Welcome to “Practical Statistics.”

This feature provides examples of the use of statistics in validation and compliance. We intend to present these concepts in a meaningful way so as to enable their use in daily work situations. Our objective for this column: Useful information.

The 2008 US Food and Drug Administration’s draft process validation guidance recommends multiple specific applications for statistics in the lifecycle approach to process validation. These applications were identified in stage 1 process design, stage 2 process qualification, and stage 3 continued process verification—through the entire product or process lifecycle. FDA recommendations are quite specific for these respective stages, indicating agency focus on statistical methods. The guidance describes several specific details of statistics applications, including design of experiment studies in formulation and process development; statistical metrics in performance qualification; and trending of material, process, and product data in monitoring and maintaining validation. The importance of expertise in statistics is emphasized throughout the guidance.

“Practical Statistics” provides relevant practical examples of using statistics in the various stages of validation. This journal also provides “Statistical Viewpoint,” which addresses more theoretical topics in statistics. The respective contents of “Statistical Viewpoint” and “Practical Statistics” provide readers with theory and practice on topics relevant to validation. Reader understanding of this vital subject in validation should be enhanced through these respective discussions.

The first article in “Practical Statistics” discusses general areas identified in the draft process validation guidance that recommend applications of statistics—an introduction to the future content in “Practical Statistics.” Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Please contact column coordinator Paul Pluta at paul.pluta@comcast.net or journal coordinating editor Susan Haigney at shaigned@advanstar.com with comments, suggestions, or case studies for publication.

KEY POINTS
The following key points are discussed in this article:

• The US Food and Drug Administration’s 2008 draft guidance on process validation provides clear statements on the need for statistical procedures in process validation
• Statistical applications should be used throughout the entire product lifecycle—development through ongoing commercialization
• FDA has clearly redefined validation to include activities taking place over the lifecycle of product and process
• Development efforts should include statistically-designed experiments to determine relationships and interactions between inputs and outputs
• Manufacturers should understand the sources of variation, understand its impact on process and product, and control variation commensurate with the risk. Statistical methods should be used to quantify and monitor variation
• Statistical methods should be used in support of sampling and testing in performance qualification and throughout the process verification stage as appropriate. Sampling plans should reflect risk and demonstrate statistical confidence.

• Validation protocol sampling plans should include sampling points, numbers of samples, sampling frequency, and associated parameters. Sampling in performance qualification (PQ) should be more extensive than is typical during routine commercial production.

• Acceptance criteria should include statistical methods to analyze data.

• Continuing process verification data should include data to evaluate process trends, incoming material, in-process materials, and final products. Data should focus on ongoing control of critical quality attributes.

• Personnel with adequate and appropriate education in statistics should be used for these activities.

• Analytical methods used in validation and throughout the product lifecycle must be validated using appropriate statistical methods.

INTRODUCTION
The US Food and Drug Administration’s 2008 draft guidance on process validation (1) provides clear statements on the need for statistical procedures in process validation. A review of this document provides an understanding of where statistics need to be employed during process validation. These procedures should be incorporated into the validation protocol along with appropriate acceptance criteria. The validation protocol should be used for prospective applications, and a statistician or a quality control worker versed in statistics should be consulted when the protocol is being developed.

Validation is a confirmatory activity. All validation should be approached in this manner—process, cleaning, equipment, analytical, computer, and so on. In manufacturing, validation should not be used to determine, optimize, “fine tune” or other “discovery” parameters for the manufacturing process. Development studies, especially at the pilot level, should provide data for setting good prospective acceptance criteria for processing steps that are confirmed in process validation.

In the following review of the guidance document, reference will be made to line numbers found on the PDF version of the guidance. This PDF may be downloaded from the FDA website. The line numbers indicate the beginning of the section of interest.

For a more extensive discussion of the statistical and quality methods that need to be employed in process validation as specifically identified in the FDA guidance, see Torbeck’s Validation by Design (2).

SCOPE OF GUIDANCE
It is important to know the scope of the document as with all guidance documents. Line 32 of the draft guidance provides the scope, as follows:

“The following categories of drugs are within the scope of this guidance:

• Human drugs
• Veterinary drugs
• Biological and biotechnology products
• Finished products and active pharmaceutical ingredients (API or drug substance)
• The drug constituent of a combination (drug and medical device) product.”

A footnote to this list notes that active pharmaceutical ingredients (APIs) or drug substances do not have their own good manufacturing practice (GMP) but are subject to the GMPs required in the Food, Drug, and Cosmetic Act. API process validation is discussed in the International Conference on Harmonisation’s (ICH) Q7A document (3).

As important as the listing of what is within the scope of the guidance is the listing of what is not covered by the document. Such a list starts on line 40, as follows:

“The following categories of products are not covered by this guidance:

• Type A medicated articles and medicated feed
• Medical devices
• Dietary supplements
• Human tissues intended for transplantation regulated under section 361 of the Public Health Service Act.”

These substances are covered by other regulations. However, the principles given in this guidance may be studied for use with the process validation requirements if required for the above products.

LIFECYCLE APPROACH TO PROCESS VALIDATION
As a starting point, the guidance document mentions that process validation is a part of the lifecycle of a product. Line 27 states, “the lifecycle concept links product and process development, qualification of the commercial manufacturing process, and maintenance
of the process in a state of control during routine commercial production.”

The maintenance of the process in a state of control is important. As Deming and other statisticians have noted, if a process is not under statistical control, there can be no reliance on the results of any study, and any prospective acceptance criteria based on such a process will be unreliable. Therefore, the company must establish the ability of the process to operate in a state of control during development studies. Basic \( C_p \) or \( C_{pk} \) studies will be useful here.

Line 93 of the draft guidance defines process validation “as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products. Process validation involves a series of activities taking place over the lifecycle of the product and process.”

This establishes the idea that consistency is the goal, and thinking and planning for the eventual validation study should begin from the process design stage. It is often noted among GMP workers that the GMPs are aimed at establishing a consistent process, not a perfect or best process, and the planning and data collection should begin early for any study. Last minute or retrospective studies often leave many things undone or inadvertently ignored.

Line 97 describes the stages of process validation activities as follows:

“This guidance describes the stages of process validation activities in three stages:

• Stage 1–Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
• Stage 2–Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.
• Stage 3–Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.”

The stage 1 process definition should be based on statistical studies conducted during process development work. Stages 2 and 3 will basically require statistical analysis to establish an acceptable level of variation of the process and the ability to operate within those levels. This work will require the determination of the precision of individual steps and the reproducibility of the process.

IDENTIFICATION AND CONTROL OF VARIATION

The draft guidance notes the ability to detect and control variation beginning on line 122, as follows:

“Manufacturers should:
• Understand the sources of variation
• Detect the presence and degree of variation
• Understand the impact of variation on the process and ultimately on product attributes
• Control the variation in a manner commensurate with the risk it represents to the process and product.”

Statistically this will start with measurements of standard deviations and move on to the analysis of variance. The calculations needed are fairly basic and uncomplicated. The difficulty that will arise, especially with the issue of controlling variation, is in the design of the experiments that will be required to understand the variations.

Line 133 repeats the necessity for maintaining a state of control and states, “After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change.”

The latter part of this statement is important because companies who have adopted the “do it once and forget it” approach to validation often ignore the changes that must inevitably occur when manufacturing a successful product.

SAMPLING AND TESTING

Line 174 of the draft guidance introduces the GMP requirements for valid sampling plans, as follows: “CGMP regulations require that batch samples represent the batch under analysis (see, e.g., § 211.160(b)(3)) and that the sampling plan result in statistical confidence (§ 211.165(c) and (d)) that the batch meets its predetermined specifications (§ 211.165(a)).”

This requires that effective individual sampling plans be developed for each point where testing will be performed in process validation.

Line 181 furthers the need for on-going statistical studies and states, in-process “specifications . . . shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate.” This requirement, in part, establishes the need for manufacturers to
analyze process performance and control batch-to-batch variability.

Line 264 states the need for full statistical studies, as follows:

“Designing an efficient process with an effective process control approach is dependent on the process knowledge and understanding obtained. Design of Experiment (DOE) studies can help develop process knowledge by revealing relationships, including multifactorial interactions, between the variable inputs (e.g., component characteristics or processing parameters) and the resulting outputs (e.g., in-process material, intermediates, or the final product).

“Risk analysis tools can be used to screen potential variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained. The results of DOE studies can provide justification for establishing ranges of incoming component quality, equipment parameters, and in process material quality attributes.”

The use of design of experiment (DOE) techniques requires a statistician who understands processes as well as statistics. The factors for the DOE study will also require the application of risk analysis tools not only to determine the factors to be studied but to define the amount of variability that would be acceptable.

This work will test the strength and depth of a quality control (QC) department. Companies who look upon quality control as a simple testing function and staff their QC department accordingly will find that their approach was short sighted.

When performance qualification (PQ) studies are contemplated, the need for additional statistical techniques is stated in lines 383 and 392, as follows:

“The approach to PQ should be based on sound science and the manufacturer’s overall level of product and process understanding. The cumulative data from all relevant studies (e.g., designed experiments; laboratory, pilot, and commercial batches) should be used to establish the manufacturing conditions in the PQ.

“In addition, we strongly recommend firms employ objective measures (e.g., statistical metrics), wherever feasible and meaningful to achieve adequate assurance.”

Line 394 extends this to require a higher level of sampling plans and states, “In most cases, PQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance. The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch during processing. This greater scrutiny accompanied by a higher level of sampling should continue through the process verification stage, as appropriate.” The appropriate number of samples should be determined by statistical procedures once the levels of acceptable risk and variation are established.

Line 413 of the draft guidance creates the need to place these requirements in the PQ protocol. This protocol should, therefore, be reviewed by an individual with statistical qualifications. The guidance states, “We recommend that the protocol discuss: The sampling plan including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination. Sampling during this stage should be more extensive than is typical during routine production.”

This is extended beginning with line 434, which states, “We recommend that the protocol discuss: Criteria that provide for a rational conclusion of whether the process consistently produces quality products. The criteria should include: A description of the statistical methods to be used in analyzing all collected data (e.g., statistical metrics defining both intra-batch and inter-batch variability).”

DATA ANALYSIS

Lines 495 and 506 refer to continued process verification in stage 3. The guidance states, “An ongoing program to collect and analyze product and process data that relate to product quality must be established (§ 211.180(e)). The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the critical quality attributes are being controlled throughout the process.” This will require that trained personnel monitor the performance of the process as operations proceed. The use of statistical process control techniques would be appropriate here.

Line 513 introduces the expectations for the background of some of the personnel involved with the study. It states, “We recommend that a statistician or person with adequate training in statistical process
control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability. Procedures should describe how trending and calculations are to be performed. Procedures should guard against overreaction to individual events as well as against failure to detect process drift. Production data should be collected to evaluate process stability and capability. The quality unit should review this information.

Line 527 of the draft guidance introduces a clear recommendation. The lines states, "Many tools and techniques, some statistical and others more qualitative, can be used to detect variation, characterize it, and determine the root cause. We recommend that the manufacturer use quantitative, statistical methods whenever feasible."

The draft guidance creates a need for continuous monitoring of the process. Line 533 states, "We recommend continued monitoring and/or sampling at the level established during the process qualification stage until sufficient data is available to generate significant variability estimates. Once the variability is known, sampling and/or monitoring should be adjusted to a statistically appropriate and representative level. Process variability should be periodically assessed and sampling and/or monitoring adjusted accordingly." The involvement of a statistically qualified person is clearly needed on an on-going basis.

ANALYTICAL METHODS

Line 615 introduces a discussion on analytical methodology, "For data to have value in predicting process outcomes, it is essential that the analytical tests be scientifically sound (as required under 21 CFR 211.160). While validated analytical methods are not required during product- and process-development activities, methods should be scientifically sound (e.g., specific, sensitive, and accurate), suitable, and reliable for the specified purpose." Although this paragraph states that validated methods are not required during product and process development activities, it proceeds to state that methods should be specific, accurate, sensitive, suitable, and reliable even at the development stage.

For those who have worked in the analytical method validation area, this statement seems to invoke all of the requirements for a validated method. One would think that a prudent company would want to employ validated test methodology in a process validation. How can a process be validated if its validation is derived from measurements and conclusions that are based on un-validated methods? If a test method cannot meet its validation criteria at some later date, what happens to the process validation study that was dependent on its results?

Many will note that the FDA draft guidance document does not require the use of procedures that a statistician would regard as advanced techniques. Consequently, it may not be necessary to employ a full-time statistician for this work. A statistically trained quality control analyst or a statistical consultant could be employed for this work. Companies should be warned that statistics, like many professions, has a variety of specialties, and the statistician who is good with clinical studies may not be the best choice for work on process or method validations. Many jokes are made about patients confusing proctologists with neurologists (after all they’re both MDs). The company that makes the same type of mistake in regard to statisticians will, like the patient, find that the expenditure of much money, pain, and suffering has lead to an unsatisfactory result.

REFERENCES