The Validation Consultant®

A Publication of Booth Scientific, Inc.

Vol. 4 No. 3 | Your Link to Regulatory, Quality and Sterilization Compliance | March 1997

QUALITY TOOLS

Valid Sampling Plans: A Case Study

FDA now requires sound rationale for selection

Lynn D. Torbeck, Statistician

The following conversation could be occurring in countless medical device and pharmaceutical quality departments. The FDA now requires sound rationale for the selection of the sampling plans used to support validations and inspection plans as outlined in Subpart O of the new QSR regulation. Here is a summary of the prevailing thinking on sampling plans relative to the FDA requirements and current industry practice.

The door to the Quality Assurance Director's office stood half open. David, the Manager for Quality Control, tapped on the door and put his head through the opening as he said, "Joyce, do you have a minute?"

Looking up, Joyce nodded vaguely. "Sure, come in David, what's up?"

"Well," he continued, "as part of our annual product review, I had Matt read some recent 483s and warning letters other companies have received, and there seems to be a change in the FDA's comments on sampling plans over the last several years."

"Sampling plans!" Joyce straightened up a bit. "What could be changing with sampling plans?"

"Here is one of the FDA's comments." David replied. "Sampling plans are not based on appropriate statistical criteria. For example, the use of Military Standard 105E Special Inspection level S4 and an AQL 0.0 for critical defects does not result in an appropriate and valid sampling plan."

Used in combination, sampling plans provide immediate protection against major failures, while control charts protect against minor sustained problems.

Now Joyce sat upright and said. "Valid? What's valid got to do with sampling plans? And what's wrong with Mil Standard 105E? Everybody in the world uses 105E!"

David continued reading. "'A sampling plan based on an acceptable statistical rationale is required under 21 CFR 820.160. In your response, you propose to use a previously established sampling plan, MIL STD 105E."

Joyce responded. "Statistical rational, statistical criteria? Mil. Standard 105E is sta-

Continued on page 2

In This Issue...

Valid Sampling Plans: A Case Study 1

FDA now requires sound rational for selection.

What Does ASTM Do, Anyway? 6

Test Methods are Defined

Nine Top Trends in cGMP Calibration Compliance 8

See How These Trends Correspond With QSR Requirements

Cleanroom Design Considerations Know Your Needs Before You Start 12

Quality Tools *Continued from page 1*

tistically rational and based on statistical criteria. It was developed by statisticians as far back as 1942. What are they talking about?"

David nodded agreement and said. "That's only two; we have more. How about this one? 'Receiving inspection sampling plans are not always statistically valid, and established AQLs for the inspected attributes are not always based on defect classification (critical vs non critical).' "

Shaking her head, Joyce mumbled, "Statistically valid? I thought if we specified 105E, it would be statistically valid."

David looked up. "Well, yes and no. Companies have always had to be careful about specifying 105E. Some were given 483 citations for saying they would use 105E and then not using the switching rules. It sounds to me that the FDA is just taking that idea and carrying it further."

"As usual," noted Joyce continuing. "Have Matt do a literature search and see if he can find anything that addresses this issue. And David, I want you to review our SOPs for the specific wording we are using for sampling plans."

"Will do." David replied as he went out the door.

Two days later, Joyce, David and Matt are meeting to discuss Matt's findings. Joyce opened the meeting. "Matt what did you find out?"

"A couple of good papers," Matt replied. "The first is from 1966 by Olson and Lee. Here is a quote. 'For practical purposes the need to design a sampling plan has been eliminated by a series of government-sponsored sampling plans, 2 (sic) of which are MIL-STD-105D for attribute single, double, and multiple sampling plans; and MIL STD-414 for variables sampling plans.' These books have gained acceptance throughout most of the United States industry in a manner much like the U.S.P. and N.F. Government contracts for the purchase of pharmaceuticals usually refer to one or both of these books. The obvious advantage of selecting plans from either of these books is communicability and acceptance throughout industry. Hence, there is little or no advantage to specially designed sampling plans."

The Validation Consultant offers analysis and advice on regulatory, quality and sterilization practices and policies impacting the medical device and pharmaceutical industries. Most reports are written by independent industry consultants and provide important updates and specific guidance on accepted methods of meeting regulatory compliance. Opinions and information in each article are those of the author.

Anne F. Booth	Bob Forc	Linda Baker	Kaye Verner
Publisher/Executive Editor	Production Manager	Senior Editor	Office Administrator

The Validation Consultant is published by Booth Scientific, Inc., 421 N. Northwest Highway, Suite 201, Barrington, Illinois 60010. Phone: 847-304-4838; Fax 847-304-6668; E-Mail: 75462.353@compuserve.com. Subscription rate $225 per year. First class postage rate paid at Lake Zurich, Illinois. If you have any questions about your subscription or wish to suggest topics for the *Ask the Consultant* column, please write to or telephone us. *The Validation Consultant* is a registered trademark of Booth Scientific, Inc.

Quality Tools *Continued from page 2*

"That certainly has been the case for more than 30 years." Joyce observed dryly.

Matt continued, "Statisticians have always known that specially designed sampling plans are preferred. But the calculations in 1966 and before were done mostly by hand and required considerable knowledge of sampling theory to assure that it was done correctly. That's why 105 and 414 were so popular. Even though these plans were statistical compromises put together by committees, they were reasonably correct as well as easy to use and implement."

"And universally accepted." commented David.

"So, why now, thirty plus years later, is the FDA questioning the use of these plans?" Asked Joyce.

Matt answered. "Two reasons. First, lax and incorrect implementation."

"Oh, that reminds me," David interrupted. "Remember that new vendor we visited three weeks ago? Well, while we were touring the plant, we discovered that the staff were using sampling terms in an odd way. We heard them say things like, 'We are going to AQL that batch now,' meaning, we presume, that they were going to sample the batch. Or, they would put signs on totes that said 'To be AQL,' meaning to hold for inspection. I remember thinking at the time that they must not know what AQL stands for or they wouldn't use it that way. In fact, it made them sound really ignorant about sampling in general."

"Go on, Matt. What was the second reason?" Joyce asked.

"Well, sampling philosophy is changing," Matt continued. "ANSI Z1.4 states, 'The purpose of this standard is, through the economic and psychological pressure of lot nonacceptance, to induce a supplier to maintain a process average at least as good as the specified AQL ...' Most lots now routinely meet the AQL, but the purpose is to detect a major process failure."

"OK." Joyce responded, "What else did you find?"

Continuing, Matt said, "Military Standard 105E was discontinued by the U.S. government in February 1995. I am not sure just why, but cost may have been a factor as the government tries to downsize. Further, I found that there are moves afoot in some companies to use zero-acceptance sampling plans to force work on improvements when a lot is rejected. The Total Quality Management philosophy of continuous improvement is counter to having some Acceptable Quality Level."

The population size doesn't really matter as long as the population size is at least 10 times greater than the sample size.

"You mean that 105E is not available any more?" Joyce said.

"Right." Matt answered. "Not from the government. It is available from ANSI/ASQC as Z1.4 for 105E and Z1.9 for 414. Z1.4 is compatible with and almost the same as 105E. We can still specify and use these plans if we want to, as long as it is done correctly."

Subpart O—Statistical Techniques

Sec. 820.250 Statistical Techniques

(a) Where appropriate, each manufacturer shall establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics.

(b) Sampling plans, when used, shall be written and based on a valid statistical rationale. Each manufacturer shall establish and maintain procedures to ensure that sampling methods are adequate for their intended use and to ensure that when changes occur the sampling plans are reviewed. These activities shall be documented.

"However, I found a paper by Dr. Wayne Taylor of Baxter Labs in Round Lake, IL, titled 'Acceptance Sampling Update,' published October 1995 in *Medical Device & Diagnostic Industry*. In this paper, the author talks about just this issue we are discussing; what does the FDA mean by 'statistically valid' sampling plans? In essence, it's describing the statistical characteristics of each sampling plan and the reason for using the plan. A plan is described by the sample size, n, AQL, LTPD, the acceptance value, a, and the reject value, r. The AQL or Acceptable Quality Level is the percentage defective level for which there is a high probability (95%) of being accepted and the LTPD, or Lot Tolerance Percent Defective, is the % defective level for which there is a high probability (90%) of being rejected. This can be described for any of the Z1.4 plans, but most companies have gotten careless and don't bother. By the way, Z1.4 is a not a sampling plan, but system of sampling plans that have been adjusted to work together and to work with the switching rules."

"But," Joyce commented, "what about the population size? Mil. Standard 105E was keyed to the population size. We have people recalculating the sample size everyday because the population or batch size is different each time."

"Ah," Matt replied, "that is one of the misconceptions

Continued on page 4

that have grown up around sampling and 105E in particular. The population size doesn't really matter as long as the population size is at least 10 times greater than the sample size. That is, a sample size of 80 out of a population of a 1000 is just as valid as 80 out of 10,000,000, assuming the sample is truly representative of the population, of course."

...the typical AQL for a critical defect is usually a target or specification of 0.065%.

"Then why does 105E change sample size with population size?" Joyce inquired.

Matt continued, "It's the economics of rejecting large batches. It costs more to reject a large lot than a small lot, so the plans were adjusted. The change is not needed from a statistical standpoint."

Joyce looked at David. "What did you find in our documents."

David responded. "We're in fairly good shape, but we could be more explicit about the specific characteristics of each plan. I would like to have Matt come up with a set of recommendations for changes, and then we can revise all of the documents at once. Matt, can you do that in, say, ten days or so?"

"Sure boss, no problem." Matt answered with a grin.

Two weeks later the three meet again to discuss Matt's recommendations. Joyce opened the meeting by saying: "Matt, where are you on these recommendations for our sampling plans?"

Mil. Standard 105E was discontinued by the U.S. government in February 1995.

Matt responded, "Since we last met, I found a book written by Dr. Taylor titled *Guide to Acceptance Sampling* and a paper he gave at an ASQC conference. The book is a good introduction and overview of sampling plans and 105E. Best of all, though, is the included software for doing the calculations required in each of the specific sampling plans. That was always a major hang-up and the reason most companies preferred to use 105E. Now, we can calculate the actual

Table 1:
General Procedure to Define a Sampling Plan

1. Flow-chart the process.
2. Identify critical steps and potential failure points for inspection.
3. Define the objective of the inspection point.
4. Define a product lot, i.e., number of units, time, location, common characteristics.
5. Define the units to be sampled and inspected.
6. Define the characteristics to be measured on the units.
7. Determine if defects per unit or number of defectives are to be measured.
8. Specify the validated measurement method(s) to be used.
9. Describe the physical sampling scheme.
10. Classify the defects according to severity: critical, major and minor.
11. Select the spec-AQL to be larger than the historical defect rate or that found in the validation.
12. Select a plan so the actual AQL, LTPD, sample size, acceptance value and reject value meet the objective. The actual AQL must be larger than the historical defect rate and less than or equal to the spec-AQL.
13. Document and implement the acceptance sampling plan.
14. Decide on the disposition of rejected lots.
15. Document and implement trending of the summary data.

Table 2: Sampling Plan

Category	Characteristics	Spec-AQL	AQL	LTPD	*n*	*a*	*r*
Critical	Cracked	0.065	0.0641	2.84	80	0	1
Major	Inoperative	0.65	0.630	10.5	80	1	2
Minor	Dirty	1.0	1.03	6.52	80	2	3

Continued on page 5

values for the sampling plan characteristics. For example, the typical AQL for a critical defect is usually a target or specification of 0.065%. With a sample of 80, acceptance on zero defectives and rejection on one defective, the actual AQL is 0.0641% and the actual LTPD is 2.84%. We can use this software to recalculate for each plan and give the actual values. In some situations, we can actually get better statistical protection for the same or smaller sample size. This turns out to be a hidden benefit to using the specific plans; they often save money."

"Oh, great," David interrupted. "Now we have another piece of software to validate from scratch."

Matt smiled. "Not so. Would you believe it comes with a validation package and protocol?"

Matt continued, "Based on my readings, I have written a general procedure to define a sampling plan. It's found in table 1. Also, I suggest we put the following statement and table someplace in our documents to specify and justify the statistical characteristics of each sampling plan."

Matt read the proposed paragraph. "Sampling plans are statistically justified by selecting the AQL, LTPD, *n*, *a* and *r* to meet both the scientific and statistical objectives of the plan. This plan has the scientific objective of inspecting for the characteristics given in table 2 and of making decisions on the disposition of each product lot. This plan has three statistical objectives. First, it should reject lots when there is a breakdown of a usually consistent and validated process. Thus, there is a high probability (90%) of rejecting lots that have more defectives than the LTPD. The LTPD has been selected to indicate any substantial change in the process. Second, it should accept lots that meet a predetermined specification for percent defectives. Thus, there is a high probability (95%) of routinely accepting lots that are better than the actual AQL. The specification AQL has been selected to be the % defective that can be reasonably accepted and is based on the type of defect, (critical, major or minor), the consequences of failure, process capability and current industry practice. Third, it should collect data that is plotted (trended) over time to detect small incremental changes in the percent defectives."

"The first two statistical objectives are clear, but what about the third one?" Joyce asked.

Matt replied, "We are spending the time and money to collect the data in the sample; why not use them to monitor the process, as with a control chart and as part of the Annual Product Review? As Taylor pointed out in his article: 'Used in combination, sampling plans provide immediate protection against major failures, while control charts protect against minor sustained problems.'"

"Well Matt, that's a very nice presentation. A little more preparation and I think we will be ready for the next FDA inspection. Thanks to you, Matt, and to you, David. Good job." Joyce concluded.

Lynn Torbeck is an international trainer and consultant specializing in experimental design and statistics for pharmaceutical, biopharmaceutical and medical device research and development, validation, quality control/assurance and production groups. He has 21 years of experience in the pharmaceutical industry including various management positions for G.D. Searle and Co. before opening his own business. Torbeck is a member of PDA, American Statistical Association (ASA), ASQC and is past president of the Chicago Chapter of the ASA. He holds a B.S. and M.S. degree in statistics with a minor in computer science. Contact Torbeck at 7812 Kenneth, Skokie, IL 60076-3506, phone: 847-677-8070/fax: 847-677-9073; E-mail: pharmstat@aol.com.

References

Olson, T. N. and Lee, I (1966). "Application of Statistical Methodology in Quality Control Function of the Pharmaceutical Industry," *Journal of Pharmaceutical Sciences*, January, Vol 55, No. 1, p 1.

Taylor, Wayne A. (1992). *Guide to Acceptance Sampling.* Taylor Enterprises, Inc., 5510 Fairmont Road, Suite A, Libertyville, IL, (847) 367-1032.

Taylor, Wayne A. (1995). "Acceptance Sampling," *Medical Device & Diagnostic Industry*, October 1995, p 92.

ASQC Quality Press, 611 East Wisconsin Ave., P. O. Box 3005, Milwaukee, WI 53201-3005, 1-800-248-1946, http://www.asqc.org.

Taylor, Wayne A. (1996). "Selecting Statistically Valid Sampling Plans," ASQC Quality Congress Transactions, ASQC, Milwaukee, WI. (Submitted to *Quality Engineering* for publication in 1997.) ■