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Part III: Reject Zone Efficiency and the Sampling Inspection

Implementation of Standard Procedures for Visual Inspection: NIST Traceable Automated Contaminating Particle Measurements, using the NIST^2-ParticleVision™ System

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The security of rejecting 'must-reject' particle contaminated containers is the Reject Zone Efficiency, the RZE. Knapp defined the quality of visible particle contaminated containers in three probabilistically bounded zones as shown in Table 3.

ZONE	PROBABALISTIC REJECTABILITY LIMITS, P_R	CONTAINER ACCEPTABILITY
Accept Zone	$0.0 * P_R * 0.30$	FULLY ACEPTABLE
Gray Zone	$0.3 > P_R < 0.7071$	ACCEPTABLE QUALITY CONTAINERS THAT CAN BE SACRIFICED TO ENSURE THE REJECTION OF THE 'MUST-REJECT' REJECT ZONE CONTAINERS
Reject Zone	$0.7071 * P_R * 1.0$	'MUST-REJECT' CONTAMINATION MOST DETECTABLE PARTICLE CONTAMINATED CONTAINER GROUP

TABLE 3 - Probabilistic boundaries with which visible particle contaminated container quality can be defined.

Using these quality boundary limits, RZE is the ratio of 'must-reject' containers rejected in an average inspection to the total number of containers whose rejection probability is equal to or greater than 0.70.

The Knapp-Abramson analysis uses Reject Zone Efficiency, RZE, to evaluate the security obtained in visible particle inspections. This is the ratio of must-reject containers rejected in an average inspection whose rejection probability is equal to or greater than 0.70 to the total number of such containers.

Demonstrating a match to or exceeding the manual standard RZE is the necessary and sufficient condition for validating an alternative inspection method or mechanism.

The false reject rate is a measure of the discrimination of the inspection. It is evaluated as the rate of acceptable containers rejected in an average inspection. It is calculated as the total number of rejects in the Accept and Gray Zones to the number of containers in these Zones. To achieve a correlation in the visible particle inspection data, the experimental conditions used for the inspection must be standardized and accurately replicated. The statistical significance of the data is determined by the number of Reject Zone container inspections and the inspection efficiency of the inspector.

Reject Zone Efficiency	USP Manual vs. USP Manual	USP Manual vs. Commercial Automated
0.70	1818	2206
0.75	1623	1894
0.80	1395	1550
0.85	1104	1169
0.90	779	795
0.95	411	713
0.98	170	332

TABLE 4. - Reject Zone Container Reinspections for 95% C.L. Results

Table 4 shows the Total Reject Zone container inspections for 0.05 significance level results in a validation demonstration with an equal probability of Type 1 and Type 2 errors and a 'don't care region of ±0.021.

When the diameter of the good visual acuity zone is combined with the information that the maximum heavy particle movement time from end of agitation does not exceed 250 milliseconds, the ground rules for multiple container inspection are clear. An individual agitation and inspection is required for each container inspected. When two backgrounds are used, two separate container agitations are required.

Close Focus Snellen Chart Equivalent	Visual Angle Degrees from Fovea	Particle Size in μm for 50% Detection Probability at 20cm	Visual Field Diameter cm, at 20 cm Near-Vision Distance
20/10	0	29.1	0.24
20/20	1.4	58.2	0.49
20/30	2.4	87.3	0.84
20/40	4.0	116.4	1.40
20/50	5.6	145.5	1.96
20/60	7.2	174.6	2.52
20/70	8.8	203.7	3.08
20/80	10.4	232.7	3.64
20/90	12.0	261.8	4.20
20/100	13.6	291.0	4.76

TABLE 5 - Close Focus Visual Capability of the Human Eye as a Function of the Visual Field

Table 5 relates the visual acuity measured at the 20-foot normal distance from the Snellen Chart to the close focus capability of the human eye. The visual acuity for the normal eye for an object 4.76 inches wide is 20/100. Operation within the capability of the human eye requires is essential if an effective inspection is to be obtained.

Any deviation from the inspection performance provided by manual agitation and inspection of single containers for visible contaminating particles in injectable products must be demonstrated to function at least as effectively as this benchmark before use on a USP approved product can begin.

Reject Zone Efficiency	USP Manual vs. USP Manual	USP Manual vs. Commercial Automated
0.7	1818	2206
0.75	1623	1894
0.80	1395	1550
0.85	1104	1169
0.90	779	795
0.95	411	713
0.98	170	332

TABLE 6 - The Quantity of Reject Zone Container Inspections for 95% C.L. Results increases with the complexity of the comparison.

Table 6 shows that the confidence level of the probabilistic results obtained are sensitive to any change in the volume of data analyzed. A 49% reduction of the data volume required for 0.05 Significance level degrades the significance level to 0.20; a 40% increase in that data volume improves the significance level of the results to 0.01.

Significance Level	$t_{\alpha,\beta}$	Container Inspection Ratio I(SL) / I(0.05)	Probability of Results Due to Chance
0.005	2.576	+60%	1/200
0.010	2.326	+40%	1/100
0.025	1.960	+20%	1/40
0.050*	1.645	1.00	1/20
0.100	1.282	-0.22	1/10
0.150	1.04	-0.37	3/20
0.200	0.84	-0.49	1/5
0.400	0.25	-0.85	2/5

* - 0.05 Significance Level Reference

TABLE 7 - Variation of the significance level obtained in a visible particle analysis as a ratio to the amount of data required for 0.05 significance level results with equal probability of a Type I or a Type II error.

Total Reject Zone container inspections for a validation demonstration with an equal probability of Type I and Type II errors and a "don't care" region of +0.05. The number of Reject Zone container inspections increases as the efficiency of the inspection decreases.

In Table 7 the significance of the results obtained in a visible particle inspection as the data volume varies is examined. The ratio of the data volume used is compared to the data volume required for 0.05 significance level results with equal probability of Type 1 and 2 errors.

The Road from Rejected Container Data to Process Improvement

Among those responsible for the production and quality of injectable products a nearly universal myth has been accepted. The myth is that the sampling assay provides a safety net that ensures the quality of injectable batches independently of the previous process steps. The safety net is provided by the use of the sampling procedure implemented with the ISO Tables. Review of the introduction to these Tables finds that, "inspection by attributes is inspection whereby either the unit of production is classified simply as conforming or non-conforming."

Since the 1980 publication of Knapp's PDA paper, which used detection probability as the prime analysis parameter for describing and analyzing the occurrence of visible contaminating particles in injectable products, an international consensus towards this conclusion has appeared. Raw probabilistic visible contaminating particle inspection data is therefore incompatible with accurate use of the ISO Sampling Tables. Any attempt to use such probabilistic data to make a sampling inspection accept/reject decision results in an increased ratio of good batches falsely rejected and the false acceptance of batches with undesirable quality.

Another problem in the current understanding of the use of sampling as a quality control method is the slow, asymptotic approach of the acceptance probability versus reject rate curve toward zero in the sampling inspection for extremely contaminated batches. The "Detroit lemon car" syndrome represents an example of an extreme level of poor quality. This is the chance occurrence of multiple quality failures in a single container.

When these quality control problems are re-visited, clear solutions are visible. The solutions commence with the fact that the general industrial use of the sampling inspection is employed to achieve a nominal level of quality while saving inspection time and labor. This saving is achieved by application of the sampling inspection to non-inspected units. The USP Sampling Inspection uses containers that have been 100% inspected. It will be seen that this difference eliminates the possibility that a batch of injectable product with the "Detroit lemon car" quality could be accepted. The batch reject rate will be seen to be a clear indication of the quality of any accepted batch.

This paper describes a significant change from the present implementation of the sampling procedure. Data with which to enter into the ISO sampling tables is determined from a physical measurement of the contaminating particle followed by interpretation of the accept/reject status of any particle detected in a container of the sampled group. Only those containers with 'must-reject' visible particles, as determined with the Knapp Reject Zone threshold on the calibration curve, are counted as rejects toward the sampling inspection reject limit. This makes possible a clear, accurately repeatable, evaluation of inspection results. This evaluation reduces to near zero the rejection of acceptable batches and increases the probability that undesirable batches will be accepted.

Evaluation of the size of the contaminating particles in the sampled group can be performed with a low power stereo microscope in the intact container or with new technology which automatically detects and sizes contaminating particles with NIST traceable accuracy. In either event a perspective of better quality at lower cost is now in reach.

Shifting Gears

An extension of the Knapp-Abramson 'Working Standard Analysis' from a validation tool to a batch quality assessment tool is required. This extension uses the particle visibility weighted information in the rejected containers. Two steps are required.

1) Correction of RZN to include the number of 'must-reject' containers that are in accepted stock.

2) A scale change from a fraction of the 'must-reject' containers to a fraction of the total number of containers in the batch rejected in an average inspection.

Estimating the number of Reject Zone containers for the full batch, (RZN)B, as the sum of the number of Reject Zone containers identified in the inspection of rejected containers, (RZN)E, and an $\triangle$RZN from containers in accepted stock. Where $\triangle$RZN is the fraction of the reject zone containers the have not been rejected in the 100% inspection.

$$\mathbf{(RZN)B = (RZN)E + (\triangle RZN)} \qquad \text{Equation 1}$$

Estimating $\triangle$RZN from the limit values for c in the acceptance sampling tables.

△RZN << (RZN)E Equation 2

(RZN)E is a useful approximation of the total number of Reject Zone containers in the full batch after a 100% validated inspection.

Changing from a validation tool that evaluates the proportion of 'must-reject' visible particle contaminated containers that have been rejected, the RZE, to a batch quality tool that evaluates the batch proportion of 'must-reject' visible particle contaminated containers that have been rejected, the BRZE, is accomplished with a scale change.

The scale change to convert System Validation To Batch Quality Measurements is addressed in Equation 3 in which RZE is transformed to BRZE, the Batch proportion of Reject Zone containers, those containers with an average rejection probability ≥ 0.7071 rejected.in an average inspection.

$$\mathbf{BRZE} = \frac{\mathbf{R(RZN)}}{\mathbf{(RZN)}} \cdot \frac{\mathbf{(RZN)}}{\mathbf{(N)}} \qquad \text{Equation 3}$$

Where:

N = Number of containers in a batch.

RZN = Number of containers in the batch with rejection probability ≥ 0.7071

R(RZN) = Number of Reject Zone containers Rejected in an average inspection

The transformation of RZA, the number of Reject Zone containers accepted in an average inspection an average inspection with rejection probability ≥ 0.7071 is described in Equation 4.

$$\mathbf{BRZA} = \frac{\mathbf{A(RZN)}}{\mathbf{(RZN)}} \cdot \frac{\mathbf{(RZN)}}{\mathbf{(N)}} \qquad \text{Equation 4}$$

Where:

N = Number of containers in a batch.

RZN = Number of containers in the batch with rejection probability ≥ 0.7071

A (RZN) = Number of Reject Zone containers accepted in an average inspection

The steps toward making visible contaminating particle data in injectable products correlatable and compatible with attribute sampling assay tables have been described.

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