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Part II: Visible Inspection Data 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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Raw Visible Inspection Data and the Sampling Assay

Paragraph 1.4 of the Scope statement of The American National Standard, ANSI/ASQC Z1.4-1993, "SAMPLING PROCEDURES AND TABLES FOR INSPECTION BY ATTRIBUTES" says:

> "Inspection by attributes is inspection whereby either the unit of product is classified simply as conforming or nonconformities in the unit of products is counted, with respect to a given requirement or set of requirements."

There has been general acceptance since 1980 (Knapp, J.Z. and Kushner, H.K. "Implementation and Automation of a Particle Detection System for Parenteral Products". Parenteral Drug Assoc.34, 369,1980**)** that the inspection for visible contaminating particles is probabilistic in nature. This conclusion means that direct use of raw visible particle inspection data is incompatible with the "Attribute Sampling Tables'. The incompatibility results from the probabilistic variation of the randomly sourced raw data. Correct use of the Sampling Tables requires transformation of the raw visible inspection data that is described in the Knapp-Abramson model of the visible particle inspection process. Use of the model transforms the inspection data into a form compatible with the Sampling Tables. Although the data transformation provides access to the Attribute Sampling Tables the limitations of this sampling process must be understood. The first limitation is that the sampling process has been designed to monitor major deviations of product quality. As such it is usable as an independent probabilistic confirmation that the produced batch is of acceptable quality. A more sensitive indicator of the incidence of random contamination is the reject rate recorded in a validated 100% inspection of the batch.

Minimum Change Perspective for Correct Use of the Sampling Inspection Tables

Although the Knapp-Abramson analysis yields statistically replicable results, the determination and use of probability on the factory floor is expensive in time and manpower due to the multiple inspections needed to reach the generally accepted 0.05 confidence. A time and cost effective alternative is possible when a calibration curve relating maximum particle size to the probability that it will be detected is constructed. Work on such a calibration curve has begun. Additional inspection data, recorded in the defined experimental conditions, will add to and improve the accuracy of the data on hand. This concept of a standard USP curve can then be replicated internationally to provide a level playing field for visible particle contamination quality and standards.

The road to this future starts with the construction of a calibration curve with 0.05 Significance Level relating particle size to detection probability. With the present advances in clean room manufacturing that have originated in the manufacture of digital circuitry, containers can now be prepared with a range of single particles whose dimensions are traceable to the National Standards maintained by NIST.

An initial use for this calibration curve can be the evaluation of the containers of an injectable product sampled to assure that the quality of the batch is acceptable under USP limits. Each container in the sampled group is inspected optically with a low power stereo microscope. Any particle detected in a container is sized and the particle size is evaluated with the calibration curve. Only those containers with particles equal to or greater than the particle size at the edge of the Reject Zone are counted as sampling inspection rejects. The use of the calibration curve to determine the Reject Zone status of each contaminating particle has transformed the broad manual accept/reject decision into a sharp, nearly ideal accept/reject decision.

The Sampling Inspection Operating Characteristic Curve

The probability of batch acceptance versus the number or proportion of rejects in a batch is related in an Operating Characteristic curve, the OC. This curve is a plot of the sum of the probability of batch acceptance and the probability of batch rejection versus the incoming batch reject rate. The probability of batch acceptance at a defect occurrence rate is represented by the height of a point from the X-axis. The probability of batch rejection is 1 minus the acceptance probability, the distance from the acceptance probability point to the 100% acceptance level.

The curve in Figure 1 relates the batch reject rate in the accepted batch to the probability of batch Acceptance. A quality level described by an AQL of 1% in the General Inspection Level II plan, with Inspection Efficiency = 100%, a Lot size k, $3200 \leq n \geq 1201$, n = 125, c = 3.

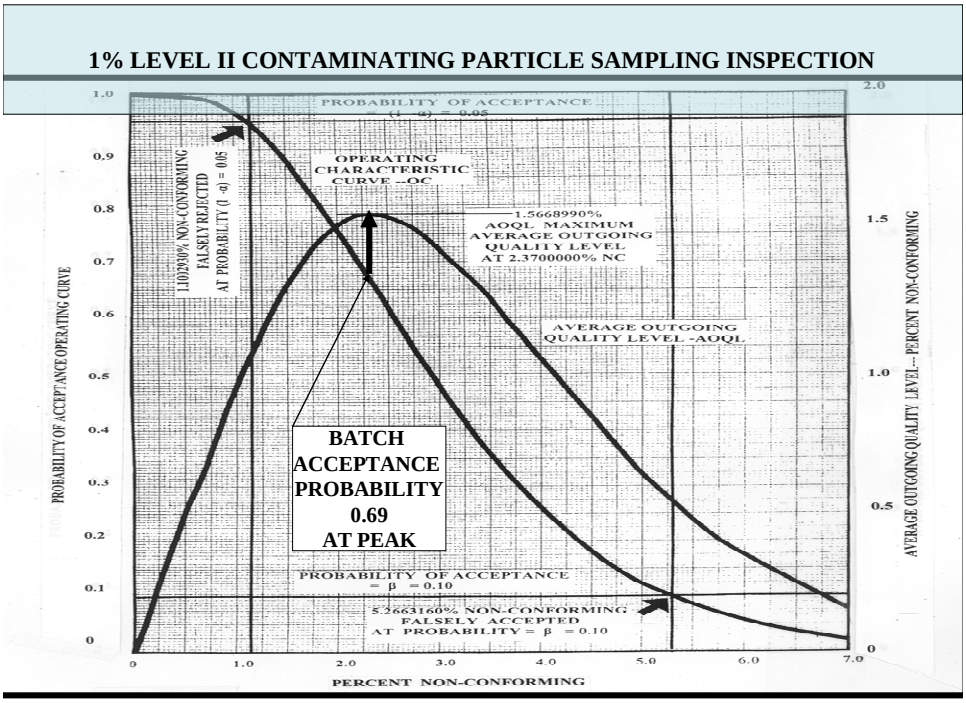

FIGURE 1 - 1% Level II Contaminating Particle Sampling Inspection

The peak of the average outgoing quality curve, the AOQL, is at an incoming reject rate of 1.7915% and an Outgoing reject rate of 1.5539% with a Probability of acceptance of 0.89817% as shown with the arrow from the AOQL peak to the OC Curve. Note that at all batch reject rates except the peak of the AOQ curve, the batch acceptance probability is not simply valued, it occurs at two different batch reject rates.

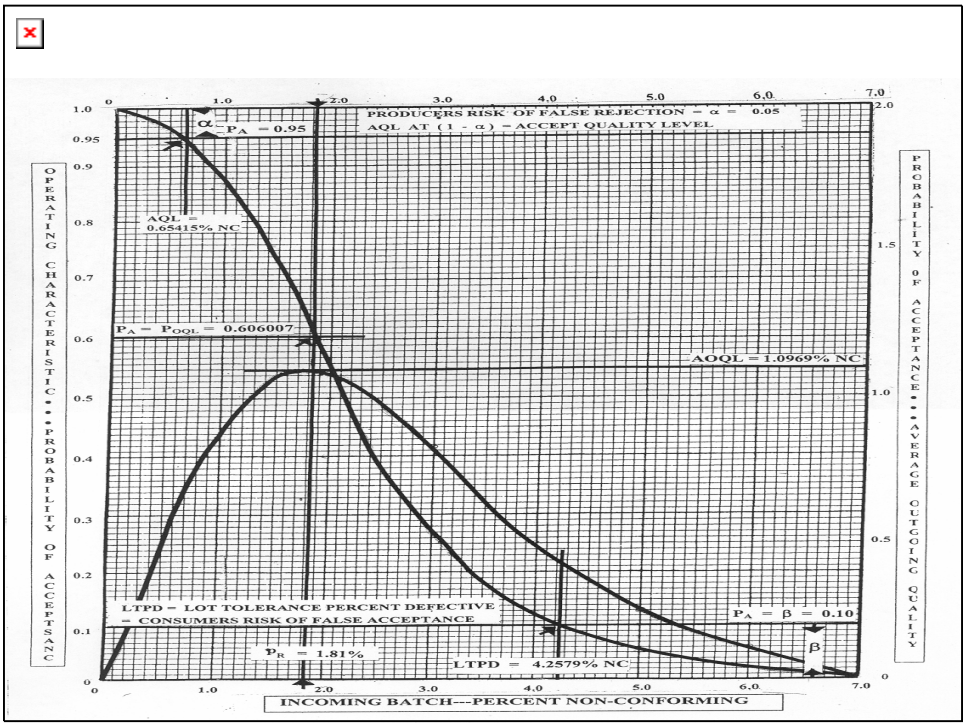

FIGURE 2 - 0.65% Level II Contaminating Particle Sampling Inspection

FDA's GMP Doctrine assisted by successive waves of technology improvement has made possible a present in which a Level II AQL of 0.65% is routinely achievable. Following a tabulation of the parameters of this move, is a graphical summary of the major features of this quality limit at 100% inspection efficiency is shown in FIGURE 2.

Inspection efficiency = 100%. Expected quality for a batch with 0.65% AQL. General inspection level II sampling plan, inspection efficiency = 100%. Lot size K, $3200 \leq N \geq 1201$, n = 125, c = 3. Note that at all batch reject rates except at the peak of the AOQ curve, the batch acceptance probability is not simply valued, it occurs at two different batch reject rates.

The peak of the outgoing quality curve is at an incoming reject rate of 1.82% and an outgoing reject rate of 1.104% with a probability of acceptance of 0.55 rate. When the batch reject rate reaches 1.0%, the acceptance probability is 0.775%.

The USP specifies the use of a Sampling Inspection for injectable products after the 100% inspection in which the batch reject rate has been established. This requirement eliminates the use of the OC estimate of a batch reject rate provided by a statistical model with a slow approach to zero acceptance probability.

Eliminating reliance on the OC to estimate the batch reject rate also eliminates the probability that the Detroit "Lemon Car Quality" can occur in an injectable health product. The Detroit "Lemon Car Quality" is the low probability of the simultaneous occurrence of many quality failures. The next Table, TABLE 2, compares the industrial use of 0.68 and 1.0% Level II AQL.

Inspection Parameter For QA in Mass Production		**100% Reject Zone Efficiency**	
		Sampling 1.0% Level II	**Tables 0.65% Level II**
AQL	95% Batch Acceptance Probability = 5% False Batch Rejects	1.0931	0.6542
IQ	50% Batch Quality	2.9376	2.140
LQL or LTPD	Reject Rate Acceptance Limit	5.3446	4.2579
AOQL	Maximum Average Outgoing Level	1.5539	1.0969

TABLE 2 Attribute Sampling Inspection Nomenclature.

Comparison Of General Inspection Level II Change From 1.0% To 0.65% For 100% Reject Zone Efficiency Inspections. Note: A batch accepted at the IQL (indifferent quality level) is one accepted with a 50% coin toss decision.

Examination of the OQL curve in the following slide shows the possibility of a new, clearer evaluation of USP sampling inspection results. When batch reject rates are limited to the maximum of the OQL curve, the AOQL, sampling inspection assay results can be interpreted with a single valued section of the OQL curve. Even for those batches where the batch reject rate exceeds the AOQL the discomfort that a batch with Detroit "Lemon Car Quality" could be accepted, no longer exists.

PROBABALISTIC VISIBLE PARTICLE INSPECTION DATA

A time tested model for the detection of visible contaminating particles can be satisfied with the use of the Knapp-Abramson probabilistic model of visual inspection. This model has been successfully used since 1980 and is considered a de facto standard.

The seminal publication by Knapp in 1980 brought statistical replicability to the USP Assay for visible contaminating particles. It was the first step away from the philosophical statement that injectable products must be absolutely free of visible contaminating particles to scientifically measurable data. The prime parameter used in the Figure 3 graph is the probability that a visible contaminating particle will be detected.

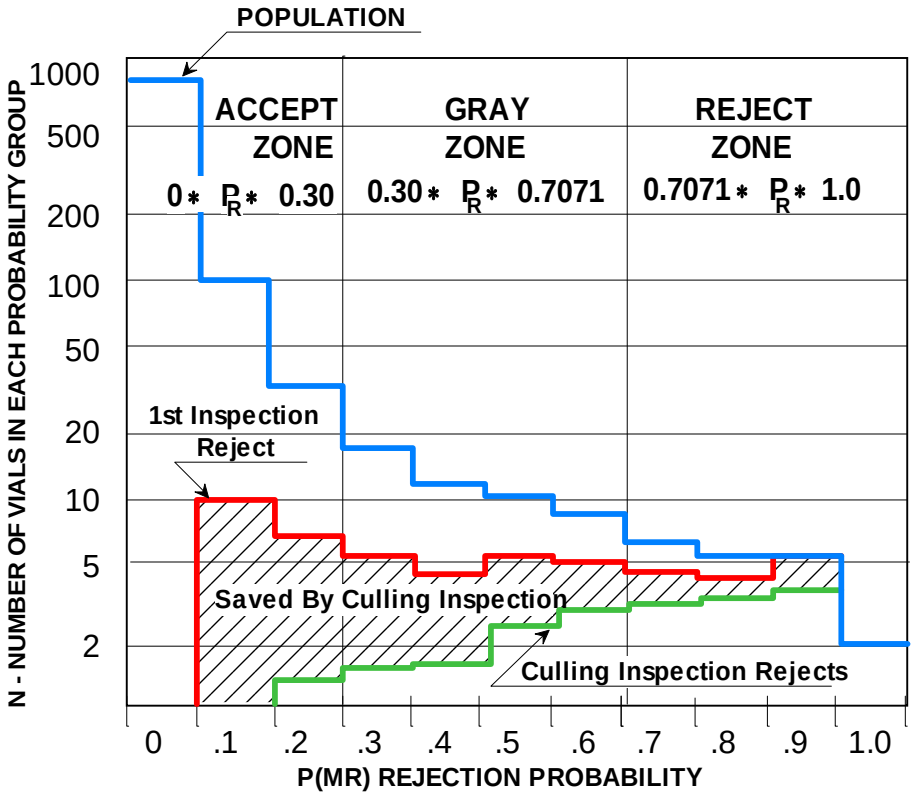

FIGURE 3 - Probabilistic Inspection Data for an Initial Inspection followed by a Culling Inspection.

The heavy line represents the number of containers rejected in 11 probability groupings from 0 to 1.0. The lower adjacent line records the number of containers rejected in the 100% inspection. The bottom-most curve represents the reduced reject rate following the re-inspection of the initial rejects in a culling inspection. An inspection of the functionality of the Culling inspection shows that to achieve validated status, the quality of the inspection must be improved. This has been shown to be both practical and economically rewarding.

The functionality of this inspection model can be compared to the Pflug sterility model[30-32] shown in Figure 4.

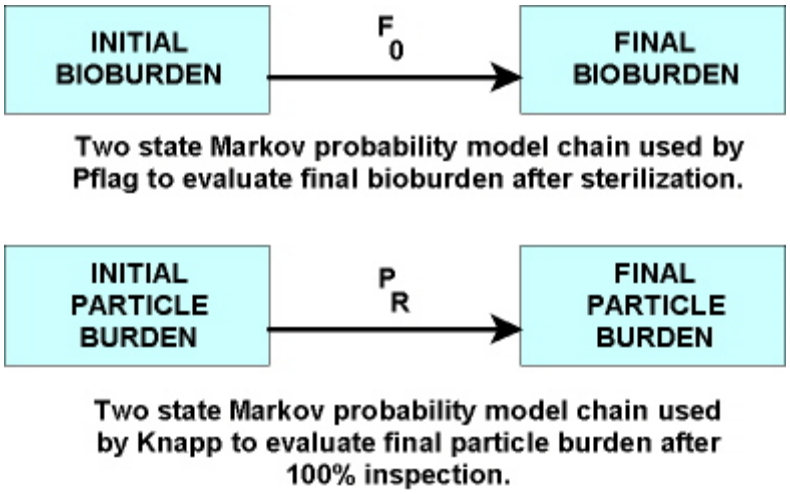

FIGURE 4 - Two State Markov Probability Model Chain Used by Pflugg for Sterility.

The Probabilistic Pflug Model for Sterility has a "1 to 1" Correspondence with the Knapp Probabilistic Model for the incidence of visible contaminating particles in injectable preparations shown in Figure 1.

As in the Pflug sterility analysis, freedom from particles in the out-going batch is determined by the efficacy of the inspection process and is related to the freedom from particles of the incoming batch. Both models describe an imperfect Process.

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