Theory 5
Transition from Manual to automated visual Inspection

- Interpretation of inspection results and validation data
- Considerations on validation program for automated inspection
- Performance measurement
- Maintaining the manual inspection

Theory 5: Transition from Manual to automated visual Inspection Some method comparison

Automated Visual Inspection (AVI)

- ✓ High speed and high capability
- ✓ Highly reproducible
- ✓ Consistent (no fatigue effect)
- ✓ Defects presentation

- ✓ High initial investment
- ✓ Works within strict condition (validated upstream process)
- ✓ Detect “only” preset defects
- ✓ Indiscriminative (i.e.: fiber and cracks are seen the same way)
- ✓ Some uncovered area
- ✓ Higher false reject rate

Semi-Automated Visual Inspection (SAVI)

- ✓ Adaptation
- ✓ Speed
- ✓ Brain
- ✓ Flexible
- ✓ Decision capable

- ✓ Inconsistent (fatigue effect)
- ✓ Not highly reproducible
- ✓ Susceptible to influence
- ✓ Some uncovered area
- ✓ Monotonous repeated work
- ✓ Significant training effort

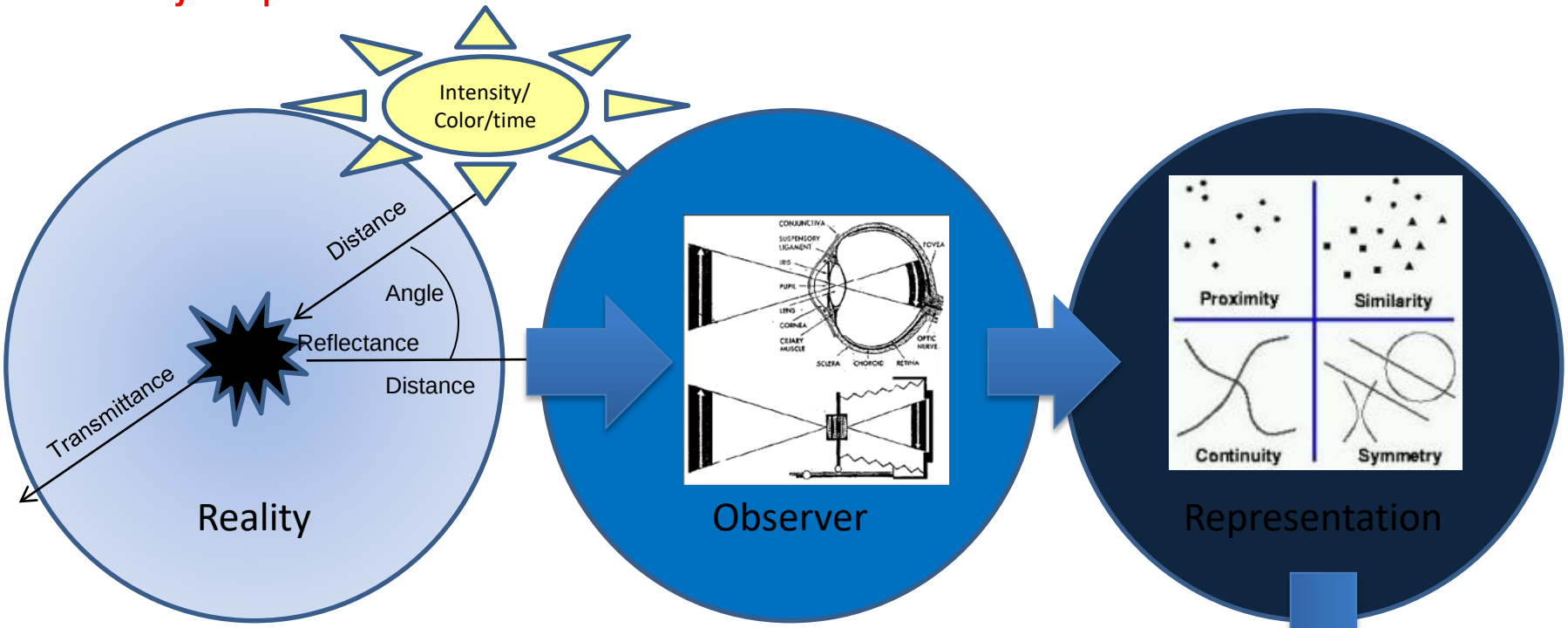
Manual Visual Inspection (MVI)

- ✓ Adaptation
- ✓ Brain
- ✓ Flexible
- ✓ Decision capable
- ✓ Classification of defects

- ✓ Inconsistent (fatigue effect, emotional)
- ✓ Not highly reproducible
- ✓ Susceptible to influence
- ✓ Slow
- ✓ Monotonous repeated work

Theory 5: Transition from Manual to automated visual Inspection
Inspection steps from object presentation to decision

Object presentation



Decision

Theory 5: Transition from Manual to automated visual Inspection
Example of MVI interpretation with color continuity : SNOW can be blue

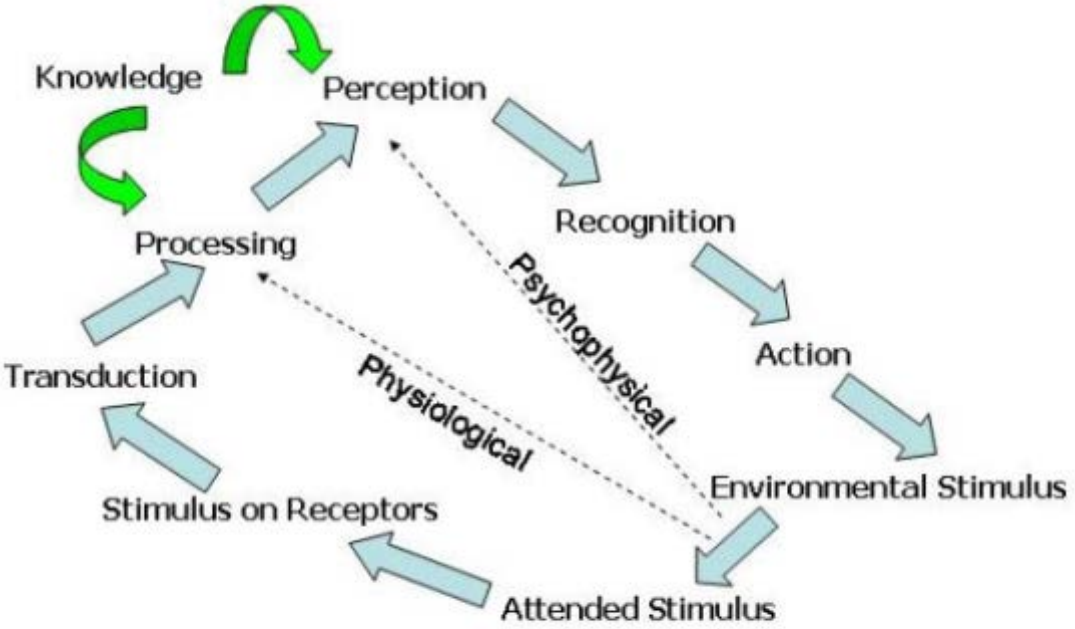
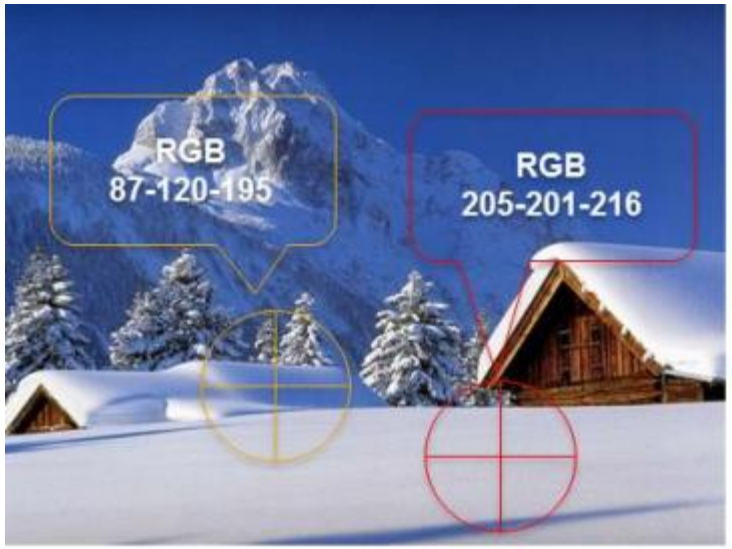
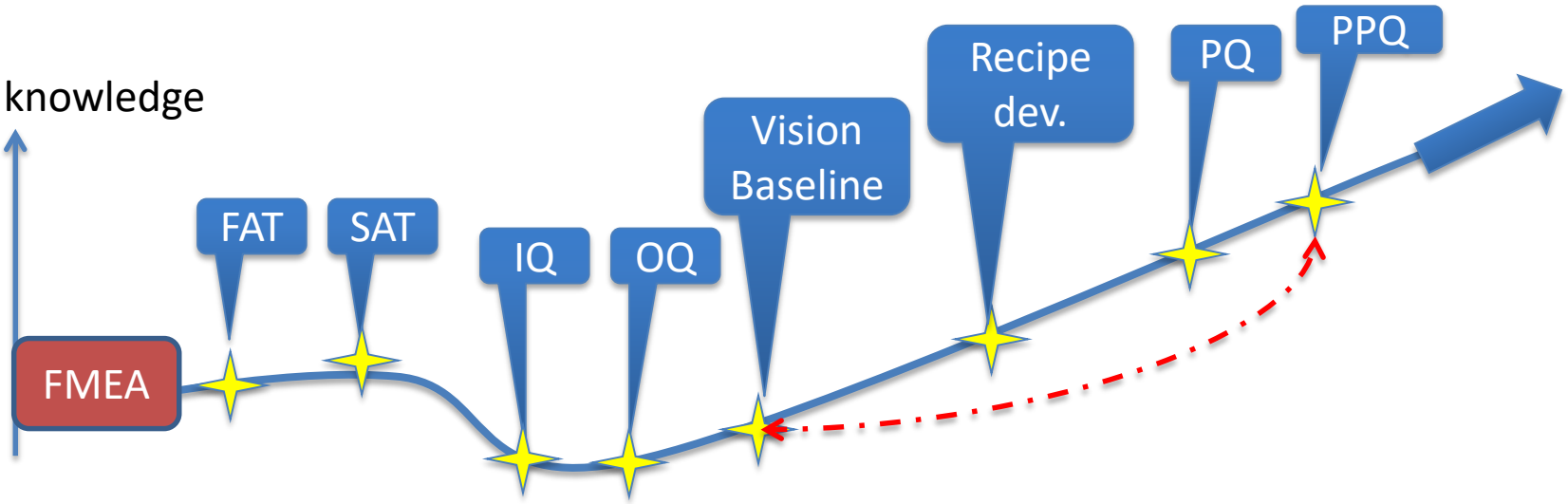


Figure 1.1: The Perceptual Process



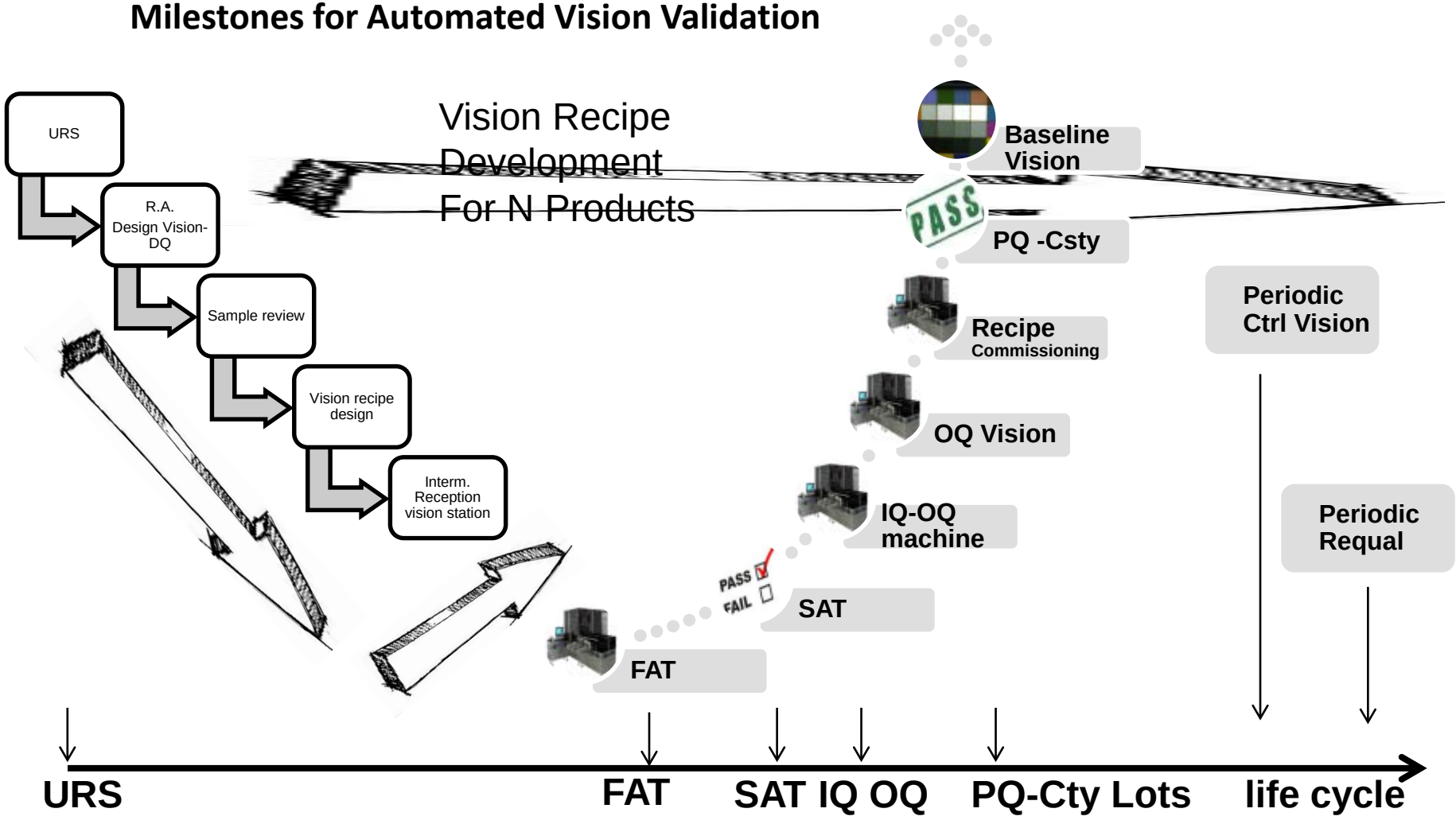
Chromatic continuity:
We see snow even when color changes drastically (RGB)

Theory 5: Transition from Manual to automated visual Inspection Machine qualification : main steps for validation



Critical Parameters for Automated Inspection Process

Milestones for Automated Vision Validation



Theory 5: Transition from Manual to automated visual Inspection Machine qualification : ICH Q9 - Risk base approach FMEA

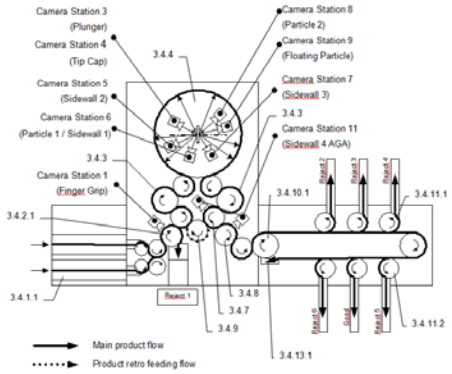
AVI Process - AVI	Description	CQA / CPP

Syringe with System closure, syringe with integer stopper, syringe without crack, syringe free of particle, syringe with correct

Seidenader

- Syringe are transported by the conveyor to the Seidenader
- Syringe are transported by several starwheels. Different cameras placed at different steps take pictures of different parts of the syringes.
- The images are analyzed in order to detect any defective syringe based on the defined defects.
- The syringes detected as defective are directed either to ejected syringes or rejected syringes.

Syringes detected as accepted move through a conveyor to the color code labeler.



Description:

Seidenader is the equipment used for automatic visual inspection in order to detect any SQIPP defect on syringe like particles, cracks, filling volume, closure system and stopper.
The equipment detects and removes defective units with an acceptable rate and sustainable false-ejection/rejection rate.
It is composed of :

- A transport system (frame, conveyors, wheels, tray etc.)
- A vision system (lights, mirrors, cameras, SVIM module etc.)
- A process control system (PLC, HMI, network architecture etc.)

For the Seidenader:

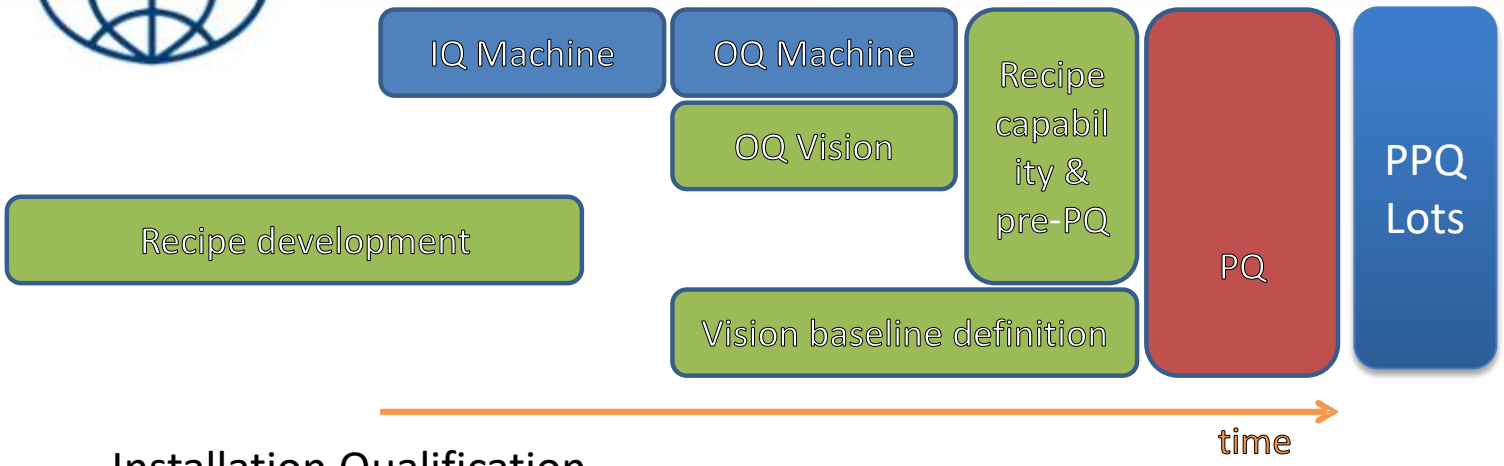
- CPP : See list below
- CQA: Syringe with System closure, syringe with integer stopper, syringe without crack, syringe free of particle, syringe with correct volume, product´s potency.

CPP	Control System	CQA
Refeed transport mode	Stress free transport validation with a refeed rate	Syringe without crack
Synchronization Electrical phase = Mechnical phase	Alignment too	Syringe with System closure, Syringe with integer stopper, Syringe without crack, Syringe free of particle, Syringe with correct volume
Rotation profile	Global Document on high rotation specification	
Rotation speed 4000 U/min		Product's potency
Transportation	Stress lree transport validation	Syringe without crack
Recipe tools and	Recipe check before production and PQ	
Mirror xx position		
Camera positions	Position control tool	Syringe with System closure, Syringe with integer stopper, Syringe without crack, Syringe free of particle, Syringe with correct volume
Camera focus		
Luminance Intensity LED (Angle, Distance, Driver output parameter)	Luminance control tool Maintenance job description	
Access Control	Settings with access control	
Time out of refrigeration xx hours	SAP Control	Product´s potency
Filter (Integrity, Presence, Cleanliness, Mounting)	SOP x	Syringe free of particle
Maintenance checking	Maintenance checklist	Syringe without crack

Theory 5: Transition from Manual to automated visual Inspection Machine qualification : ICH Q9 – Example FMEA by block function

al Failure					Current Situation						Situation with appropriate measures			Situation after appropriate measure					Traceability
2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Process step	Potential Failure	Potential failure effect	Potential failure cause	Impact on CQA (xxx	Current control measure	S	O	D	R P N	Appreciation	CPP Attribution xxx	Recommended preventive actions	Responsible	S	O	D	R P N	Appreciation	Reference / Parameter /SOP
erial – Product																			
xx	**Material**	If the syringe has not the same structure -> recipe will not analyze correctly -> High false ejection (example: flange variability)	Variability on the material design	No	Supplier notification management (Change control) and yearly business review	2	3	3	**18**	⚠	N/A	N/A	N/A	2	3	3	**18**	⚠	N/A
xx	**Product**	Change behavior of mobile particles or air bubbles -> missed particles.	Product viscosity do not fit the specification	S4	AQL	3	1	3	**9**	✓	**Rotation profile**	N/A	N/A	3	1	3	**9**	✓	N/A
xx	**Product**	Luminance and rotation impact are too high -> Illumination energy and Shear stress destruct components inside -> Strength of product decreased.	Product stability do not fit the specification	S6	Recipe detection Quality control Fixed parameter in the recipe -> List of Global Document on High Rotation Specification is given for each product.	5	1	1	**5**	✓	**Rotation profile and luminance intensity**	PE done x for xx product, machine and parameter	N/A	5	1	1	**5**	✓	N/A
xx	**Product**	Product not well homogeneous -> False high ejection rate	Sedimentation of the product does not fit the specification (offline production)	no	Tub is slightly turned to let the product been homogenized by operator. Prerotation step in Seidenader before CSI Station	2	2	3	**12**	⚠	N/A	Define the process for offline production in SOP xxxx	N/A	2	1	1	**2**	✓	N/A

Theory 5: Transition from Manual to automated visual Inspection
Machine qualification : main steps and OQ



Installation Qualification

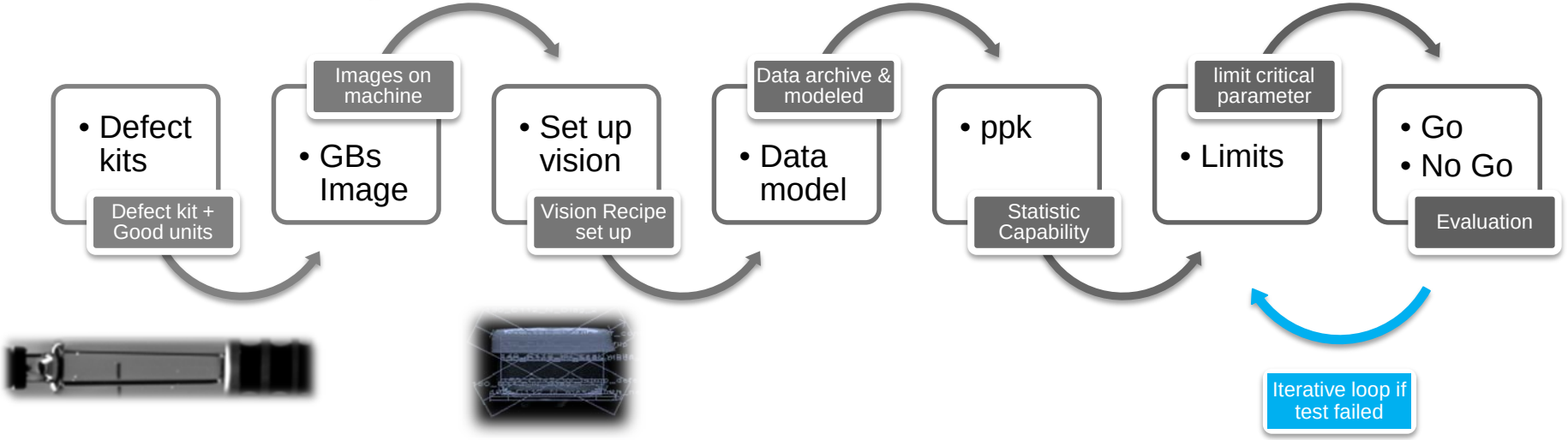
- Documentation verification , component data verification, drawings, system Installation verification , utilities, Software and IT verification

Operational Qualification

- HMI Layout verification
- Alarms verification
- Screen navigation, access verification, security verification
- ER/ES verification (electronic Records and signatures)
- MES (Manufacturing Execution System) server communication
- Backup / Restore and disaster recovery
- Containers handling
- Counters and cells control
- VI rotation at 360° control
- Recipes version verification

3. Automated Vision Development

- **Vision recipe Development Principle**



Key learning: vision development should be done by vision engineers with some statistical background

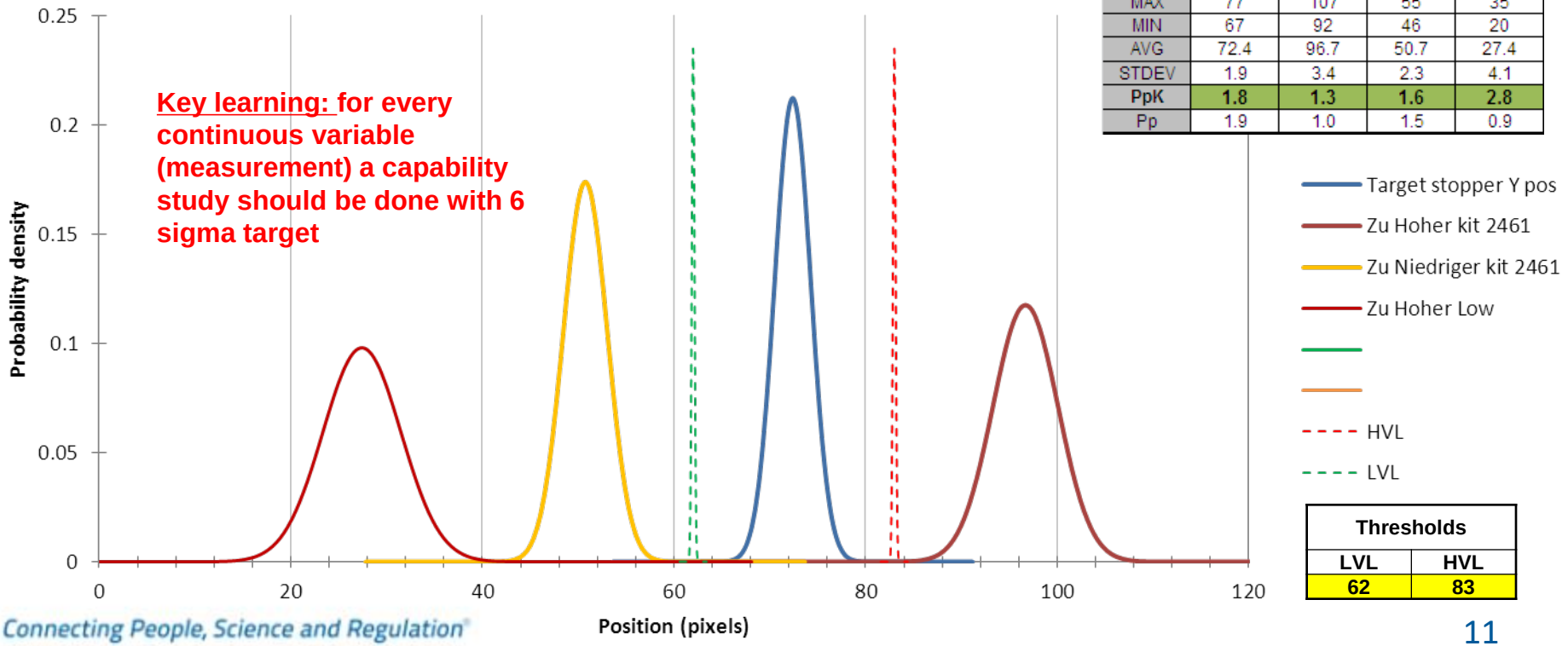
3. Automated Vision Development

- **Example of capability measurement with stopper position**

$$PpK = Min\left[\frac{USL-\mu}{3\sigma};\frac{\mu-LSL}{3\sigma}\right]$$

Normal Distribution

Batch	Target stopper Y pos	Zu Hoher kit 2461	Zu Niedriger kit 2461	Zu Hoher Low
MAX	77	107	55	35
MIN	67	92	46	20
AVG	72.4	96.7	50.7	27.4
STDEV	1.9	3.4	2.3	4.1
PpK	**1.8**	**1.3**	**1.6**	**2.8**
Pp	1.9	1.0	1.5	0.9



Thresholds	
LVL	HVL
62	83

3. Automated Vision Development

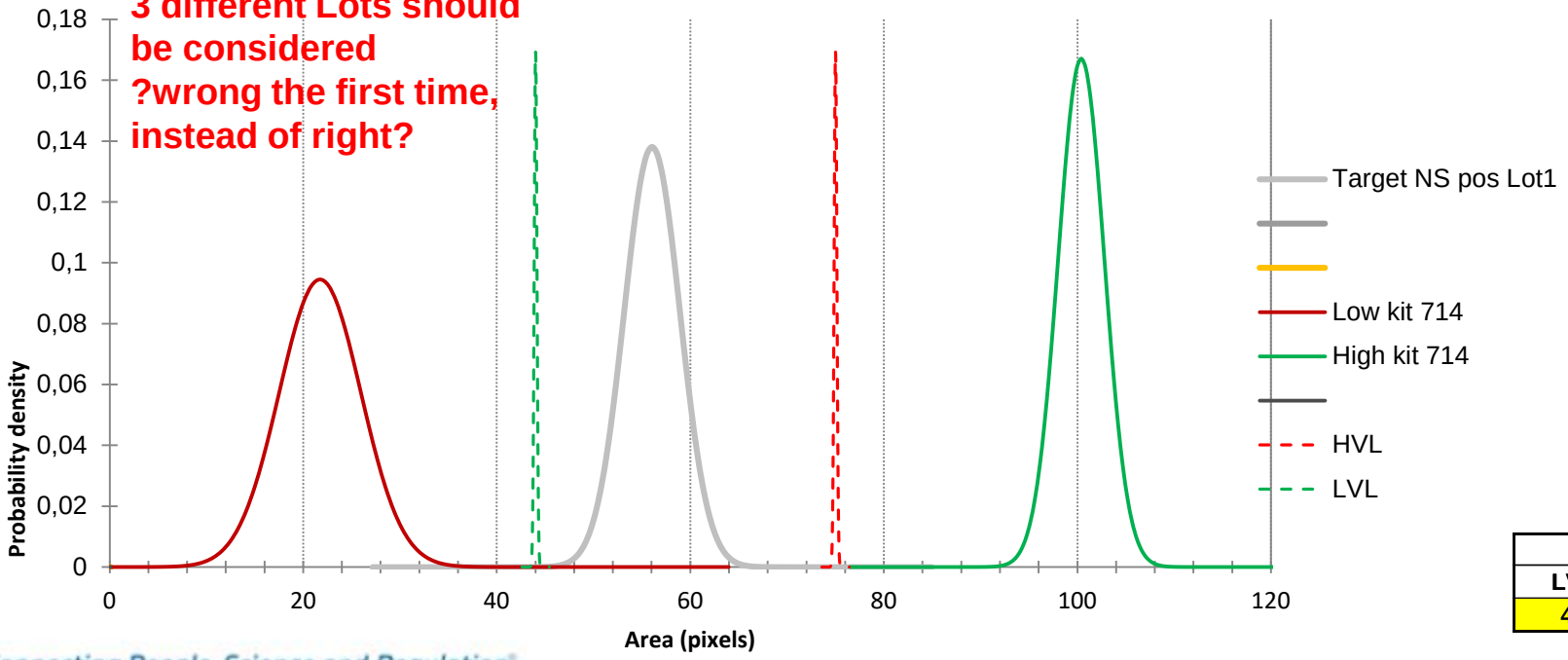
- **Example of capability measurement with Needle Shield position**

$$PpK = Min\left[\frac{USL-\mu}{3\sigma};\frac{\mu-LSL}{3\sigma}\right]$$

Batch	Target NS pos Lot1	Target NS pos Lot2	Target NS pos Lot3	Low kit 714	High kit 714
MAX	63	63	63	29	110
MIN	51	45	52	12	96
AVG	56.1	55.6	56.9	21.7	100.4
STDEV	2.9	3.5	3.0	4.2	2.4
PpK	**1.7**	**1.4**	**1.8**	**1.5**	**3.5**
Pp	1.8	1.6	1.9	1.3	2.4

Key learning: for capability study at least 3 different Lots should be considered ?wrong the first time, instead of right?

Normal Distribution



Thresholds	
LVL	HVL
41	75

Theory 5: Transition from Manual to automated visual Inspection

Julius Knapp : Deterministic ≠ probabilistic

Since the particulate visibility statement in the XIX Revision of the Pharmacopeia (9) is based upon a deterministic human inspection it is inappropriate and should be discarded.

With both manual and automated systems regarded as probabilistic, they can now be similarly evaluated and their demonstrated capability rigorously compared.

longevity estimates. The particular containers rejected in any single inspection cannot be accurately predicted except for two special cases: those containers that are absolutely clean and are never rejected and those containers with gross defects that are rejected in every inspection.

Theory 5: Transition from Manual to automated visual Inspection
Uhlir pioneer work for method comparison: Venn diagram

In terms of the two-dimensional probabilistic inspection model, Uhlir utilized two unrelated one-dimensional probability distributions: manual and machine. In consequence, the differing sensitivities of the two methods can yield the Venn diagram result shown in Figure 1. Here, the manual inspection and the automated device perform in exemplary fashion. Figure 1 indicates, however, that the sets of containers rejected by each method had few containers in common. This comparison suggests that the Uhlir evaluation methodology may not generate the demonstration of equivalence that CGMP's require in the validation of alternative inspection methodologies and devices.

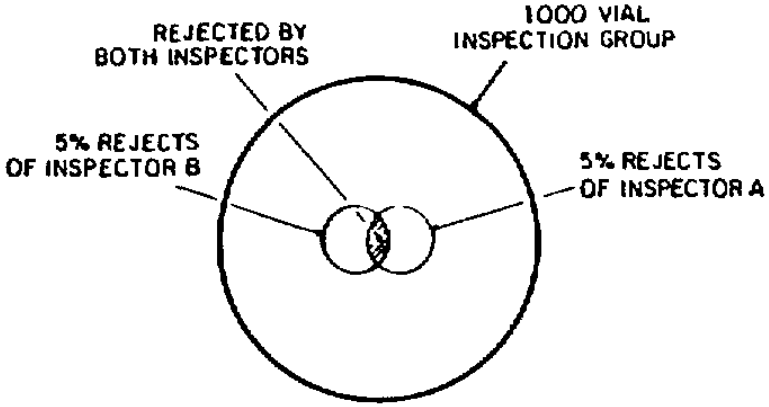


Figure 1—Venn diagram of two inspector particulate inspection demonstrating the expected paradoxial results.

Theory 5: Transition from Manual to automated visual Inspection
Why Correlogram unit by units does not make sense ?

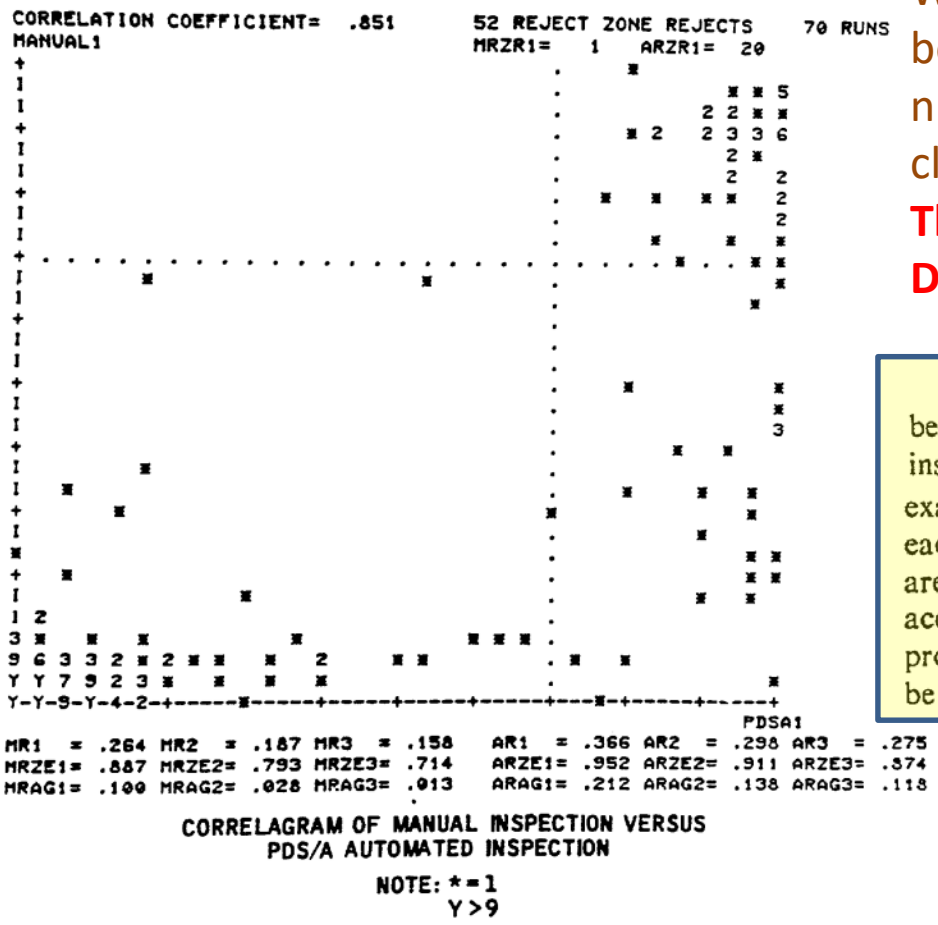


Figure 3—Correlagram comparing the results of 72 manual and 70 PDA/A inspections. A comparison summary of the two inspection methods is included in the computer printout. Of major interest is the fact that only 1 (MRZR1) of the 52 were rejected manually with a probability of 1.0. The PDA/A rejected 20 (ARZR1) of the 52 with a probability of 1.0. The plusses on each axis are the 10% increment points from a rejection probability of 0 to 1.0. The abscissa is for the automated system; the manual system rejection probability is the ordinate. The dotted lines shown are the Reject Zone boundaries for both systems. The * symbols indicate a single container at a point in the plane, a Y indicates a number of containers greater than 9. Values between 2 and 9 are shown directly. The reject rate, R, the Reject Zone Efficiency, RZE, and the undesired reject rate in the Accept and Gray Zones, RAG, are tabulated under the histogram with suffix 1, 2, and 3 to indicate sequential inspection number. The prefix N indicates manual inspection; the A prefix indicates an automatic inspection.

Comment R Veillon

When J Knapp draw a correlogram of between 2 method, each plot is the number of units in each probability class

That is NOT paired comparison per DEFECT

> The capability of one process relative to the other cannot be evaluated until the correlation between the results of both inspections is established. This correlation is based on an examination of the inspection history of each container in each inspection process. Sufficient inspection replications are required to assure statistically reproducible results with acceptable tolerance intervals. Since we are dealing with probabilistically defined quantities, statistical tools must be used. The basic questions of replicability, relative per-

Theory 5: Transition from Manual to automated visual Inspection
Classification of defects by « probability sub group »

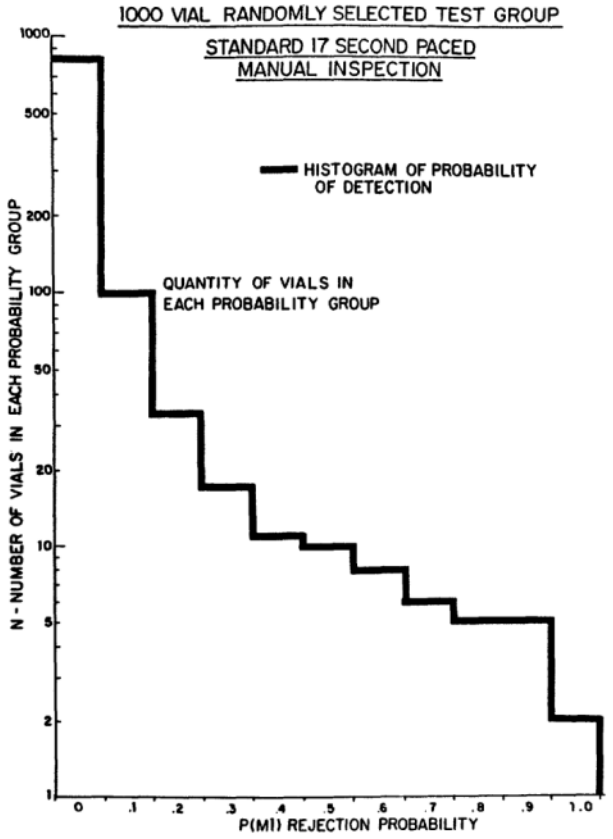


Figure 2—Histogram of probability of detection for a 1000 vial randomly selected test group. The Schering standard 17 second paced manual inspection was employed.

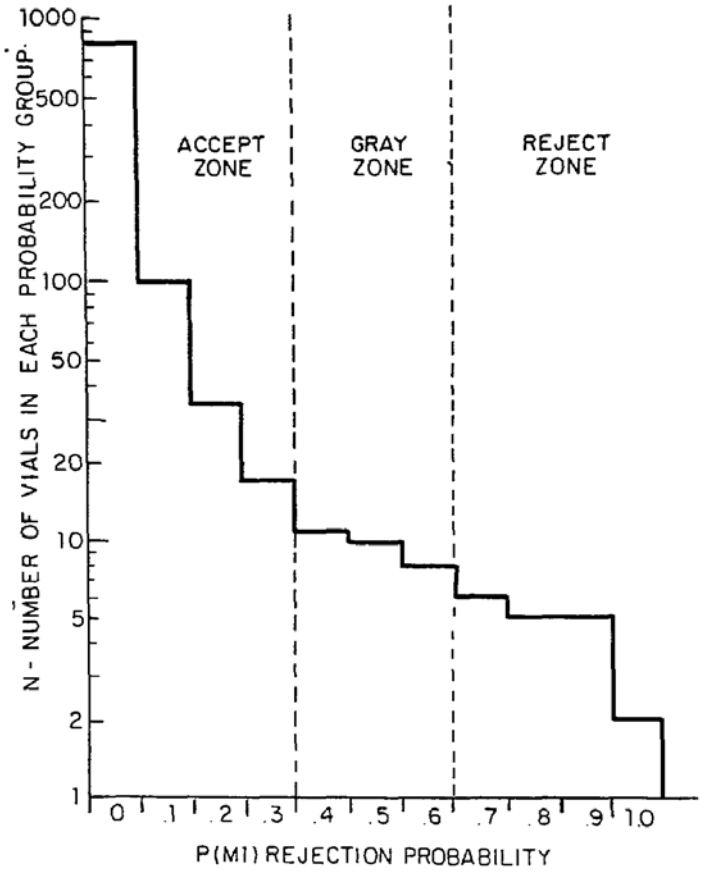


Figure A2—One-dimensional histogram of a normal batch showing the accept Gray and Reject Zones defined by the human based standard inspection.

Theory 5: Transition from Manual to automated visual Inspection Going back to Knapp

. To accomplish this evaluation, two random distributions must be compared.

When the implications of the two dimensional probability plane of Figure A2 are examined it becomes apparent that each entry in either system can be transformed into a distribution in the other system.

TABLE AII. Probabalistic Distribution of Rejection Probabilities for Containers in "Manual" Inspection and "System" I and II

	N(0)	N(.1)	N(.2)	N(.3)	N(.4)	N(.5)	N(.6)	N(.7)	N(.8)	N(.9)	(N1.0)
'MANUAL'	1	1	1	1	1	1	1	1	1	1	1
'SYSTEM' I & II	2.5	1.5	1.5	.5	0	0	0	.5	.5	1.5	2.5

Theory 5: Transition from Manual to automated visual Inspection RZEM terminology

$$RZE(M1) = \frac{RZR(M1)}{RZN} = \frac{14.7}{18} = 81.7\%$$

(Eq. 4)

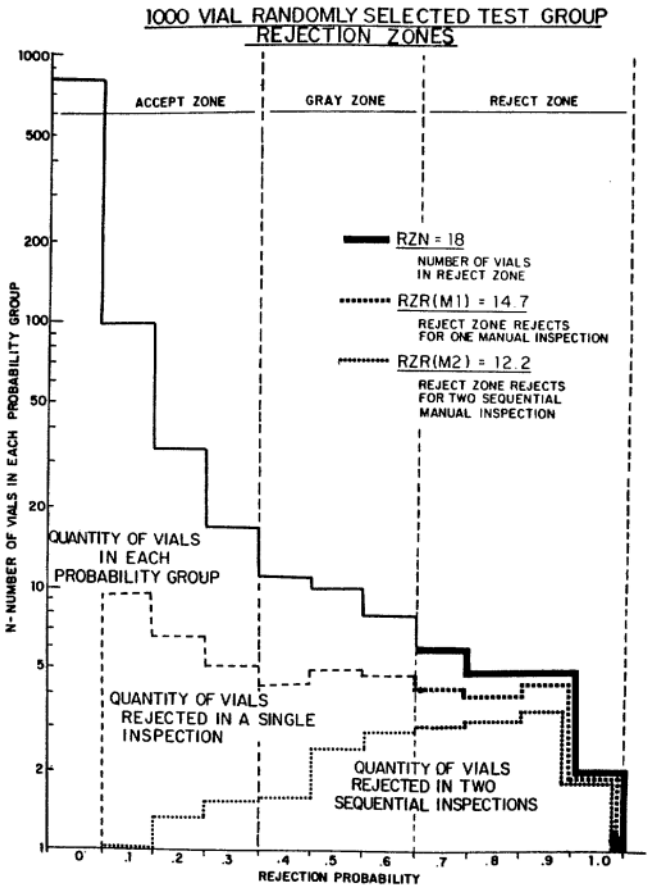
RZE(Mn) = efficiency of rejection in Reject Zone

RZN(Mn) = number of vials identified in the manual Reject Zone

RZR(Mn) = Reject Zone reject quantity as defined in manual inspection

$$RZE(M2) = \frac{RZR(M2)}{RZN} = \frac{12.2}{18} = 67.7\%$$

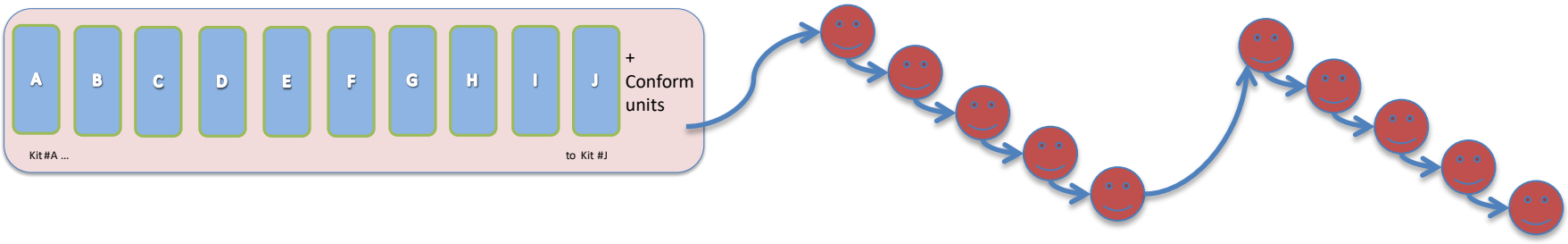
RZE = Reject zone efficiency



Key learning:
Proposal for methology for MVI baseline evaluation

Material and Methods

- [10 kits + good units] = 1 inspection lot order
- No information given to inspectors = routine inspection
- No interactions with inspectors to avoid any interferences
- Changed shift to avoid interactions between inspectors
- 1 inspection every day during 2/3 weeks, one inspector at a time
- Kit verified every day for defect state, replaced broken units to identical
- QF Result compiled for each inspector



3. Material and Methods

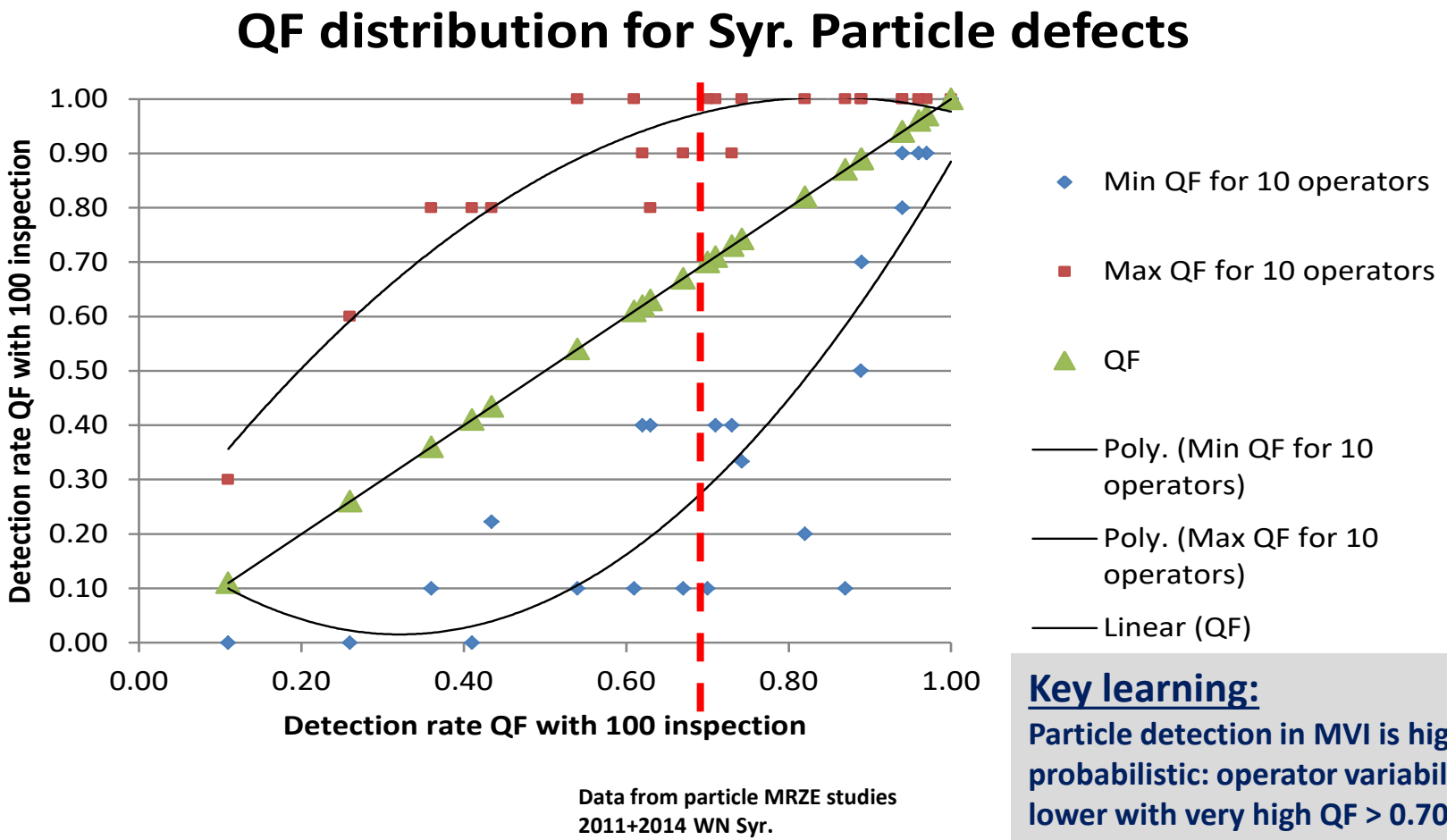
- Data reporting
  QF = number of ejected / number of inspected

	Operators	1	2	3	4	5	6	7	8	9	10	
KIT	DEFECT											
Kit A	Defect #1											QF #1A
Kit A	Defect #...											.....
Kit A	Defect #nn											QF #nn
.....	.....											
Kit J	Defect #1											QF #1J
Kit J	Defect #...											.....
Kit J	Defect #nn											QF #nn

Key learning:
Rigorous Baseline evaluation of MVI performance is key to succeed AVI validations

MRZE

Theory 5: Transition from Manual to automated visual Inspection
QF distribution in MVI



Data from particle MRZE studies 2011+2014 WN Syr.

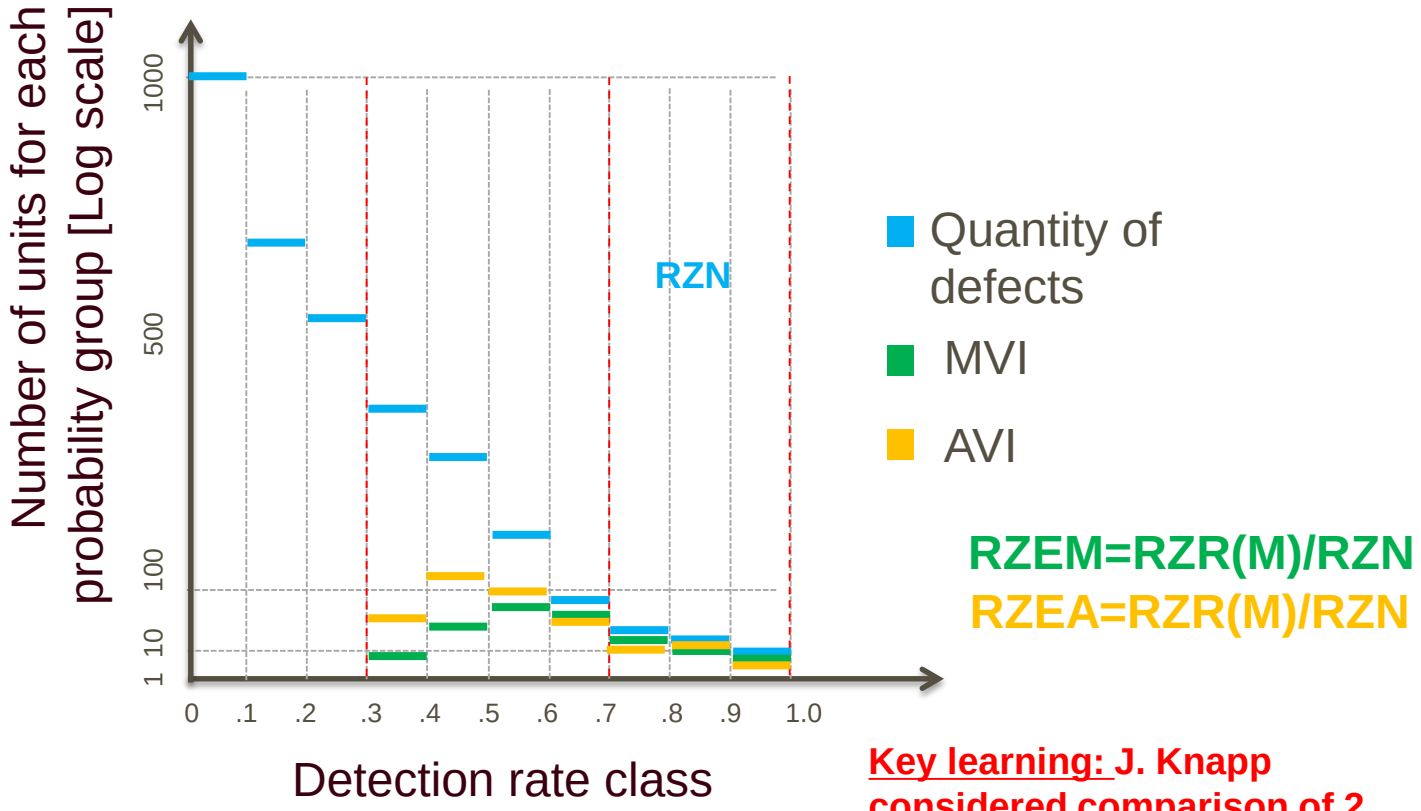
Key learning:

Particle detection in MVI is highly probabilistic: operator variability is lower with very high QF > 0.70
Operator variability higher with lower QF [0.3:0.8]

5. AVI Validation

K&K = comparison of 2 distributions with true defects

– Distributions comparison with K&K approach

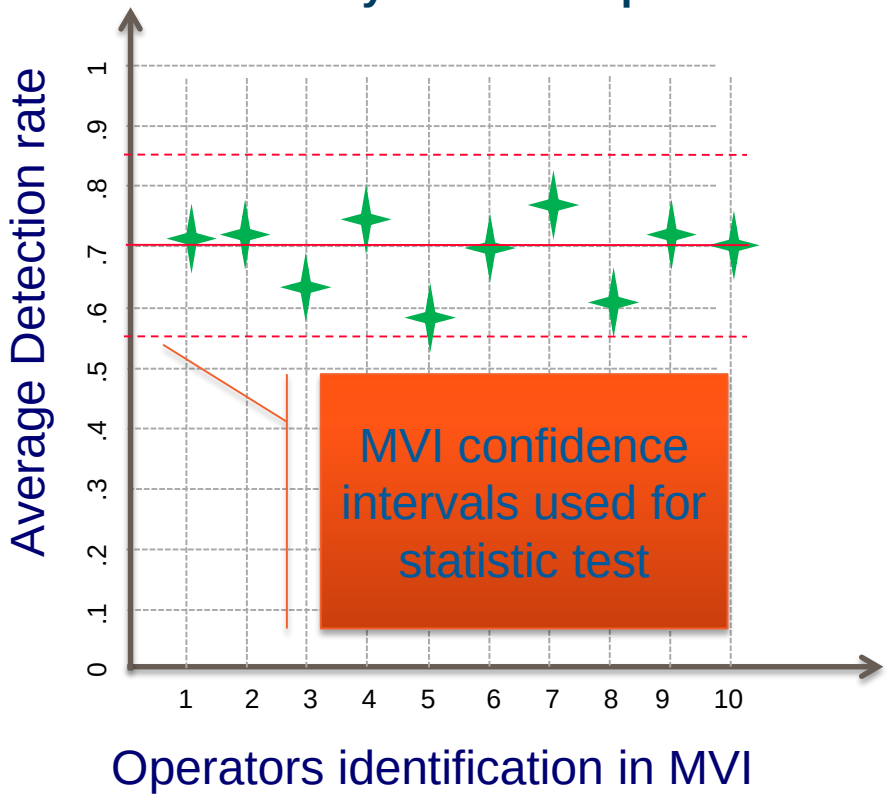


Key learning: J. Knapp considered comparison of 2 distributions on log scale

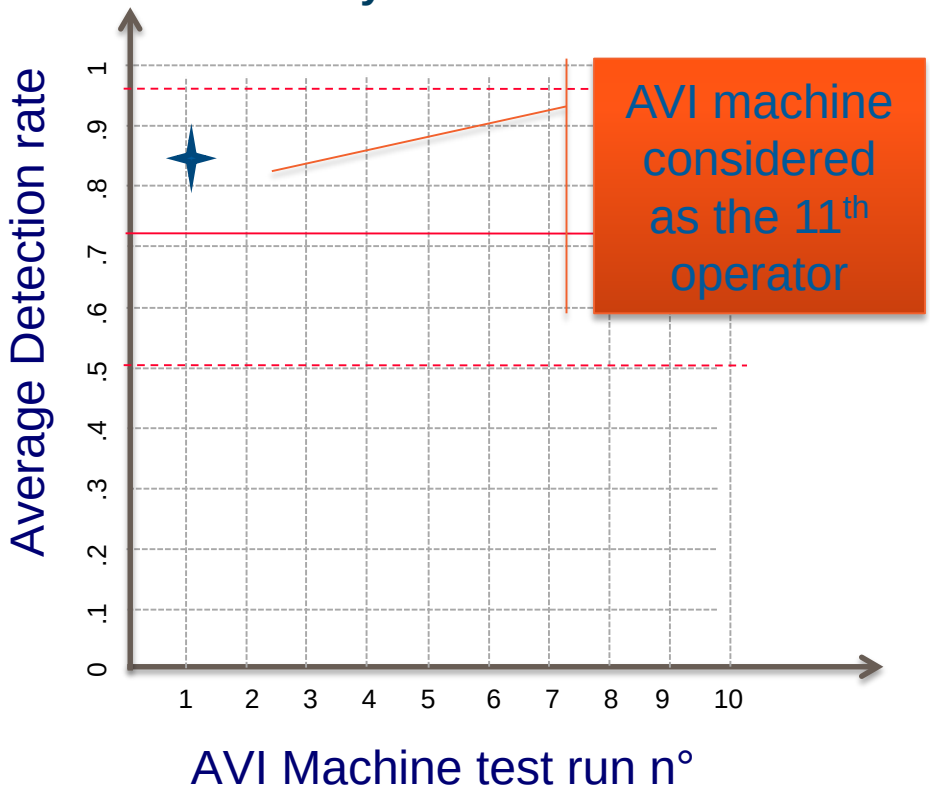
5. AVI Validation

Trend evaluation

MVI Defect detection variability for a defect family over 10 inspectors

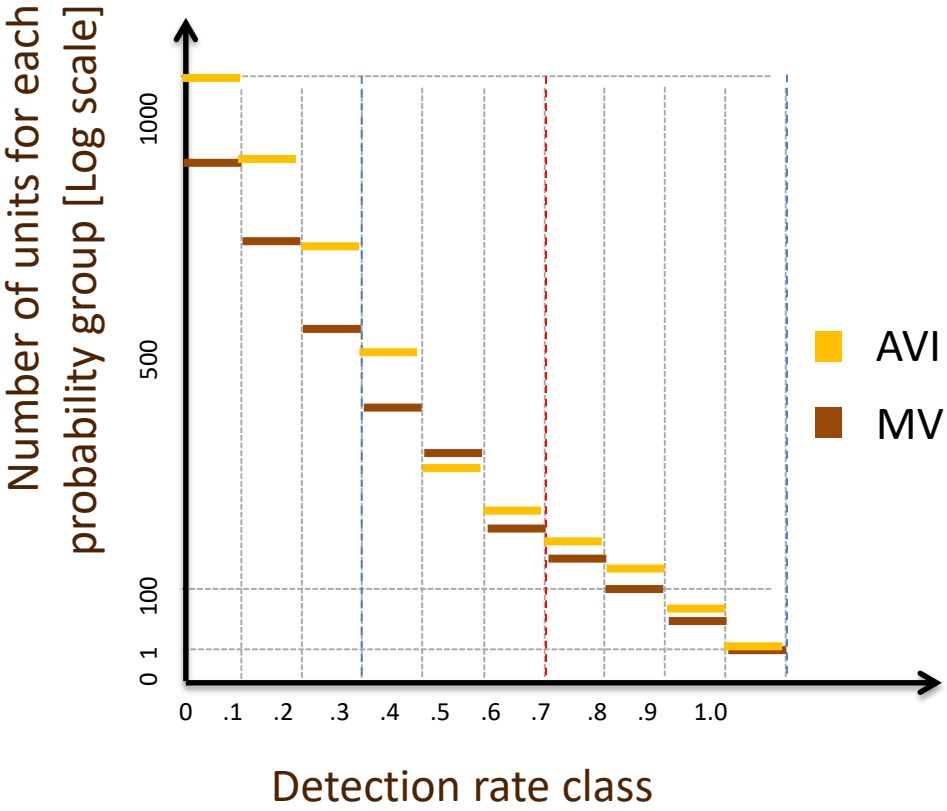


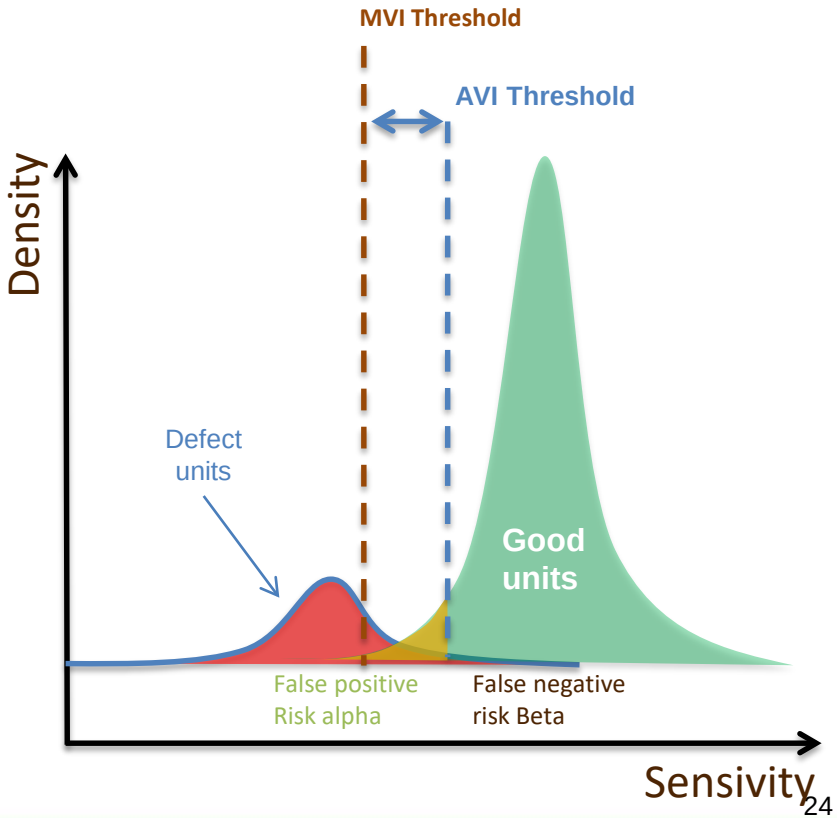
AVI Defect detection variability for a defect family over 10 machine run



Key learning: Machine compared to MVI as the 11th inspector

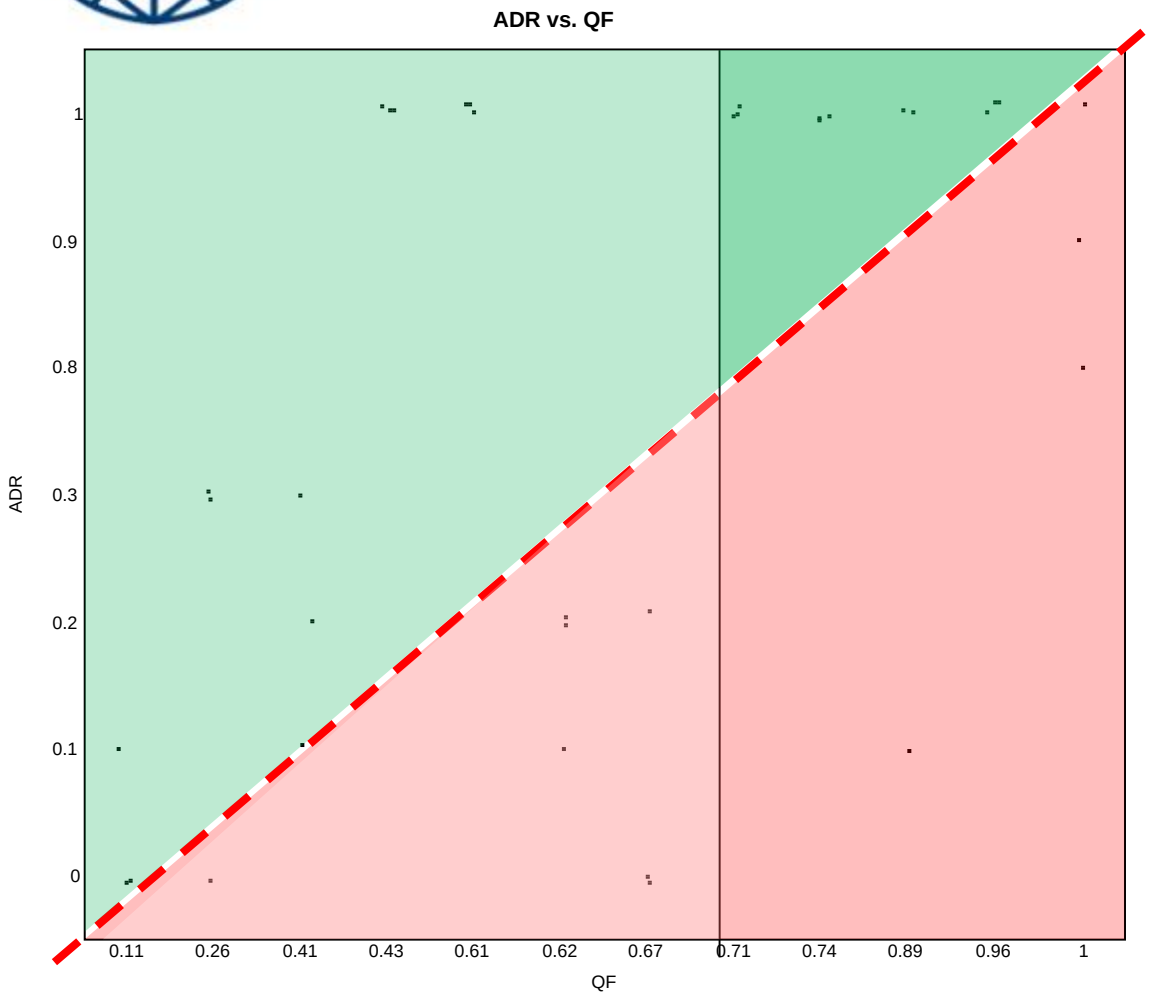
AVI qualification by Knapp





=> Comparison of 2 distributions of number of unit having same detection rate

Theory 5: Transition from Manual to automated visual Inspection
Going deeper with a statistical p value to compare AVI vs MVI



Manual Detection rate

Key learning:

Particle detection in AVI has a higher ADR and is less probabilistic than MVI
Specially in range of QF > 0.70

In range with Lower QF
ADR is higher than MVI but more heterogeneity between particles (floating/precipitating)

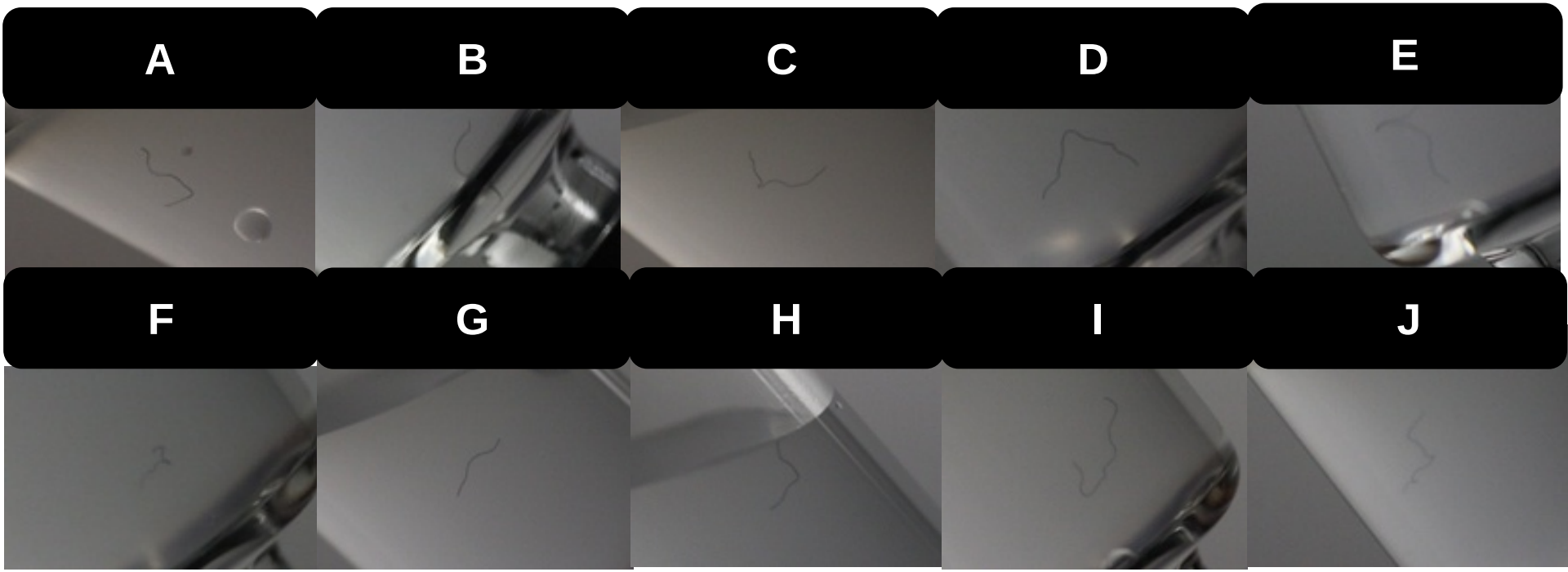
Knapp demonstrated that Validation comparison AVI to MVI should be done in True Defect Zone using "gross defects"

5. AVI Validation

"The availability of an adequate number of vials in each rejection probability set will be seen to be a prerequisite for successful validation experiments." J.Knapp

- **Replicates impact:**

practical implication with a black length precipitating particle

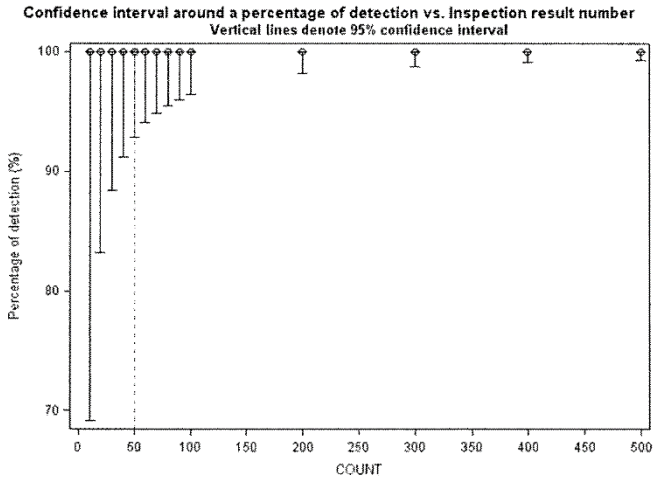


Key learning: At least 3 replicates per defect type should be considered for validation because variability of defect + defect presentation, but also 10 runs x 3 gives 30 inspection. The triple principle.

5. AVI Validation

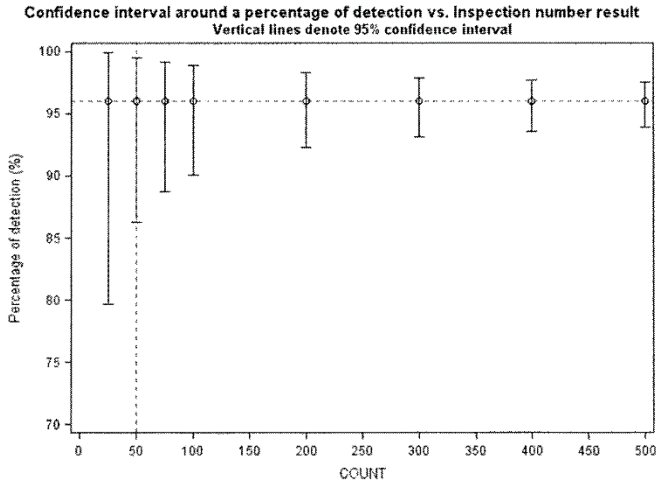
Sample size: practical impact in test run design

With Detection rate limit 100%



With hypothesis of binomial distributions
With 50 runs in validation the confidence interval at 95% is:
[92.9% ; 100%]

With Detection rate limit 96%



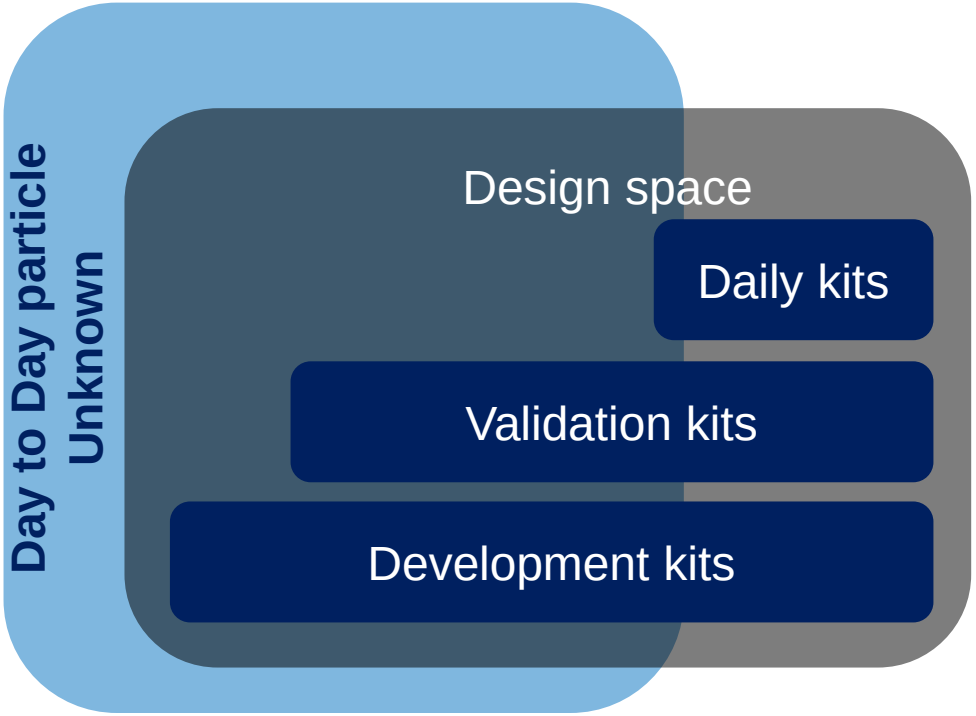
With hypothesis of binomial distributions
With 50 runs in validation the confidence interval at 95% is:
[83.6% ; 99.5%]

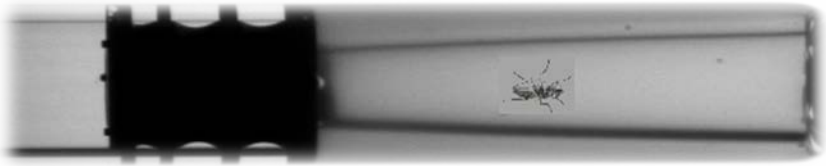
Key learning: even in case of non probabilistic detection rate criterias, the result remains in a Conf. Int. that depends of number of validation runs

Critical Parameters for Automated Inspection Process

- **AVI for Unknown**

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





!example = Fake image!

Key take away:

- In this section you have learnt:

AVI vs MVI	Machine qualification
	Interpretation of inspection results and validation data : Knapp review
	Considerations on validation program for automated inspection
	Performance measurement
	Maintaining the manual inspection