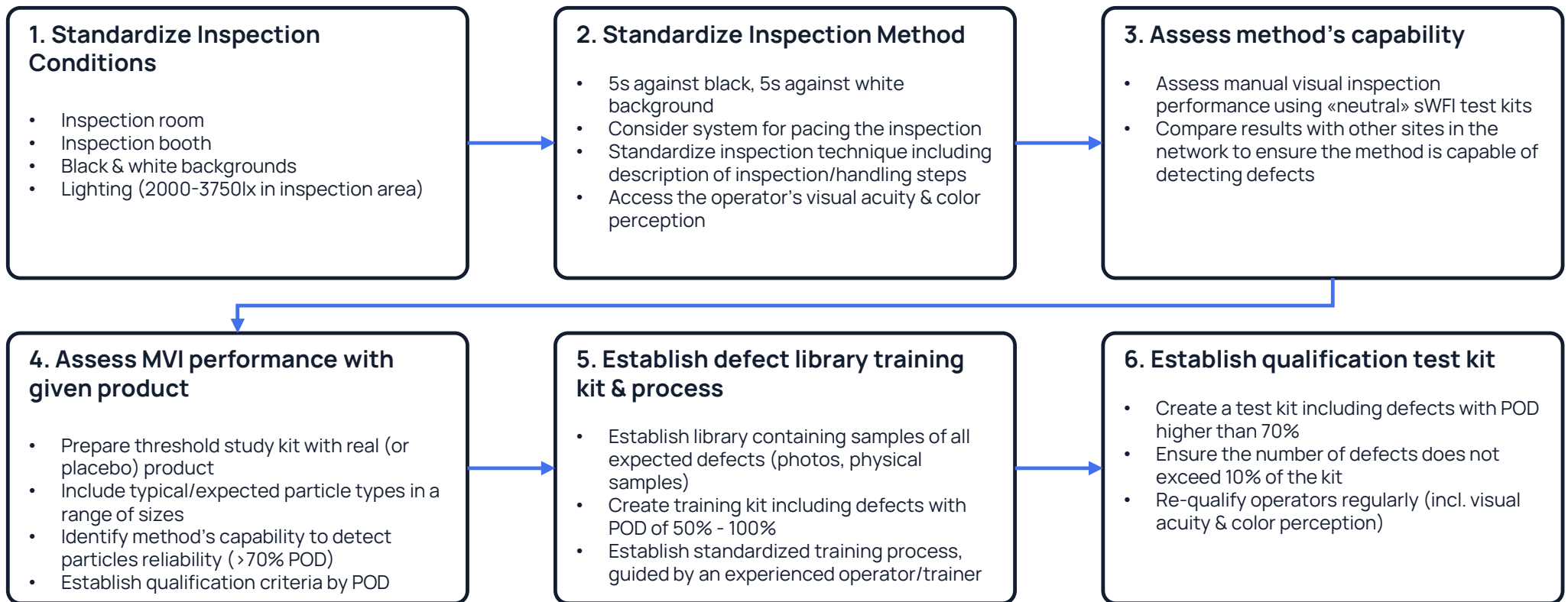


# Visual Inspection Process in compliance with Annex I





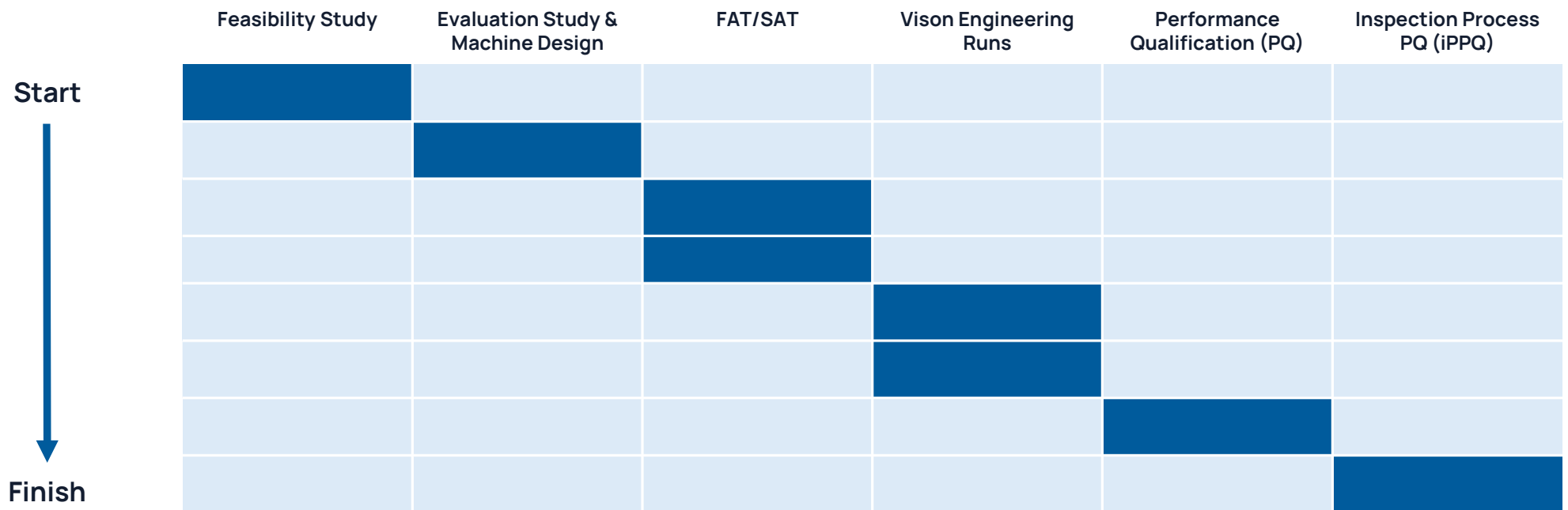
# MVI is the foundation for AVI





FROM MANUAL TO AUTOMATED

# Test Kits needed for an AVI Implementation Project



Test sets are required at each of these implementation project phases



## Which test kits are needed?

Stage	Feasibility Study	Evaluation Study & Machine Design	FAT / SAT	Vision Engineering Runs	Performance Qualification (PQ)	Inspection Process Perf. Qual. (iPPQ)
Sample set	Set 1	Set 2	Set 3	Set 3+	Set 4	Routine Lots
Test approach	Threshold Study		Knapp Test			AQL
Deliverables	Vendor selected	Machine designed & built	FAT/SAT passed	Reduced FRR while maintaining detection	PQ passed	iPPQ passed
Sample size	100-200 (80/20)	200-400 (80/20)	approx. 2000 (90/10)	3000-10000 (95/5)	approx. 2000 (90/10)	3 production lots



**Align on replacing the FAT set with vendor. No new defects, just variation!**



# Feasibility Study Test Set

## Purpose of feasibility tests

Feasibility tests serve the purpose of **assessing the suitability** of the **technology and equipment provided by vendors** for the targeted product before committing significant resources to the project.

## Test set requirements

Test sets should contain **all targeted defects and various sizes of particles**. Sizes of defects chosen should **represent the MVI capabilities**. The sets should also include units without defects to **assess expected false reject** rates.

## Vendor assessment

If possible, utilization of the **same test set across several vendors** is recommended to allow for **best comparability** of their capabilities and limitations.



FROM MANUAL TO AUTOMATED

# Feasibility Study Test Set

## Defects

All defects

## Quantity

50-100 defect samples

**Critical: NLT 3 per defect**

Major: 1-3 per defect

Minor: NLT 1 per defect

50-100 good units

## Particles

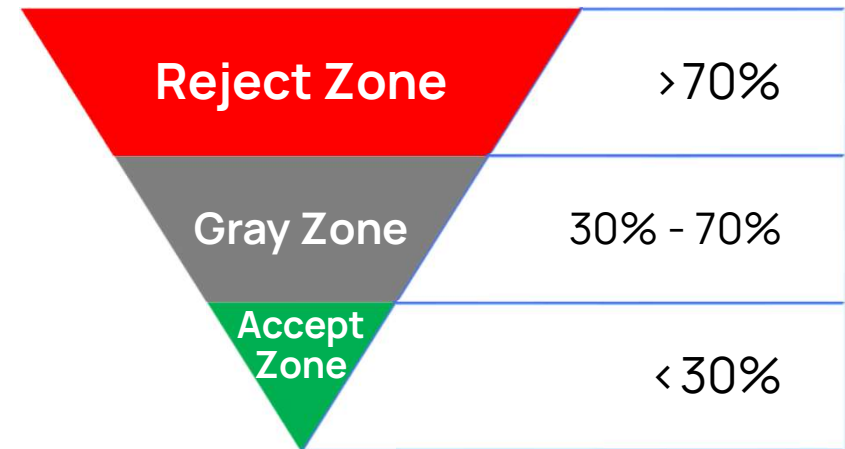
Primarily in the reject zone

Some 50-70% POD for information

## Source

Production defects preferred

Artificial defects as needed



Type	Critical Defects	Major Defects	Minor Defects
Product	<ul style="list-style-type: none"><li>Product Color Incorrect</li><li>Cake Imperfection</li><li>Incorrect Fill Volume</li><li>Turbidity</li><li>Extrinsic Particle</li></ul>	<ul style="list-style-type: none"><li>Intrinsic Particles</li></ul>	
Container	<ul style="list-style-type: none"><li>Crack</li><li>Internal Contamination</li></ul>	<ul style="list-style-type: none"><li>Bruise</li><li>Bump Check</li></ul>	<ul style="list-style-type: none"><li>Scratch</li><li>Stone / Knot</li><li>Fold</li></ul>
Closure	<ul style="list-style-type: none"><li>Loose Crimp/Cap</li><li>Missing Stopper</li><li>Wrong Crimp/Cap Color</li></ul>	<ul style="list-style-type: none"><li>Gross Stopper Imperfection not affecting container integrity</li><li>Gross Crimp Imperfection not affecting container integrity</li><li>Particulate Matter on Stopper</li></ul>	<ul style="list-style-type: none"><li>Embedded Intrinsic Material in Stopper</li></ul>



# Evaluation Study Test Set

## Purpose of evaluation study

Depending on the feasibility test results, technical complexity and innovation level, an evaluation study can be performed to **confirm the expected performance** of the proposed technical solution for the preferred vendor.

## Test set

Test sets should contain all targeted defects and various sizes of particles. Sizes of defects chosen should represent the MVI capabilities. The sets should also include units without defects to assess expected false reject rates.



FROM MANUAL TO AUTOMATED

# Evaluation Study Test Set

## Defects

All defects

## Quantity

100-200 defect samples

Based on feasibility test results

More variation in challenging defects (up to 10 per defect)

100-200 good units

More good units for variation in accepts

## Particles

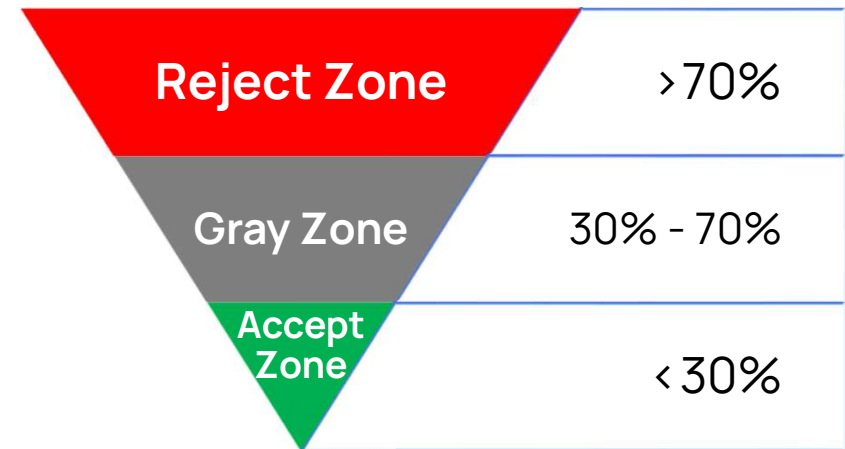
Primarily in the reject zone

Some 50-70% POD for information

## Source

Production defects preferred

Artificial defects as needed



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# FAT / SAT Test Set

## Purpose of FAT / SAT

Factory acceptance testing (FAT) is performed to **confirm machine performance** as defined in the URS before it is shipped to the site.

Site acceptance testing (SAT) is performed to **confirm machine performance is consistent before and after shipping to the site.**

## Test set recommendation

A test set should be specifically designed for this purpose. It should replace the test set supplied to the vendor for development. The FAT/SAT test set shall have the same specification (no new defects!) as the development set but should be comprised of new/other samples and more variation to assess the equipment performance.

The **same test set is used for FAT and SAT.**

## Vendor alignment

Ensure to align on the FAT / SAT strategy with your vendor upfront.



FROM MANUAL TO AUTOMATED

# FAT / SAT Test Set

## Defects

All defects (same as before, no new defects)

## Quantity

200+ defect samples

more variation in defects than in evaluation study

±1800 good units

More good units with variation to assess FRR

## Particles

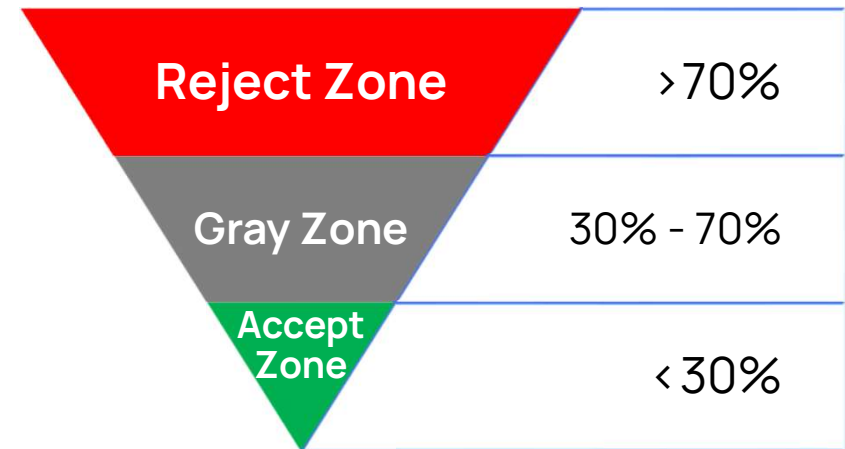
Primarily in the reject zone

Some 50-70% POD for information

## Source

Production defects preferred

Artificial defects as needed



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# AVI Validation: Regulatory Requirements

## EU GMPs Annex 1

**8.32** Where automated methods of inspection are used, the process should be validated to detect known defects (which may impact product quality or safety) and be equal to, or better than, manual inspection methods. The performance of the equipment should be challenged using representative defects prior to start up and at regular intervals throughout the batch.

### USP <1790>

#### Ch 6.3:

“Validation of the automated inspection equipment should be based on **comparison with the compendial manual inspection** process with an expectation that alternative inspection methods demonstrate **equivalent or better performance**. Significant effort is required to program these systems and to test their performance **against a range of known defects**, as well as **acceptable containers**.”

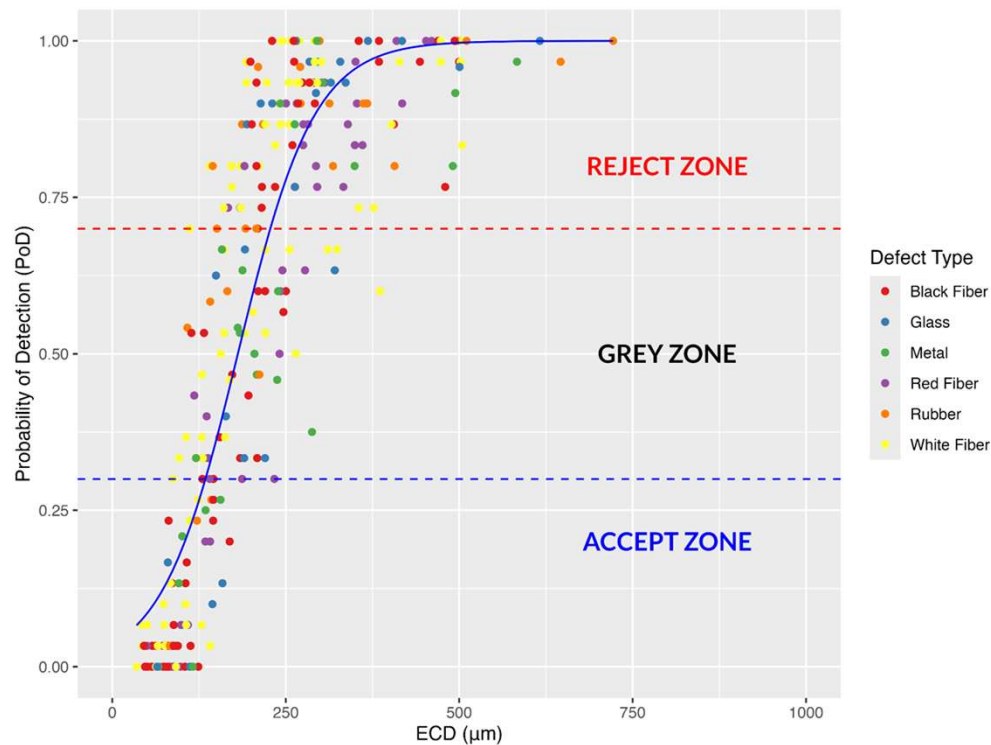
#### Ch 7.4

“The Knapp methodology recognizes that the **detection of particles is probabilistic**, and **repeated** inspections with strict controls on lighting and inspection pacing/sequencing **generate the statistical confidence** to assign a **reject probability** to each standard unit.”

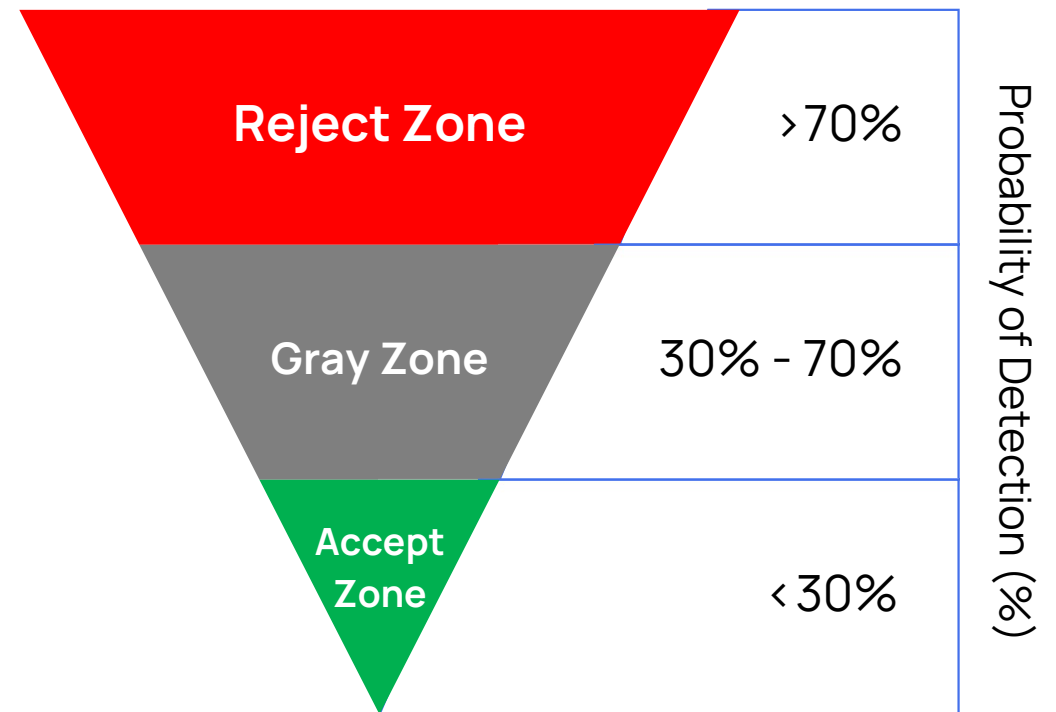


FROM MANUAL TO AUTOMATED

# Knapp Methodology



Julius Z. Knapp splits units in a kit in 3 zones based on their POD.



Knapp JZ, Kushner HR. "Implementation and automation of a particle detection system for parenteral products." *J Par. Sci Technol.* 1980;34(5):369-393



# Knapp Study Design

## Use only qualified operators

- Include a **broadly representative group** of operators (veterans as well as new operators, young and not so young, etc.) – do not select e.g., the best or the worst
- Ensure operators **stick to the inspection technique** (sequence) and duration (pacing is important!)
- Do not exceed **one inspection run per operator and day**
- **At least 30 inspection runs** to allow for statistical evaluation of results
  - e.g. 10 inspectors/ 3x runs each



## Test Kit Requirements

**A thoroughly characterized and qualified (!) test kit with a certificate/inventory list included.**

- Photo, size, and composition of each particle
- Photo, size, and position of each “static” defect
- Not more than #1 particle/defect per unit
- Thoroughly inspected and confirmed units without defects (good units)
- #1 sample per **defect variation (size)** in the test kit
- Not much more than **10% defects** in the test kit
- The test kit should consist of **enough units to mimic** at least the **maximum duration of a routine inspection** before the operator would be required to take an eye break



## Knapp execution

### Repeated manual inspections (10-30)

of a test set to determine the **manual probability of detection** (PoD) of the individual particles and fibers contained in the test set

**PoD** = (Number of times rejected) / (Number of times inspected)

Defect population  
< < 20% for not  
**biasing** operators  
Paced inspection

### Repeated automated inspection (10-50)

(at least equal to number of manual inspection runs) of reject zone ( $\geq 70\%$  PoD) particles and fibers to determine the **automated PoD**

Grey zone (30-70% PoD) particles and fibers and Good (0-30% PoD) may also be ran on the machine for informational comparison

### Compare average manual and automated detection

rate of all **manual reject zone particles and fibers** – comparison of **rejection zone efficiency** (RZE)  
 $mRZE \leq aRZE$



PRODUCT RANGE

June 2026

## Inspection Machines For Parenteral Products

Brevetti CEA offers a comprehensive range of

**automatic inspection and leak detection machines for any type of injectable pharmaceutical products**

contained in syringes, vials, cartridges, ampoules, bottles, IV-bags and BFS.

The integration of **sophisticated no-contact handling solutions** permits a **fully automatic cycle**, including de-nesting and re-nesting activities on both glass and plastic containers. All Brevetti CEA systems **grant smooth mechanical handling** throughout the process.

[brevetti-cea.com](http://brevetti-cea.com)



PRODUCT RANGE

# Glass and Plastic Containers

Max  
36000  
pz/h



Vials

Ampoules

Syringes

Cartridges

LV

IV-Bags

BFS



PRODUCT RANGE

# Products



Liquid



Freeze-Dried



Vaccine-Suspension



Cell-Therapy



Gel



Plasma-Derived Products

# Detection



Particles



Cosmetics

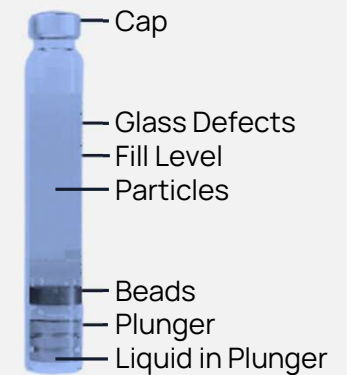
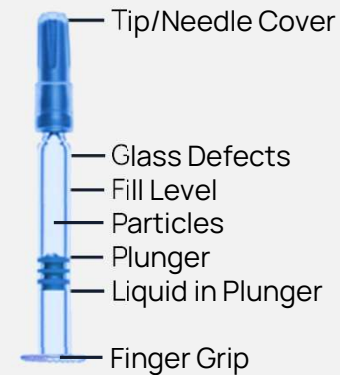
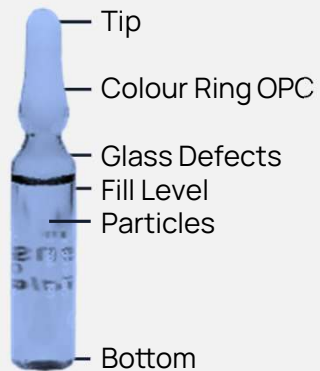


CCI



PRODUCT RANGE

# Standard Defects



High Voltage

Laser Spectroscopy (HGA)

Colour Analyzer

Turbidity Analysis

OCR/OCV

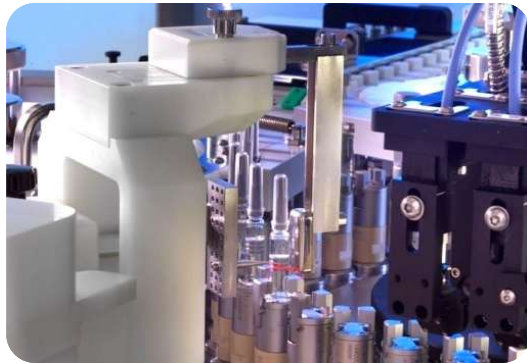


PRODUCT RANGE

# Container Closure Integrity

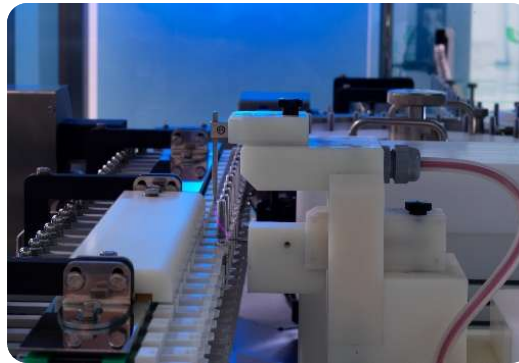


Brevetti CEA offers **integrated** and **stand-alone leak testing solutions** for liquid and freeze-dried pharmaceutical products based on different **non-invasive, non-destructive testing methods** that meet and exceed the evolving requirements outlined in the **new EU GMP Annex 1**.

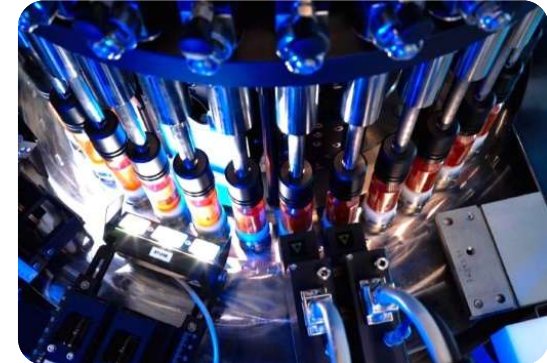


**High Voltage Leak Detection in Liquid**

HV principle based on the measurement of **electrical conductivity of sealed containers** using a high voltage electric field.



**High Voltage Leak Detection in Pierced Needle Shield**



**Head Space Gas Analyzer in Freeze-dried (HGA)**

The system can discern **oxygen-free** (good) containers from the ones **contaminated by oxygen**.



## Knapp in practice: comparison of inspection results of the samples with $mPoD \geq 70\%$

for individual samples  
aPoD < mPoD is acceptable

Particle Type	mPoD	aPoD	Particle Type	mPoD	aPoD	Particle Type	mPoD	aPoD
250 SS	72%	50%	150 G	72%	88%	150 P	90%	100%
300 SS	80%	74%	200 G	78%	94%	150 P	82%	98%
300 SS	88%	90%	200 G	80%	100%	200 P	86%	100%
500 SS	98%	100%	250 G	88%	100%	200 P	84%	100%
500 SS	100%	100%	250 G	88%	98%	250 P	94%	100%
700 SS	100%	100%	300 G	90%	100%	300 P	100%	100%
700 SS	100%	100%	300 G	86%	100%	500 P	100%	100%
700 WF	76%	80%	500 G	96%	100%	700 P	100%	100%
1000 WF	90%	88%	500 G	98%	100%	700 DF	86%	90%
1000 WF	88%	92%	700 G	100%	100%	1000 DF	84%	98%
2000 WF	96%	100%	700 G	100%	100%	1000 DF	90%	96%
2000 WF	94%	100%				2000 DF	88%	100%
						2000 DF	90%	100%

Legend:  
SS = Stainless Steel  
G = Glass  
P = Plunger  
WF = White Fiber  
DF = Dark Fiber

Average manual PoD (mRZE) = 89.8%  
Average automated PoD (aRZE) = 95.4%  
aRZE  $\geq$  mRZE

- Detection rates for **each particle** type can be compared for **informational purposes only**
- Manual **grey zone detection** rates for each particle type may also be compared for informational purposes
- **Monitor and document false reject rate** for acceptable container in good zone detection



FROM MANUAL TO AUTOMATED

## Knapp in AVI: guided procedure



All Brevetti CEA machines are supplied with the Knapp Test Program.

It allows for calculating the efficiency in an automatic way and printing out a detailed report of the test itself.

The printouts include the container numbers, the mPoD and aPoD tables, and a graphical distribution of both.

List of the Knapp Test created in the interface; here you can create a new Knapp Test or open an old one.

The screenshot displays the Brevetti CEA AVI interface. At the top, it shows the product 'Product 50ml \_ 20mm D40(V.1: In progress)' and the batch 'Batch Evaluation Tests'. The sub-batch is 'Sub Batch KT\_50ml\_20MM\_D40\_Bottom Light'. The date and time are '14:34:17 06-04-2017'. The main section is titled 'Testing - Summary'. It contains a table with the following data:

Knapp Test name	KT_50ml_20MM_D40_Bottom Light
Product	Product 50ml _ 20mm D40(V.1: In progress)
Creation date	03-04-2017 10:55:19
User	Brevetti

Below the table, there is a 'Containers number' field set to '250'. To the right, there are two columns of data for 'Runs A' and 'Runs B':

Runs A	10	Runs B	10
RZE A	99.39 %	RZE B	97.31 %
RAG A	0.55 %	RAG B	8.95 %
Eff. A vs B	81.55 %	Eff. B vs A	89.69 %

At the bottom, there are buttons for 'New Knapp Test', 'Open Knapp Test', 'Accept Knapp Test', 'Delete Knapp Test', 'Current KT report', and 'Selected KT report'. The interface also includes a sidebar with 'Current KT' and 'Graph' buttons, and a bottom navigation bar with 'Home', 'Alarms', 'Live', 'Parameters', 'AVI', 'PBS', 'Events', and 'User' buttons.



FROM MANUAL TO AUTOMATED

## Knapp in AVI: Knapp result table

Enter the FQAs data from manual inspection and then view and print out all the information displayed.

FQBs are automatically loaded from the AVI if the Knapp test mode is available.

The software calculates the relevant metric as from EU/USP and graph the results in a histogram

The screenshot displays the Brevetti cea software interface for the 'Testing - Detail' section. The top header shows the product 'Product 50ml \_ 20mm D40(V.1: In progress)' and the sub-batch 'Sub Batch KT\_50ml\_20MM\_D40\_Bottom Light'. The main data table is titled 'Knapp Test name' and contains the following information:

Knapp Test name	Product	Creation date	User	Runs A	Runs B	Containers #	RZE A	RZE B	RAG A	RAG B	Efficiency A vs B	Efficiency B vs A
KT_50ml_20MM_D40_Bottom Light	Product 50ml _ 20mm D40(V.1: In progress)	03-04-2017 10:55:19	Brevetti	10	10	250	99.39 %	97.31 %	0.55 %	8.95 %	81.55 %	89.69 %

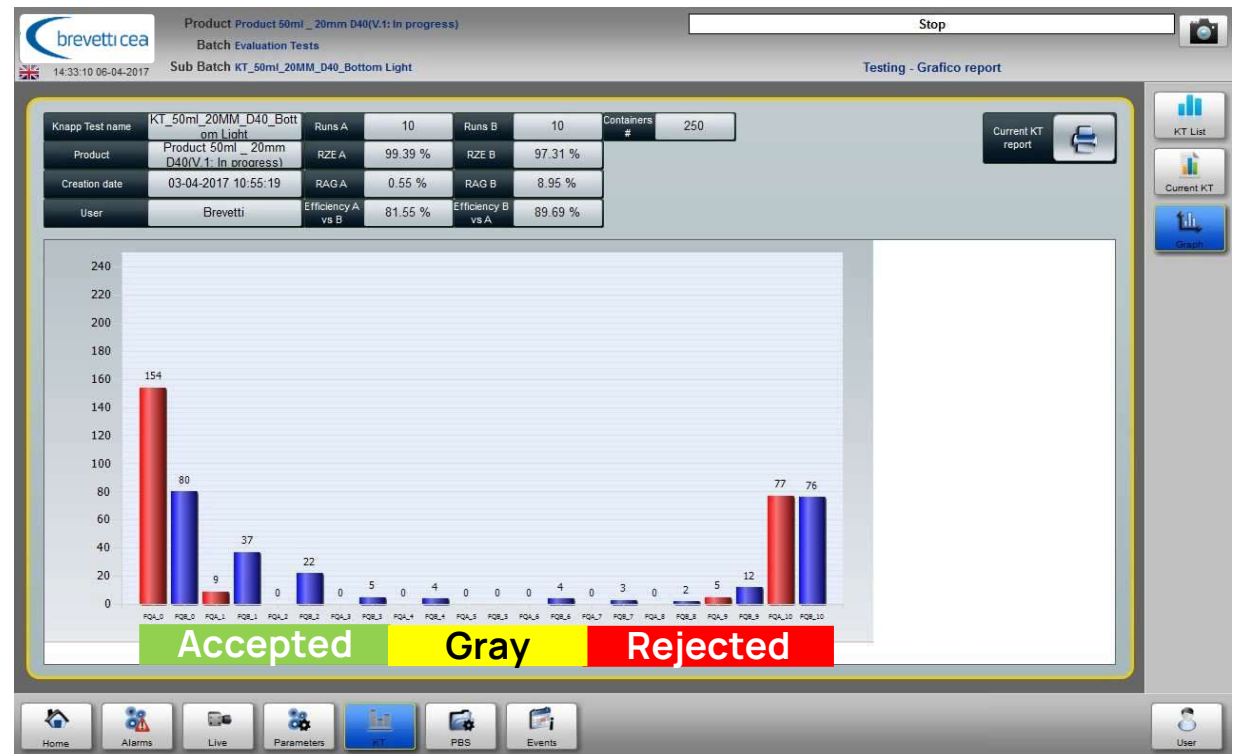
Below the table, there are controls for 'Add containers' (0) and 'Remove containers' (0). The main data table is a large table with columns: #, Comment, Val A, Val B, QF A, and QF B. It contains 26 rows of data. The bottom of the interface features a navigation bar with icons for Home, Alarms, Live, Parameters, KT, PBS, Events, and a User profile icon.



FROM MANUAL TO AUTOMATED

## Knapp visualization by histogram

Binning	FQ
0	$0 \div 0.9$
1	$1 \div 1.9$
2	$2 \div 2.9$
3	$3 \div 3.9$
4	$4 \div 4.9$
5	$5 \div 5.9$
6	$6 \div 6.9$
7	$7 \div 7.9$
8	$8 \div 8.9$
9	$9 \div 9.9$
10	10





## Knapp additional metric

For each inspection system, the efficiency of rejection in the Reject Zone (RZE) is calculated to evaluate inspection quality, while, for economic considerations regarding false rejects, the average rejection probability in the Accepted and Grey Zone (RAG) is calculated for each system.

***RZE is the average rejection probability in the Reject Zone ( $PoD \geq 7$ ) in %***

Possible values are in the range 70% (all samples having FQA = 7) and 100% (FQA = 10 for all samples).

The bigger the value of **RZE** the higher is the repeatability of the inspection system in the Reject Zone

***RAG is the average reject probability in the Accepted + Grey Zone ( $PoD < 7$ ) in %***

A low value of RAG means that the repeatability of the system is good and false rejects is low.



FROM MANUAL TO AUTOMATED

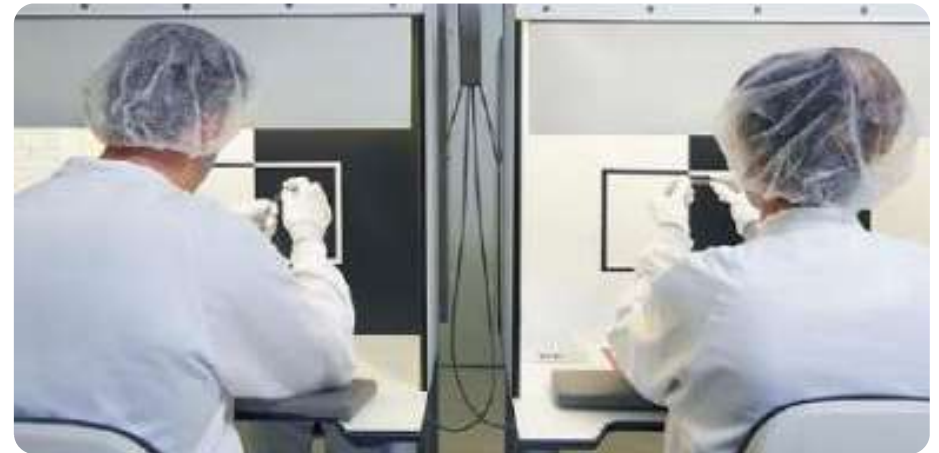
# How many Knapp test run needed?

## Question:

**How many inspections runs are necessary** and appropriate to demonstrate that the machine can perform equal to or better than humans?



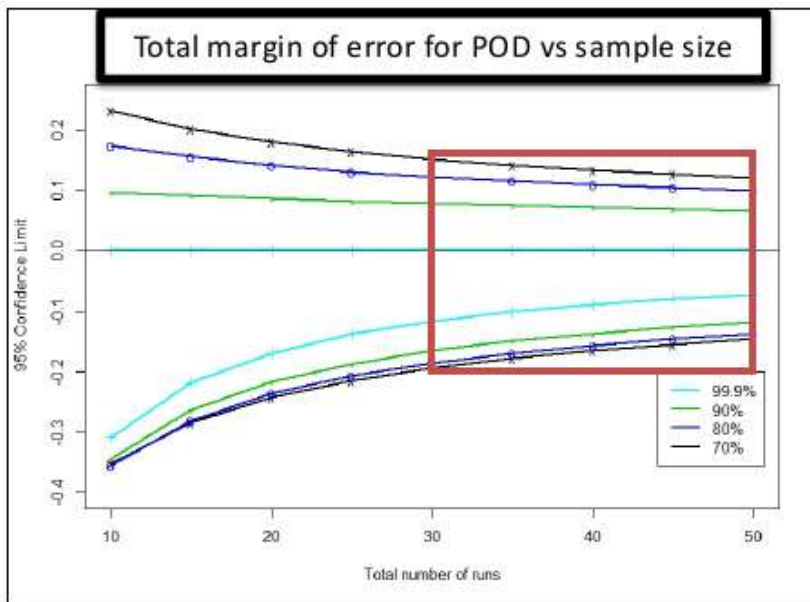
IV





## How many Knapp test run needed?

$$Error \sim Z * \sqrt{\frac{p(1 - P)}{n}}$$



### USP<1790> Ch.7.4

“Secure probabilistic data for particulate standards can be achieved with **30 – 50 inspections** of each container.”

Main factor of influence for **upper margin** of error:  
**Probability of detection**

*The lower the probability of detection for the defect, higher the chances for overestimating the probability of detection*

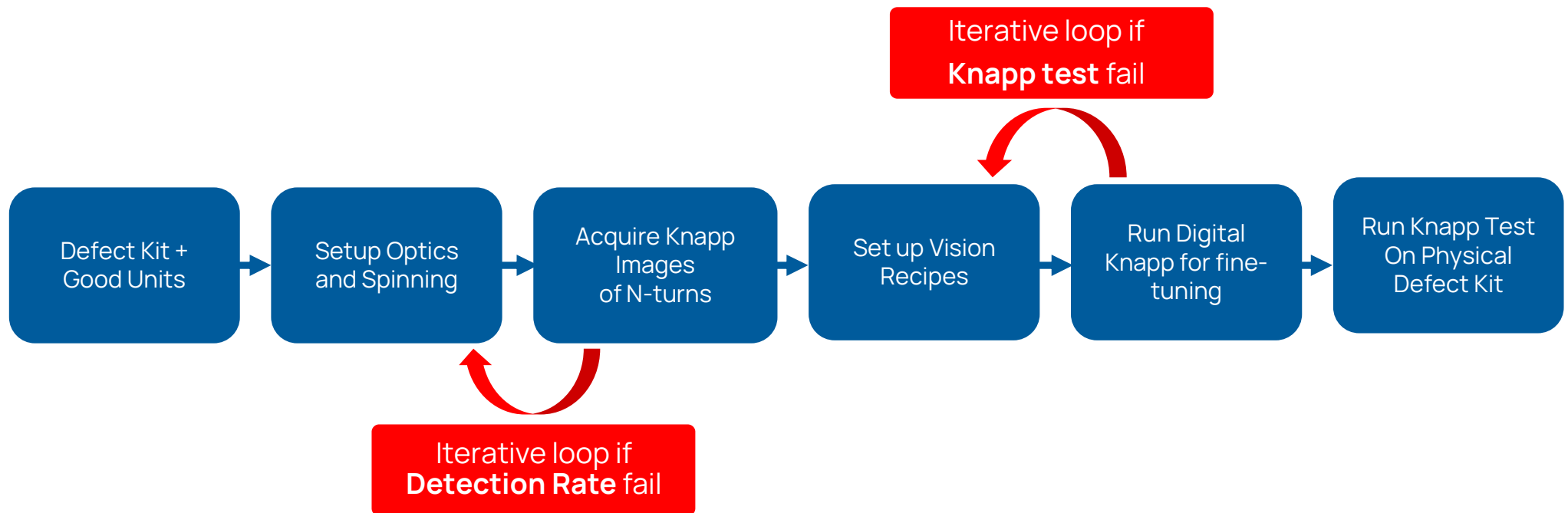
Main factor of influence for **lower margin** of error: **Number of inspection per defect**

*The likelihood of underestimating the probability of detection is significantly reduced with increasing the number of inspection runs*



## How do we fine-tuning the recipe? => DigiTwin Plus

Saving images is a big help, but you can't rely only on it!





FROM MANUAL TO AUTOMATED

## DigiTwin technology shorten the recipe development time

Using the DigiTwin it is possible to load and elaborate all the images of a Knapp Kit and execute the vision controls to determine the Efficiency, RZE and RAG. Repeating the parametrization on the digital images reduces the time to fine-tune the recipe. It is also possible to parallelize the development or do it remotely.



Dedicated Hardware / Software for  
high-framerate real-time acquisition

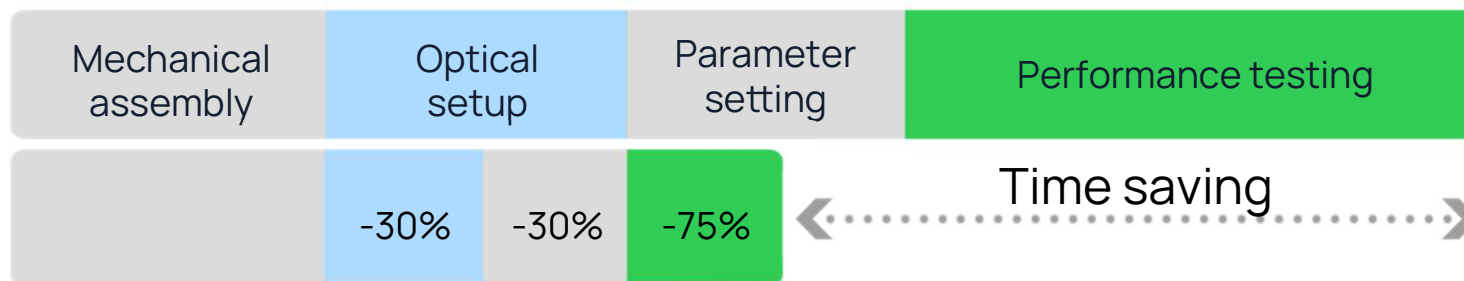
Workstation/Cloud for  
Off-line elaboration



FROM MANUAL TO AUTOMATED

## DigiTwin technology advantages

- Samples manipulation reduced consistently
- Prevention of samples ageing
- Prevention of samples loss and damage
- Setup time: drastically reduced
- Downtime: drastically reduced
- Support: Brevetti expertise directly involved from remote





FROM MANUAL TO AUTOMATED

# PQ Test Set

## Defects

All defects

## Quantity

200+ defect samples (following defect Risk Assessment)

5-10 per critical defect

3-5 per major defect

NLT 1 per minor defect

±1800 good units

NMT 10% level of defects

## Particles

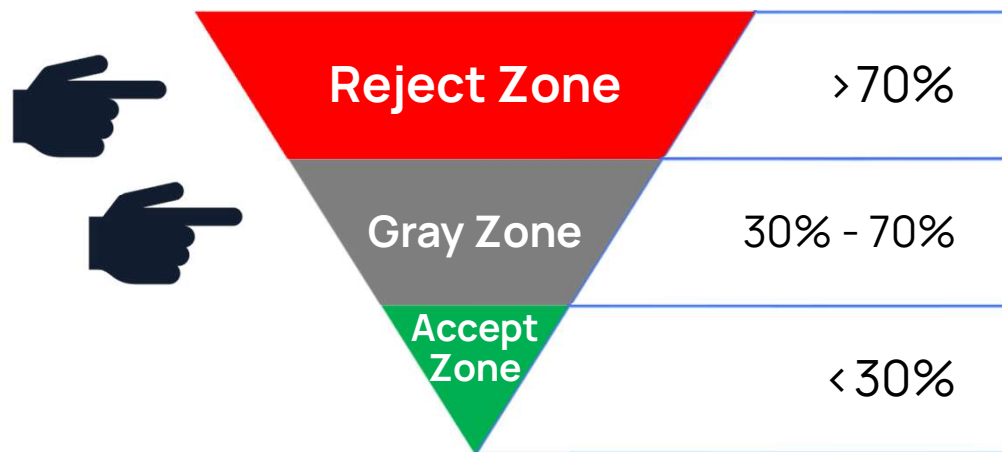
Primarily in the reject zone

Some 50-70% POD to assess limit of reliable detection for comparison

## Source

Production defects preferred

Artificial defects as needed



Type	Critical Defects	Major Defects	Minor Defects
Product	<ul style="list-style-type: none"><li>Product Color Incorrect</li><li>Cake Imperfection</li><li>Incorrect Fill Volume</li><li>Turbidity</li><li>Extrinsic Particle</li></ul>	<ul style="list-style-type: none"><li>Intrinsic Particles</li></ul>	
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