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Statistical Tools for Development and Control of Pharmaceutical Processes: Statistics in the FDA Process Validation Guidance

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Peer Reviewed: Statistics

Welcome to "Statistical Tools."

This feature provides discussion and examples of statistical methods useful to practitioners 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: Useful information.

The recently issued FDA Process Validation Guidance *recommended 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 (PQ), and Stage 3 Continued Process Verification. FDA recommendations were quite specific for these respective stages, indicating Agency focus on statistical methods. The guidance described several specific details of statistics applications, including design-of-experiment (DOE) studies in formulation and process development, statistical metrics in PQ, and trending of material, process, and product data in monitoring and maintaining validation. The importance of statistical expertise was emphasized throughout the guidance.*

"Statistical Tools" will provide relevant practical examples of using statistics in the various stages of validation. The content of "Statistical Tools" will 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 part of "Statistical Tools" discusses general areas identified in the guidance that recommend applications of statistics—an introduction to the future content in "Statistical Tools."

Comments, questions, and suggestions from readers are needed to help us fulfill our objective for this series. Suggestions for future discussion topics or questions to be addressed are invited. Readers are also invited to participate and contribute manuscripts for this column. Case-studies sharing uses of statistics in validation are most welcome. We need your help to make "Statistical Tools" a useful resource. Please contact column coordinator Paul Pluta at paul.pluta@comcast.net or IVT Community Manager Cale Rubenstein at crubenstein@advanstar.com with comments, questions, suggestions, or case-studies for publication.

Abstract

The recent US Food and Drug Administration Process Validation Guidance has provided clear statements on the need for statistical procedures in process validation. FDA has redefined validation to include activities taking place over the lifecycle of product and process—from process design and development through ongoing commercialization. New applications have

evolved as result of this guidance. Statistical applications should be used in process validation and related applications to improve decision-making. 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 monitor and quantify variation. Statistical methods should be used in support of sampling and testing in process qualification (PQ). Sampling plans should reflect risk and demonstrate statistical confidence. Validation protocol sampling plans should include sampling points, numbers of samples, sampling frequency, and associated attributes. 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. FDA recommends that personnel with adequate and appropriate education in statistics should be used for these activities.

Introduction

FDA issued *Process Validation: General Principles and Practices* (1) in January 2011. This guidance transformed process validation from an individual and singular event to an ongoing continuum of activities during the entire lifecycle (i.e., development through commercialization) of a pharmaceutical product. The guidance incorporates quality-by-design (QbD), process analytical technology (PAT), risk management, and other modern concepts into a comprehensive approach to process validation. The application of statistical methods is an important part of implementing the guidance in pharmaceutical process validation programs. FDA also recently issued (draft guidance) *Analytical Procedures and Methods Validation for Drugs and Biologics* (2). This document describes statistical analysis and models appropriate for validation of analytical methods. The principles and approaches described above are also being applied to other processes (e.g., cleaning, packaging), qualifications (e.g., equipment, facilities, utilities, control systems), hybrid systems (e.g., water, heating, ventilation, and air conditioning [HVAC]), and quality systems. Measurement is itself a process. Statisticians play a role in evaluating capability of the measurement process, without which no other work can be done. Pharmaceutical processes often comprise multiple sub-processes; inside each further sub-sub-processes are nested, and so on. At the base of all of these is the measurement process itself, without which it is impossible to study any of the higher-order processes. Statistical methods are tools to be utilized for better risk-based decision-making in the face of variation and uncertainty.

Guidance Definition

Process validation is defined in the 2011 guidance as follows (1):

"*Process validation* is defined 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 product. Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes the 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 lifecycle approach to process validation is based on the following basic tenets as stated in the guidance (1):

- "Quality, safety, and efficacy are designed or built into the product.
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.
- Each step of a manufacturing process is controlled to assure that the finished product meets all design characteristics and quality attributes including specifications."

The above is proposed by FDA for application to human drugs, veterinary drugs, biological and biotechnology products, active pharmaceutical ingredients, finished products, and the drug component of combination drug and medical device products. The above does not specifically apply to process validation of medical devices. However, these same general stages and their respective inclusions have previously been published for medical devices (3).

FDA Expectations – Variation, Control, and Statistics

The FDA guidance document changed and expanded the scope of process validation. The guidance further raised expectations regarding scope and content of validation activities. Application of statistical methods has become a significant part of these expectations.

A brief section in the opening pages of the FDA guidance clearly states expectations for industry validation programs. This section describes the expanded view of validation for new and legacy products. Key concepts in this section include recognition of variation and associated control of variation throughout the entirety of the product lifecycle. Collection and analysis of data are critical to this effort. Specifically:

> "A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that result in products with the desired quality attributes. Manufacturers should:
>
> - Understanding sources of variation
> - Detect the presence and degrees of variation
> - Understand the impact of variation in the process and ultimately on product attributes
> - Control the variation in a manner commensurate with the risk it represents in the process and product.
>
> Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in the manufacturing process to justify commercial distribution of the product. Focusing exclusively on qualification efforts with also understanding the manufacturing process and associated variation may not lead to adequate assurance of quality. 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.
>
> Manufacturers should use ongoing programs to collect and analyze product and process data to evaluate the state of control of the process. These programs may identify process or product problems or opportunities for process improvements that can be evaluated and implemented through some the activities described in Stages 1 and 2.
>
> Manufacturers of legacy products can take advantage of the knowledge gained from the original process development and qualification work as well as manufacturing experience to continually improve their processes. Implementation of the recommendations in this guidance for legacy product and processes would likely begin with the activities described in Stage 3." (1).

Regulatory Requirements and Recommendations

Process validation is a legally enforceable requirement in the pharmaceutical good manufacturing practices (GMPs). The guidance identifies two areas to exemplify emphasis on recognition of variation and control. Both sampling and in-process specifications are mentioned as aspects of process validation. Statistical analyses are explicitly mentioned in both these areas. Sampling plans must result in statistical confidence that product batches meet predetermined specifications. In-process limits must be determined by application of statistical procedures. The guidance also provides a list of recommendations that further emphasize recognition of variation and associated control. FDA recommends a team approach to process validation, including representation of expertise in statistics.

Stage 1—Process Design

The Stage 1 Process Design stage of process validation comprises work conducted towards providing fundamental understanding of the product and process. It includes laboratory-scale experimental studies conducted to determine basic technical relationships between formulation ingredients, process parameters, and product attributes. It also includes work conducted at an increasing scale culminating at the full-scale commercial process. Good understanding of the manufacturing process must be technically and scientifically based. Critical quality attributes and critical process parameters must be identified and their relationships understood. The work of Stage 1 should be commensurate with the identified or expected risk for the product and process.

Stage 1 recommendations address development activities that will ultimately be reflected in the master production record and

control records. The guidance clearly states the goal of Stage 1, “To design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes.” (1). Two general topics are discussed in the guidance: 1) building and capturing process knowledge and 2) understanding and establishing a strategy for process control.

Application of Statistics

Product and process scientists and engineers working in development of pharmaceutical products must understand and utilize statistical methods whenever possible. Their work provides the bases for future manufacturing and selection of parameters in pharmaceutical processes. Documentation of their work will be utilized in regulatory submissions, regulatory audits, change control, and other activities supportive to products and processes. The FDA guidance specifically comments on the use of DOE studies to develop process knowledge; reveal relationships, including multivariate interactions; screen variables; and other applications. The guidance mentions applications of DOE in establishing ranges of incoming component quality, equipment parameters, and in-process material quality attributes. Also mentioned are experiments at laboratory or pilot scale that may assist in evaluation of conditions and prediction of process performance. Application of statistical methods are useful in these and associated activities.

Stage 2—Process Qualification

The Stage 2 Process Qualification stage comprises performance of the commercial process by means of conformance lots. This stage confirms work of Stage 1 Process Design and demonstrates that the proposed manufacturing process is capable of reproducible commercial manufacture. Process Performance Qualification (PPQ) conformance lot manufacturing includes increased testing to demonstrate acceptability of the developed formulation and process. The testing of Stage 2 should be commensurate with the risk identified for the product and process.

The FDA guidance specifically discusses design of facility, utilities, and equipment, Process Performance Qualification (PPQ), the PPQ protocol, and PPQ protocol execution and report in Stage 2, all of which are directly connected to specific process validation. PPQ is intended to confirm the process design and development work and demonstrate that the commercial manufacturing process performs as expected. This stage is an important milestone in the product lifecycle. PPQ should be based on sound science and experience as developed in Stage 1 studies and activities. PPQ should have a higher level of testing and sampling. The goal of PPQ is to demonstrate that the process is reproducible and will consistently deliver quality products.

PPQ Protocol and Application of Statistics

A written protocol is essential for acceptable PPQ. Specific requirements mentioned in the FDA guidance, many of which requiring statistical methods, include the following:

- Manufacturing conditions, process parameters, process limits, and raw material inputs
- Data collection and evaluation
- Testing and acceptance criteria
- Sampling plan, including sampling points and number of samples
- Number of samples, which demonstrate statistical confidence
- Confidence level based on risk analysis
- Criteria for a rational conclusion of whether the process is acceptable
- Statistical methods that are used to analyze data, including statistical metrics defining both intra-batch and inter-batch variability
- Provision to address deviations and non-conformances
- Design of facilities and qualification of equipment and facilities
- Personnel training and qualification
- Verification of sources of materials and containers/closures
- Analytical method validation
- Review and approval by appropriate departments and the quality unit.

Stage 3—Continuing Process Verification

The Stage 3 Continued Process Verification stage comprises the ongoing commercial manufacturing of the product under the same or equivalent conditions as demonstrated in Stage 2 Process Qualification. This phase continues throughout the entire commercial life of the product/process. Maintenance activities of Stage 3 should be commensurate with the risk identified for the product and process.

Assuming good development of the process, identification of potential sources of variation, and control of this variation, the manufacturer must maintain the process under control over the product lifetime (i.e., the work of Stage 3). This control must accommodate expected changes in materials, equipment, personnel, and other changes throughout the commercial life of the product, and it must do so based on risk analysis.

Application of Statistics

Specific items in this section of the guidance requiring statistical application include the following:

- Ongoing program to collect and analyze process data, including process trends, incoming materials, in-process material, and finished products
- Statistical analysis of data by trained personnel
- Procedures defining trending and calculations
- Evaluation of inter-batch and intra-batch variation
- Evaluation of parameters and attributes at PPQ levels until variability estimates can be established
- Adjustment of monitoring levels based on the above
- Timely assessment of defect complaints, out-of-specification (OOS) findings, deviations, yield variations, and other information
- Periodic discussion with production and quality staff on process performance
- Process improvement changes
- Maintenance of facilities, utilities, and equipment to ensure process control.

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.

Expertise in Statistics

The guidance clearly shows scope, objectives, and criticality of data analysis and statistical treatment of data in Stage 3. Specific FDA recommendations regarding expertise in statistics are noteworthy:

> “An ongoing program to collect and analyze product and process data that relate to product quality must be established. The data collected should include relevant process trends and quality of incoming materials or components, in-process materials, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process.
>
> We recommend that a statistician with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedure used in measuring and evaluating process stability and process capability. Procedures should describe how trending and calculations are to be performed and should guard against overreaction to individual events as well as against failure to detect unintended process variability. Production data should be collected to evaluate process stability and capability. The quality unit should review this information. If properly carried out, these efforts can identify variability in the process and/or signal potential process improvements.” (1).

The following paragraph from the guidance provides another clear recommendation:

> “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.” (1).

Series Discussion Topics

The tentative plan for the content in this series will begin with discussion of basic principles. Fundamental topics in this area will include types of data, graphical representation, distributions, central tendencies, dispersions, and probability. Confidence intervals and tolerance intervals will be discussed. Subsequent topics will address areas particularly applicable to the respective lifecycle stages of process validation. These will include topics such as experimental design, including screening studies and multivariate experimental studies. Discussions on metrology, process capability, control charts, trending, and other related topics are planned. Example case-studies and calculations will further describe the above topics. *Validation by Design® The Statistical Handbook for Pharmaceutical Process Validation* by Torbeck (4) is recommended for a comprehensive summary of statistics topics associated with process validation.

As mentioned above, the objective for this series of discussions on statistical topics is useful information. Reader input through comments, questions, and other discussion is needed. Suggestions for future discussion topics are invited. Readers are also invited to participate and contribute manuscripts reflecting actual experiences utilizing statistical tools for development and control of pharmaceutical processes or analytical methods.

References

1. FDA, *Process Validation: General Principles and Practices* (Rockville, MD, Jan. 2011).
2. FDA, *Analytical Procedures and Methods Validation for Drugs and Biologics (Draft Guidance)* (Rockville, MD, Feb. 2014).
3. GHTF, *Quality Management Systems – Process Validation Guidance*, Edition 2, January 2004.
4. L. Torbeck, *Validation by Design®. The Statistical Handbook for Pharmaceutical Process Validation*, PDA and DHI Publishing, 2010.

Also See:

Blog: Statistical Tools for Process Qualification

GXP: FDA’s 2011 Process Validation Guidance: A Blueprint for Modern Pharmaceutical Manufacturing

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