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# Statistics in Pharmaceutical Development and Manufacturing

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The pharmaceutical industry is undergoing rapid change and facing numerous challenges, including the demands of global competition, the need to speed up the drug-development process, and the Food and Drug Administration's (FDA's) expectations for the incorporation of the principles of quality by design (QbD) and process analytical technology (PAT) in process and analytical development. Statistical thinking and methods play a significant role in addressing these issues. This article provides an overview of the use of statistical thinking and methods in the R&D and manufacturing functions of the pharmaceutical industry. The exposition includes the history of pharmaceutical quality and regulation, phases of pharmaceutical development and manufacturing and the basic quality and statistical tools employed in each, emerging statistical methods, the impact of statistical software and information technology, and the role of statisticians in pharmaceutical development and manufacturing. Four case studies are included to illustrate how these issues play out in actuality. A summary provides a succinct synopsis of those issues and concludes that the complex, technical nature of pharmaceutical development and manufacturing offers many opportunities for the effective use of statistical thinking and methods and that those who use these methods can become catalysts for both process-development understanding and product-quality improvement. Additional details can be found in our technical report (Peterson et al. (2009)).

Key Words: Design Space; Drug Manufacturing; FDA; ICH; Opportunity; PAT; Pharmaceutical Industry; Quality by Design; R&D; Statistical Methods; Statistical Thinking; Technical Change.

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STATISTICAL concepts and tools have been successfully applied for decades in such sectors as chemicals, automobile manufacturing, and computer-chip manufacturing, but their use in the far more regulated pharmaceutical industry presents some unique challenges. For example, many pharmaceutical companies hesitate to invest heavily in large-scale manufacturing-process quality before a drug is approved for marketing because failure in the clinic means product failure. Because time from inception to clinical approval may span 12–15 years, 60–75% of product patent life may have expired by the time the Phase III (confirmatory) trials have been completed. Even after a successful set of Phase IIA (dose determination) and Phase IIB (proof of concept) clinical trials are completed, 40–50% of product patent life may have expired. In addition, one in three drugs is expected to fail in Phase I (first time in man) trials for assessing safety, tolerability, and drug blood levels. Pharmaceutical companies are therefore under considerable economic pressure to file for approval of the new drug application (NDA) with regulatory authorities as soon as possible after completing successful Phase III clinical trials, when a considerable amount of money must be invested in product launch. As a result, quality and process understanding initiatives must compete for time and money with potential losses from considerable ‘at-risk’ development activities.

Nevertheless, a number of factors are converging to increase the need for sophisticated, statistics-driven approaches to quality and process understanding in the pharmaceutical industry, including:

- *Regulatory Trends.* Recent regulatory guidelines from the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the International Conference on Harmonisation (ICH) encourage scientifically based approaches to quality and compliance. Implementing the concepts embodied in those guidelines—process analytical technology (PAT), quality by design (QbD), and design space—will require new, more statistically rigorous and risk-based ways of doing things.
- *Inherent Characteristics of Pharmaceutical Manufacturing.* Many of these inherent characteristics—and the challenges they present—clearly call for the increased use of sophisticated statistics-driven approaches. For example, in most other manufacturing industries, product specifications are clearly tied to product performance. In pharmaceuticals, however, it is difficult to tightly connect, say, ‘tablet dissolution’ rates to drug efficacy and safety over a vast array of potential product users, each with different body size, age, lifestyle, genetics, and drug-metabolism chemistries. Furthermore, pharmaceutical companies must maintain quality in a many-step production process that creates a complex molecule that must have the proper molecular structure and be free of serious chemical impurities or biological contaminants. In addition, up to now, there has been a lack of incentive for continuous improvement in pharmaceutical manufacturing *after* regulatory approval. This is due primarily to the fact that substantial changes in the manufacturing process or recipe required formal regulatory approval. But new regulatory guidance has been recently introduced to provide more flexibility with regard to continuous improvement in manufacturing. However, pharmaceutical manufacturers will have to show clear process understanding and prediction ability in order to be granted such flexibility. To meet all these complex challenges, pharmaceutical companies need more, not less, statistical thinking and practice.
- *Economic Pressures.* Many companies, faced with thin product pipelines, major patent expirations, and downward pressure on pricing, now need to cut their manufacturing costs, improve yield and productivity, and generate bottom-line savings that can be used to drive growth and innovation. Statistically driven improvement methodologies found in QbD are critical for success in these efforts.
- *Increased Need for Effective Technology Transfer.* Virtually every drug at some stage of its development or manufacture must be transferred from one site to another. Furthermore, mergers, acquisitions, the rise of “global” generics, the ongoing rationalization of manufacturing, and other factors have increased the frequency with which pharmaceutical manufacturing organizations must effectively and efficiently transfer products and manufacturing processes from one location to another. Cost pressures, market needs, government regulations, tax benefits, and logistic issues have also greatly magnified the importance of efficient, compliant, and cost-effective technology transfer—whether it’s to a nearby plant or a site a world away. Success-

ful transfer requires a degree of understanding of products and processes that can be greatly improved by statistical techniques.

As these trends continue and converge, the role of statistics and statisticians will only grow larger in the industry. To provide readers with a wider perspective on the status and use of statistical tools and methods in the pharmaceutical industry—now and in the future—the sections that follow treat these key issues:

- The history of pharmaceutical quality and regulation
- The phases of pharmaceutical development and manufacturing and the basic quality and statistical tools employed in each
- Emerging statistical methods
- The impact of statistical software and information technology
- The role of the statistician in pharmaceutical development and manufacturing

The article concludes with four case studies that illustrate how these issues play out in actuality, and an article summary provides a succinct synopsis of the issues and their implications for the future. This article will not address statistical methods or quality in the conduct of clinical trials. The interested reader should see Cleophas et al. (2006) for statistical methods in clinical trials and Griffin and O'Grady (2006) for a review of quality in the conduct of clinical trials. Two books that review statistics in the pharmaceutical industry more broadly are by Millard and Krause (2001) and Buncher and Tsay (2005). A list of key abbreviations and acronyms are given in the Appendix at the end of this article.

## History

To understand the forces that have shaped the use of statistics in pharmaceutical development today, it is essential to understand the history of the regulation of the industry. Although bills to regulate food and drugs were introduced in the U.S. Congress as early as 1879, the modern history of pharmaceutical regulation may be divided into two distinct eras: (1) the period of largely reactive legislation that lasted through most of the 20th century and (2) the period of science-based regulatory initiatives that began with the dawn of the 21st century and continues today. Though the two periods overlap to some extent, the new era, with its emphasis on increased

process understanding, promises to be markedly different in terms of industrial statistical focus. Table 1 provides a summary of the key regulatory events.

## The 20th Century: Regulation and Reaction

In the United States, the precedent for federal regulation of biological products was first established in the Biologics Control Act of 1902, which came in response to the deaths of 13 children caused by a contaminated diphtheria vaccine and the deaths of 9 children caused by a contaminated smallpox vaccine. The act created the Center for Biologics Evaluation and Research (CBER, which became one of the centers of the FDA in 1972).

In 1906, the United States enacted the Food and Drugs Act, known as the “Wiley Act.” Although the law focused largely on adulterated food, it also sought to prevent false claims on product labels and to force the acknowledgement of product ingredients such as alcohol, opium, and morphine.

In 1927, the precursor to the current agency dropped all research functions and the current name, FDA, was applied in 1930. In response to 107 deaths from a poisonous solvent used in the manufacture of a sulfa drug, the 1938 Federal Food, Drug, and Cosmetic Act (FDCA) required sellers to prove that their products were safe. The Act also authorized factory inspections and supplemented penalties to include injunctions as well as seizures of product and criminal prosecution. The early 1940s saw the death of some 300 people from a contaminated sulfa drug, leading to stricter manufacturing standards, which would eventually come to be known as the Good Manufacturing Practice (GMP) standards. Also during this period, the FDA enacted batch certification for some products. This required producers to submit a sample of every batch of product to the FDA for testing.

The 1960s witnessed the birth of some 10,000 deformed infants in Europe from a compound called thalidomide. The compound was not marketed in the United States, but resulted in the Kefauver–Harris Drug Amendments of 1962 passed to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers were required to prove to the FDA the effectiveness of their products before marketing them. In addition, testing in animals was required before any human dosing and the FDA's power to inspect manufacturing facilities was expanded.

The Prescription Drug Marketing Act (PDMA)

TABLE 1. Key Regulatory Events

Year	Event	Purpose
1906	Pure Food and Drug Act	Prevent false claims
1930	FDA takes its current name	Agency is purely regulatory—no research functions
1938	Federal Food, Drug, and Cosmetic Act	Require proof of safety before marketing
1949	First publication of FDA “Guidance to Industry”	Address the appraisal of toxic chemicals in foods
1962	Kefauver–Harris Drug Amendments	Require proof of efficacy and safety before marketing
1987	Prescription Drug Marketing Act	Ensure that pharmaceutical products purchased by consumers are safe and effective, and free from counterfeit, adulterated, misbranded, subpotent, or expired drugs
2004	Pharmaceutical cGMPs for the 21st Century—A Risk-Based Approach	Emphasize risk-based approaches to development and manufacturing
2004	PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance	Achieve greater understanding of drug development and manufacturing processes. Data acquisition and multivariate analysis cited as important tools
2005	ICH Harmonized Tripartite Guideline: Pharmaceutical Development, Q8	Foster quality by design and the understanding of design space—emphasis on design of experiments to define interactions and work in multidimensions
2005	ICH Harmonized Tripartite Guideline: Quality Risk Management, Q9	Encourage the use of quality risk-management tools in all phases of a product’s lifecycle
2007	ICH Harmonized Tripartite Guideline: Pharmaceutical Quality System, Q10	Enhance science- and risk-based regulatory approaches

of 1987 was designed to halt the sale of counterfeit, adulterated, and expired drugs. The FDA moved to expedite the approval of drugs for life-threatening diseases such as AIDS and eased access to drugs for patients with limited possibilities for treatment.

This history of pharmaceutical regulation in the 20th century could be viewed as a succession of quality regulations, with heavy legislative involvement deriving from the potential for pharmaceuticals to cause harm to human life. In parallel, the quality of products and processes in nonpharmaceutical industries has evolved largely as a result of market forces.

### The 21st Century: The Rise of Science- and Risk-Based Approaches

The focus of the FDA and regulatory agencies in many other parts of the world is currently expanding to include a greater emphasis on fundamental understanding of manufacturing processes as the basis for a knowledge-driven, risk-based approach to quality. In the early 2000s, the FDA began a program to focus on what it called manufacturing science. The FDA defined manufacturing science as encompassing

knowledge about products and processes, technology used to manufacture and control these processes, and the underlying foundation of a robust quality system at the manufacturing site. This represented a clear shift away from a long-standing position of rigid regulation and inspection to achieve quality standards.

The knowledge base to support these changes begins in research and development and continues through technology transfer and commercial manufacturing. Information related to the active pharmaceutical ingredient (API) and drug product formulation, manufacturing processes and analytical methods, critical-to-quality parameters and attributes, and product specifications are all key elements of the knowledge base. With this knowledge, the firm and the FDA can determine the potential for events to affect fitness for use (i.e., risk). A product’s risk potential can be assessed through a mutually developed risk classification system. By sharing risk-mitigation strategies with the FDA, a manufacturer may have a product reclassified to a lower risk class. This is one of the key benefits of a science- and risk-based approach to GMPs.

These new approaches to regulation, compliance, and quality were embodied in a series of guidelines issued to the industry by the FDA and The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH is a unique project that brings together the regulatory authorities of Europe, Japan, and the United States. The last five rows of Table 1 summarize some of the key documents. They are readily accessible on the FDA and ICH websites.

While regulatory submissions relating to drug product manufacturing have traditionally focused on prescriptive validation and product testing, and less on process design, the increased process understanding pointed to by these 21st century guidelines could lead to increased regulatory flexibility for drug manufacturing. In an effort to streamline costs and improve product quality, the pharmaceutical industry has become increasingly interested in working with regulators to modernize drug development and quality programs. Science- and risk-based regulatory processes will ensure that FDA resources are focused on the highest risk areas and firms are encouraged to use innovative technology to mitigate risk. However, it is incumbent upon the firms to ensure that low- and medium-risk areas remain in an appropriate state of control because these risk classes will receive less regulatory attention.

Additional historical evidence of the growing importance of statistics to the pharmaceutical industry may be found in the eventual creation of a Biopharmaceutical Section within the American Statistical Association (ASA). Initially, a subsection of the more general Biometrics Section, full section status was driven by the need to have a professional organization to bring together industry, academia, and regulators to help meet the specialized needs of the industry. The early leaders in the creation of the subsection were Joe Dresner, Charlie Dunnett, Mike Free, Joe Ciminera, Ron Gauch, Marti Hearron, and Joe Meyer. Early in the life of the Biopharmaceutical Section, the primary preclinical topics were those related to toxicology—especially carcinogenicity studies. Process development and manufacturing issues have only come to the forefront with recent FDA initiatives. Professional organizational homes for these topics are currently spread across ASA and the American Society for Quality (ASQ).

Below is a short summary of some of the early contributors to the area of “industrial” statistics in the pharmaceutical industry. (This is not meant to be

a definitive list and we apologize for any inadvertent omissions of names or contribution areas.)

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Shein-Chung Chow	Product stability
Joseph Ciminera	Control charting, process monitoring
Mike Free	Product stability
John R. Murphy	Screening designs, content uniformity
Earl Nordbrock	Product stability
Charles B. Pheatt	Product dissolution
Steven Ruberg	Product stability
David Salsburg	Methods comparison
Charles B. Sampson	Quality control
Jun Shao	Product stability
Wayne A. Taylor	Sampling plans
Lynn Torbeck	Process validation

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### **Drug Development, Manufacturing Processes, and Analytical Methods**

Following the discovery of an API, pharmaceutical development takes place along five parallel paths: (1) clinical trials, (2) preclinical assessment, (3) API development, (4) drug product development (final dosage form), and (5) analytical method development (Figure 1). The objective of this work is the submission and approval of an NDA. Once clinical development begins, it usually drives the time lines for the other four development paths.

Except in the smallest companies, no individual statistician is responsible for supporting all five paths. This section treats API development, drug product formulation, and analytical development, including the statistical methods and tools that are applied in pharmaceutical development and manufacture. It also demonstrates how these activities fit into a QbD paradigm. Although API development, drug product formulation, and analytical development are presented sequentially here for the sake of clarity, they usually proceed in parallel and they also support the manufacture of clinical trial supplies. Furthermore, all three development paths are periodically affected by how the drug product is faring in the clinical trials. This section, and indeed the entire article, focus primarily on the activities in the gray arrows in the box in Figure 1.

Table 2 shows how API, drug product development and manufacturing, and analytical-method de-

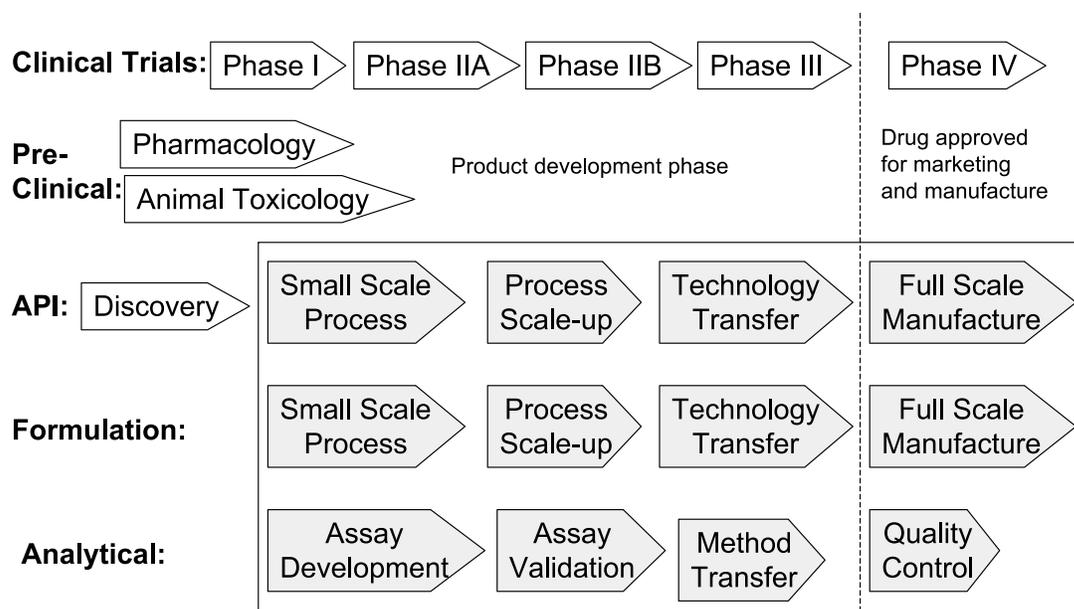


FIGURE 1. Schematic of Pharmaceutical Development and Manufacturing Processes.

TABLE 2. Phases of Development for API, Drug Product, and Analytical Methods

	API	Drug product	Analytical methods
Definition	The active ingredient in the medicine	The medicine as administered to the patient (e.g., a pill or injection)	Procedures for quantifying the amounts of active ingredient or impurities in either the API or drug product
Stages:			
Preclinical	Molecule selection, synthetic route development, creation of supplies for animal testing	Animal studies	Determine measurement needs, select analytical methods, develop standards
Phase I	Start GMP manufacturing process for clinical trial investigation of physical properties	Consider formulation, investigate supplies, stability requirements	Analytical-method optimization
Phase II	Scale-up of chemical synthesis	Drug-product formulation optimized, shelf-life studies begin	Analytical-method validation
Phase III	Clinical-trial supply manufacture, identification of critical process characteristics, process validation	Manufacture of clinical trial supplies, scale-up of drug product process, shelf-life determination, process validation	Product and process specifications finalized, process monitoring (e.g., control charts) established
Phase IV	Technology transfer from R&D to commercial manufacturing facility	Technology transfer from R&D to commercial manufacturing facility	Product and process monitoring for statistical control and quality improvement

velopment for small-molecule therapeutics interlink with the phases of clinical studies. The relationships are detailed and discussed in this section of the article.

### **API Development: R&D, Tech Transfer, and Manufacturing**

The API in a medication or vaccine is the substance or organism that fights the symptom or illness that is being treated or induces immunity to the pathogen. After the discovery of a molecule that has pharmaceutical activity, work is done on this candidate API to further refine the material, to create the manufacturing process, and to scale it up to the desired production levels for full-scale manufacturing.

In the case of small-molecule pharmaceuticals, the first step is the chemical synthesis of the API and the testing of candidate synthetic routes to determine the most effective (chemistry) route from a manufacturing perspective. Next, work is done to verify what was made and how to make it at larger scale—for example, a move from 2–3-gm to 50-gm batches, which are needed to supply preclinical studies in animals. Work is then done to move to bigger batches (1–5 kg) using small-scale commercial equipment or scalable equipment (not beakers). With Phase III clinical studies, API manufacturing eventually grows to its largest scale to date, at least one tenth of commercial batch size.

Much of the statistical thinking and many of the methods and tools used in the development and manufacture of an API are the same as those used for chemical processes. Also, much of process and product development involves experimentation—the key tool, of course, being design of experiments (DoE). Experimentation includes screening experiments, product/process understanding studies, regression modeling, process optimization, and robustness studies. In manufacturing, statistical process control (SPC) is used extensively to monitor and improve processes. On the improvement side, approaches using statistical techniques such as Six Sigma, Lean Manufacturing, PAT, Design for Six Sigma, and QbD are increasingly being used.

It should be noted that the preceding discussion of API applies to drugs developed from synthetic chemicals, the so-called “small molecules”. Biologics and vaccines that are produced in biological systems are referred to as “large-molecule” drugs (e.g., proteins), as they are typically much larger molecules. Large- and small-molecule drug production methods have a

lot in common, with the principal differences being that large molecules are associated with many raw materials, numerous upstream and downstream process steps, a variety of operating conditions, and numerous types of equipment. Because large-molecule drugs are produced from living organisms, variability is also higher and viral contamination can be an issue. Nevertheless, the associated statistical methods and approaches used are similar to those used for small-molecule drug production. Additional discussion of drug products from small and large molecules is included in this section.

### **Drug Product Development and Commercial Manufacture (Small Molecules)**

Table 3 describes the important formulation and process development activities that must be performed and the milestones that must be achieved in preclinical assessment and in clinical trials to demonstrate acceptable drug product safety and efficacy to regulatory authorities.

The last column of Table 3 lists standard statistical techniques and methodologies that are routinely applied in support of the corresponding stage of drug product development.

Figure 2 illustrates a typical tablet manufacturing process. The API is blended with excipients to form the tablet (i.e., the drug product). The excipients are ingredients that help to keep the tablet intact in storage and then to dissolve at a particular rate after ingestion by the patient.

### **Drug Product Development and Commercial Manufacture (Large Molecules and Vaccines)**

The primary differences in drug product development between small molecules and large molecules (biologics and vaccines) relate to the route of administration of the product and to drug product stability. Most biologics and vaccines are injectables and must be formulated to cause a minimum amount of discomfort to the patient. Some formulation components, such as salts, produce stinging. These are necessary, however, to help stabilize the molecule throughout product shelf-life. Some vaccines, such as live attenuated-virus vaccines, must be stored refrigerated or frozen, and many undergo a formulation process called lyophilization, which is freeze drying under carefully controlled time, temperature, and pressure conditions. Similar to the development of a small-molecule formulation, a large molecule or a vaccine formulation is expedited through the use of

TABLE 3. Drug Product Development and Statistical Support

Milestones	Activities	Statistical support
Nominate an API for clinical development	Discover the API and perform various preclinical studies	Multiple comparison techniques for combinatorial chemists; analysis of genomic data; design and analysis of animal safety studies, etc.
Perform Phase I clinical studies	Determine Phase I dosage type (e.g., liquid, capsule, tablet [or new technology])	Analysis of historical data; statistical thinking (design and analyze experiments)
	Excipient compatibility studies	Design and analyze experiments
	Accelerated stability studies	Regression analysis
Perform Phase IIA (dose ranging) and IIB (proof of concept) clinical studies	Determine Phase II dosage type (new technology)	Analysis of historical data; statistical thinking (design and analyze experiments)
	Evaluate excipient compatibility (if not performed previously)	Design and analyze experiments
	Develop Phase II dosage formulation	Design and analyze factorial and/or mixture experiments
	Develop Phase II manufacturing process	Design and analyze factorial and/or response surface experiments
	Stability studies	Regression analysis
Perform Phase III clinical studies	(If necessary, determine Phase III dosage type)	(Design and analyze experiments to investigate scalability and/or economic concerns with Phase II dosage type)
	Develop and/or scale Phase III dosage formulation	Design and analyze factorial and/or mixture experiments
	Develop and/or scale Phase III manufacturing process	Design and analyze factorial, mechanistic, and/or response surface experiments
	Develop PAT applications	Multivariate analysis
	Transfer technology to commercial manufacturing division	Write reports and consult
Submit new-drug application	Develop and/or scale commercial formulation and process	Design and analyze factorial, mechanistic, mixture, and/or response surface experiments
	Define design and knowledge spaces for DP formulation and process	Design and analyze product- and process-understanding experiments
	Conduct ICH campaign	Analyze ICH stability studies (set expiry)

TABLE 3. *Continued*

Milestones	Activities	Statistical support
Produce commercial product	Establish QA procedures	Assess process capability and establish quality systems to control the process (SPC, PAT, establish sampling plans, etc.)
	Monitor DP stability	Analyze data from annual stability lots
	Improve the process	Data mining, DoE, Six Sigma techniques, Lean techniques, JIT manufacturing, etc.

multifactor design of experiments. Another key area of statistical support is stability study design and manufacturing modeling. For some of the less stable vaccines, release specifications and manufacturing targets must be supported by strategic, and sometimes innovative, stability and manufacturing studies, in order to obtain reliable data to establish a release potency that guarantees safe and effective product through expiry and to establish a robust manufacturing process.

Another feature unique to large-molecule pharmaceuticals and vaccines is related to the complexity of their structure. These products can not usually be comprehensively characterized and, therefore, process or facility changes require carefully designed comparability studies. The industrial statistician may work with engineers to design an efficient and effective study.

**Analytical Methods**

*Analytical methods* are used by pharmaceutical manufacturers and regulatory authorities to help guide development and to characterize and control production and distribution of drugs, biologics, and vaccines to the public. Most methods are used to help demonstrate the quality of a product, its potency, and purity. Methods evolve over the course of development in correspondence to need and regulatory requirements. Statisticians are involved throughout the method lifecycle. This includes development of processing strategies for complex methods, such as bioassay and near infrared spectroscopy, employment of multifactor DoE to optimize the method, validation design and analysis to demonstrate the method is *fit-for-use*, and control strategies for maintaining satisfactory method performance. Methods range from measurement of physical characteristics of a

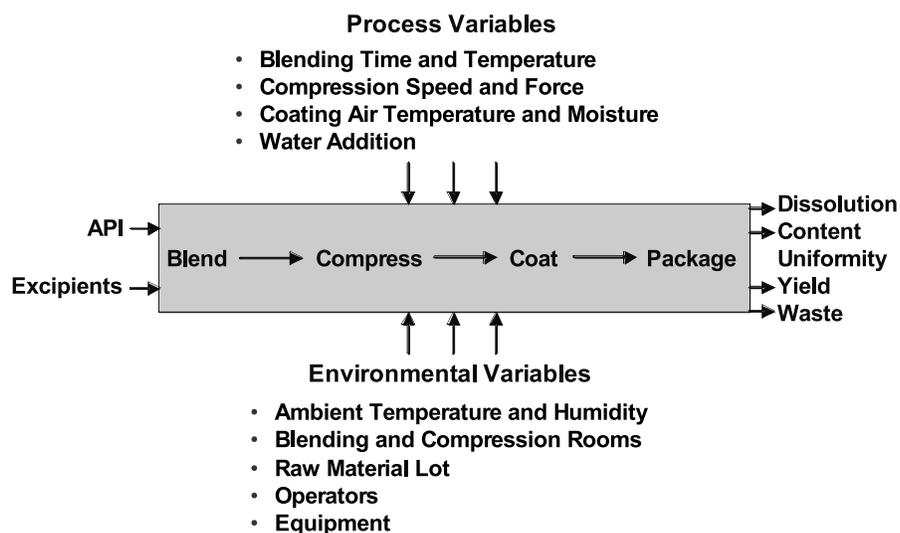


FIGURE 2. Tablet Manufacturing Process and Its Variables.

drug, to chemical composition, to biological activity in vivo.

Methods used to control pharmaceutical products are required to undergo validation in order to demonstrate that they are reliable measures of product quality. Validation standards are outlined in the *United States Pharmacopeia* (USP (2005)) and the ICH guidelines. These guidelines specify the parameters requiring validation, as well as validation methodology. Design considerations and other methods of analysis of validation studies are described in Schofield (2003) and Boulanger et al. (2007).

Pharmaceutical substances and pharmaceutical products are controlled and monitored through specifications and process capability or control limits. Specifications are defined in ICH (1999) as “a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described.” The limits may be specified in regional compendia such as the *United States Pharmacopeia* and the *British Pharmacopeia*, or developed by the manufacturer. Once defined, these are used to assure the quality of products or their intermediates.

The ideal pharmaceutical quality system is composed of specification limits, release limits, and process-capability limits. We denote by LSL, LRL, and LCL the lower specification limit, the lower release limit, and the lower capability limit, respectively. USL, URL, and UCL denote the respective upper limits. The specification limits (LSL, USL) reflect restrictions within which product is *fit for use*, and must conform throughout shelf-life. The release limits (LRL, URL) assure these limits are met at release and throughout product shelf-life and may be calculated per Apostol et al. (2008), while the control or process capability limits (LCL, UCL) describe both process and assay variability. See Figure 3 for an example.

Methods that have been developed and validated in the research laboratories must be transferred for implementation in the manufacturing quality-control

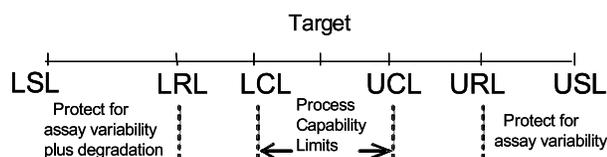


FIGURE 3. Assay Quality-Control Limits.

(QC) laboratory. Various approaches are utilized to help assure that the method is performing properly. An equivalence approach correctly addresses the hypotheses of interest. The change in the average response between laboratories and the increase in variability are held to restrictions that must be met using methods similar to those used to establish bioequivalence (Schuirmann (1987)). Another approach using an  $\beta$ -expectation tolerance interval, similar to its use in method validation, has been advocated to demonstrate that measurements made in the QC laboratory conform to an acceptable shift from the distribution in the development lab (Dewé et al. (2007)).

A key element of the quality assessment of product during development is the determination of product shelf-life. ICH Q1E provides a formulation for the design and analysis of development stability data (ICH (2003)). Studies are usually performed for each product image, which includes different dosages and container/closure profiles. A fixed-effects analysis is performed on stability measurements, which are designed over time to capture changes in important properties of the drug, such as potency and degradants. Rules for pooling the slopes and intercepts of the batches use hypothesis testing at an increased significance level, such as  $\alpha = 0.25$ , in order to improve the power of the test to detect meaningful differences among lots. After pooling has been assessed, shelf-life is estimated as the intersection of the one-sided 95% confidence interval on the mean and the product specification. Other approaches based on prediction interval (Carstensen and Nelson (1976)) and tolerance-interval concepts (Kiermeier et al. (2004)) have been proposed but do not appear to be much used in practice as yet.

Statisticians have contributed to development-stability studies by offering design strategies, such as bracketing and matrixing of stability time points, which greatly improve efficiency with little impact on the effectiveness of the study (Nordbrock (1992)). Bracketing is a strategy wherein extremes of a product image are tested rather than all images. Thus, if product is to be sold as 20-, 50-, and 100-mg doses, a bracketing study might study only the 20- and 100-mg doses. Matrixing involves testing only a subset of the batches at selected time points (a type of incomplete block design). The combination of bracketing and matrixing leads to a parsimonious evaluation of product stability. Mixed-effects modeling of “random batches” has been proposed by others (Chow and Shao (1991)). Efficient strategies for monitoring

stability of commercial product have been described in Fairweather et al. (2003).

Quality-control testing of manufactured product is carried out to help assure safe and effective product and to monitor the process for shifts or trends. Statisticians work with the QC labs to establish test strategies designed to obtain reliable estimates of product-quality attributes related to dose, potency, and purity. Replication may be utilized to increase the precision of the reportable value, and thereby reduce the risks to the customer of an out-of-specification (OOS) result. Some laboratories employ sequential-test plans in which product is tested using a variable number of assay measurements. The statistician works with the quality laboratory to establish acceptable quality criteria with minimum risk to the manufacturer and customer alike.

Regulatory guidelines prescribe a rigorous investigation of the QC laboratory and the manufacturing process when an OOS result is obtained (FDA (2006)). Statisticians may contribute to the process by providing the laboratory with retest and resampling strategies.

Over time, methods may change or a new method may be developed to measure a particular quality attribute of a product. When this is done, the laboratory performs a concordance analysis. Samples are tested across a range of responses, and a concordance correlation coefficient is determined as a measure of the agreement of the two methods (Lin (1989)). A related measure is the concordance slope (Schofield (2003)). This can be obtained from an eigenanalysis of the two assays, and it measures the slope of the relationship between the two methods.

## Emerging Statistical Methods

Satisfying the FDA's encouragement of the pharmaceutical industry to achieve better understanding of their manufacturing processes and to quantify the risks associated with an OOS product requires a wider set of statistical tools than that commonly used in pharmaceutical manufacturing. This need is in large part driven by new technologies supported by the PAT initiative and by the need for better technology transfer from development to manufacturing plant.

Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to evaluate quality. A key component of PAT is the de-

sire to implement continuous, real-time quality assurance. As previously noted, the FDA considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality (FDA (2004a, b)). PAT is expected to produce gains in quality, safety, and efficiency by (1) reducing product-cycle times by using on-, in-, and/or at-line measurements and controls, (2) enabling real-time release, (3) increasing automation, and (4) facilitating continuous processing.

Many PAT tools tend to be multivariate in nature (in both the independent- and dependent-variable sense). Pharmaceutical products and processes involve complex, multifactorial systems. The understanding of these systems is achieved through the use of multivariate mathematical approaches, such as statistical design of experiments, response surface methodologies, process simulation, and pattern recognition tools, in conjunction with knowledge-management systems.

Such data is often collected by way of process analyzers. Such analyzers include those that take univariate process measurements (e.g., pH, temperature, pressure) and those that nondestructively measure biological, chemical, and physical attributes. These measurements may be taken at line, in line, or on line. Process analyzers typically generate large volumes of data. Multivariate statistical methods are often needed to extract critical process knowledge for real-time control and quality assurance (e.g., principal-components analysis, projection to latent structures, time series, batch modeling). Sensor-based measurements may provide a useful process signature.

One of the chief technologies associated with the PAT initiative is near-infrared (NIR) spectroscopy (Skibsted (2006)). This technology is a spectroscopic method utilizing the near-infrared region of the electromagnetic spectrum (from about 800 nm to 2500 nm). NIR spectroscopy produces a spectral trace that may characterize subtle physical and chemical properties of a substance (e.g., chemical intermediate or tablet excipient) (see Figure 4).

Such a trace is a high-dimensional vector response. As the number of experimental units ( $n$ ) will be much smaller than the dimension of the vector ( $p$ ), we have a "large  $p$ /small  $n$ " statistical inference situation. Such situations are typically dealt with by latent-

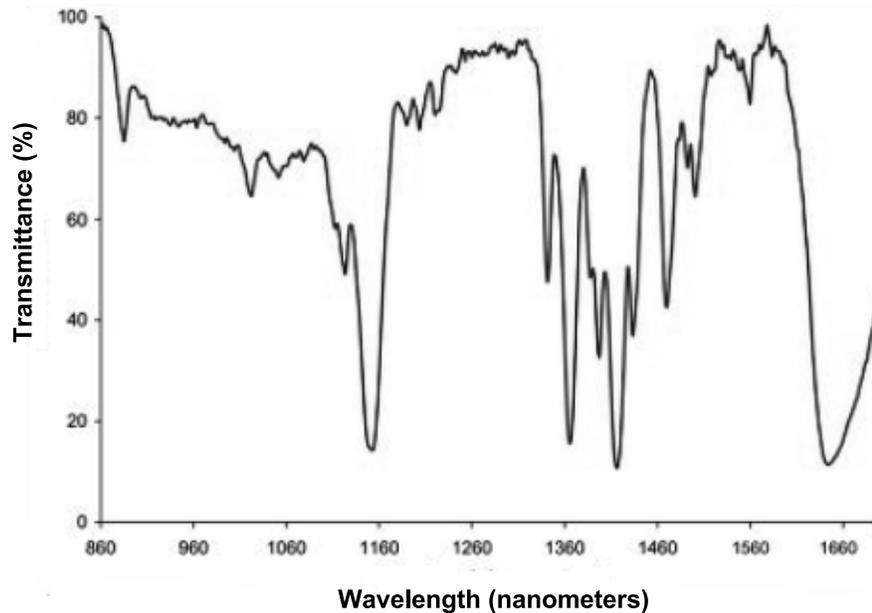


FIGURE 4. An NIR Trace.

variable methods. Such methods are popular in the field of chemometrics, which typically uses partial least squares (PLS) to analyze and reduce the dimensionality of such data.

Spectroscopy, or other technologies that produce traces of output across space or time, produce what is known as functional data, that is, an observation viewed from the perspective of a 'profile' rather than a point in a one- or low-dimensional space. (See Ramsey and Silverman (2002) for examples of functional data and associated statistical-analysis techniques.) Because of the increase in functional data due to new technologies, the field of quality and industrial statistics is adjusting by starting to create new methods for statistical process control based on such data (Jeong et al. (2006)) and for process optimization (Nair et al. (2002)) involving functional data.

The use of data-mining statistical methods may help provide a better fundamental understanding of processes measured by functional response traces. However, practitioners need to understand that data mining is not magic and that the acquisition of new knowledge (or law-like relationships) among factors affecting a process requires the purposeful variation of factors according to well-designed experiments. However, the careful use of data-mining techniques to detect high-dimensional special causes may help here (Pamias (2005)).

Another technology being considered by some pharmaceutical companies is quasi- (or semi-) continuous manufacturing (Leuenberger (2001)). The idea here is to produce many small batches, similar in size to those produced for clinical-trial supplies. This obviates the need for scale-up and also produces rich batch-to-batch variation information, which invites the use of Bayes and empirical Bayes techniques. A recent overview of Bayesian approaches to process monitoring, control, and optimization can be found in Colosimo and del Castillo (2007).

Despite a predominance of batch manufacturing, a case can be made for utilization of continuous manufacturing, at least for some situations (Kossik (2002)). As such technology becomes integrated where needed in the pharmaceutical industry, it will generate a corresponding need for statistical feedback-control procedures (Box and Luceño (1997)) and for more sophisticated statistical process-monitoring methodologies (e.g., Alt (2007)).

It should be kept in mind that data-intensive methods may benefit from better data-gathering techniques (Steinberg et al. (2008)). Data mining as a practice is oriented toward analyzing a given collection of data. This alone may be acceptable for those industries for which it may be difficult to conduct designed experiments (e.g., credit-card companies). However, for an industry such as pharmaceuti-

calcs, where most data is obtained from experiments, concepts of experimental design should be used for improving data gathering in the presence of data-intensive technologies.

In the various QbD regulatory documents, the word ‘risk’ turns up often, usually in reference to the fact that regulatory authorities see new quality initiatives for pharmaceutical manufacturing from a ‘risk-based’ perspective, with an eye to low risk to the patient. From a quality and industrial statistical viewpoint, this brings up two primary statistical methodologies, more directly those related to risk assessment and quantification (see ICH Q9 (2005)) and more indirectly those related to variation determination.

ICH Q9 stresses identification and assessment of associated risk likelihoods and consequences of risk events. Classical quality risk-analysis identification procedures, such as failure modes and effects analysis (FMEA) and fault tree analysis (FTA), are recommended. Probabilistic risk assessment is only mentioned briefly as associated with “supporting statistical tools.” However, it does appear that some regulators recognize the important role of probability models for risk assessment. See, for example, Claycamp (2008). While sophisticated risk-assessment methodologies may be new to the pharmaceutical industry, the changing regulatory atmosphere appears to welcome any sound procedure for improving risk assessment. Probabilistic risk assessment and systems reliability are areas where quality professionals can make important contributions to pharmaceutical manufacturing.

Clearly, the determination of risk depends on variation. For example, a probabilistic reliability computation involving a normally distributed endpoint requires knowledge of variation as well as knowledge of the mean. Therefore, a proper reliability quantification may require a careful variance-components quantification. However, a more insidious issue is that both quality engineers and statisticians may simply follow statistical methods designed primarily for statistical inference on the means as a way to address assurance of quality. One example is the use of “overlapping mean response surfaces” as a way to find the “sweet spot” (Lind et al. (1960), Anderson and Whitcombe (1998)) of a multiple-response process with regard to meeting process-response specifications. Peterson (2004) shows that the probability of meeting specifications when operating well within such a sweet spot can be associated with a disap-

pointingly small value. What is needed is a process-optimization approach tied directly to the probability of meeting specifications.

*Design space*, a key concept associated with risk in ICH Q8 (2005), actually is not directly related to experimental design. Rather, it is related to a region of process capability. The ICH Q8 guidance defines design space as the “multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.” The issue of risk is embodied in the phrase “assurance of quality.” The guidance goes on to state that “working within the design space is not considered as a change.” Of course this begs the question: “How much assurance?” Further, the ability to modify the production recipe without regulatory approval (if one stays within the design space) means that manufacturers could pursue continuous improvement with their manufacturing processes.

Currently, however, pharmaceutical manufacturers may have little business incentive for continuous improvement in their manufacturing processes after regulatory approval—for two reasons. First, typical manufacturing processes require costly and lengthy regulatory approval for any change in the specified manufacturing conditions. Second, there is the perceived risk of product batch failure due to changing the manufacturing conditions (i.e., process parameters and input variables).

However, a valid design space, approved by regulators, would provide pharmaceutical manufacturers with the ability to make small-to-moderate changes in their manufacturing conditions (within the design space) without the time-consuming process of regulatory approval. This would also allow manufacturers to safely experiment within the design space and thereby gain important information about their manufacturing process *after* approval by regulators.

The ICH Q8 Annex (2007) appears to suggest the classical approach of “overlapping mean response surfaces” as a way to construct a design space. But, as previously noted, such an approach does not quantify “how much assurance” of acceptable product, and the resulting “sweet spot” may possess factor combinations associated with poor process reliability.

A Bayesian approach to the ICH Q8 definition of design space has been given by Peterson (2008), although such a region for an HPLC assay had been

suggested earlier by Peterson (2004, Fig 6). Two case studies are also illustrated in Stockdale and Cheng (2009). Here, design space is defined as

$$\{\mathbf{x} : \Pr(\mathbf{Y} \in A \mid \mathbf{x}, \text{data}) \geq R\}, \quad (1)$$

where  $\Pr(\mathbf{Y} \in A \mid \mathbf{x}, \text{data})$  is the posterior predictive probability that a new vector of relevant production responses,  $\mathbf{Y}$ , will fall within the specification (i.e., acceptance) region,  $A$ , given the experimental data and a vector of controllable process factors,  $\mathbf{x}$ . Here,  $R$  would be some prechosen level of reliability. (See Peterson (2008) for some comments on the choice of a value for  $R$ .) For the design space in (1), the input variables (e.g., raw material attributes) could be treated as noise variables.

On the other hand, a design space could be defined as

$$\{(\mathbf{x}, \mathbf{z}) : \Pr(\mathbf{Y} \in A \mid \mathbf{x}, \mathbf{z}, \text{data}) \geq R\}, \quad (2)$$

where  $\mathbf{z}$  is a vector of input-material measurements. The design space in (2) would be useful for feed-forward control procedures where movement within the design space would be motivated primarily by input-material measurements (MacGregor and Bruwer (2008)). A further discussion of other applications of the Bayesian approach can be found in the authors' technical report, Peterson et al. (2009).

### The Impact of Statistical Software and Information Technology

For drug-discovery research, the pharmaceutical industry has already witnessed the rapid increase in software for number crunching and information storage and retrieval. Part of this has been due to the genomic revolution and the associated 'omic' technological platforms for generating such data. However, with the advent of the PAT initiative, technology will again be driving the need for more sophisticated software and information technology to store data, retrieve it, and manage it. Further, emerging statistical methods, as outlined in the previous section, will also require, to some degree, additional computing support or application development. Meanwhile, increased computing speed, storage, and interactive capability are also affecting quality and industrial statistics in the pharmaceutical industry. On one hand, need will, in some cases, drive software creation. On the other hand, software availability will guide what statisticians and quality engineers are willing to do with statistics and graphics.

The increased availability of easy-to-use statistical commercial software allows scientists, engineers, and

various technicians to do their own analyses. Such software is useful not only for statisticians but for teaching and the enablement of (nonstatistical) engineers and scientists. It can also help to empower a trained statistical "champion."

The pharmaceutical industry is inundated with sophisticated assay equipment and measuring devices (e.g., for image or spectroscopic analyses). Some of this equipment has built-in proprietary algorithms that are statistical in nature. It can be difficult to ascertain how well these algorithms perform or what "fine print" assumptions are required for reliable statistical analyses. Some statistical packages have their algorithms well documented, while others do not.

Along with data mining, opportunities in the field of high-dimensional information visualization arise with PAT as well. Shop-floor technicians and chemical/biochemical engineers will have a strong desire to view information in their data whether or not it may be high dimensional. The visual package Spotfire<sup>®</sup> (Spotfire Inc.) can help here, but much more is possible in theory (see, e.g., Fayyad et al. (2002)).

Further opportunities for information technology to contribute lie in the field of database and knowledge management. A pharmaceutical-industry survey (Morris (2005)) has indicated that only 10% of database information has been leveraged to improve overall competitiveness and compliance. So good opportunities exist for database and knowledge-management professionals to impact the pharmaceutical industry from both competitiveness and regulatory perspectives. As mentioned above, the PAT initiative will only increase these needs due to data complexity and volume.

In addition to communication among repositories of collected data, there is a need for related databases of information that allow for easy storage and retrieval of data analyses (graphs, point estimates, confidence intervals, etc.) along with the language code and software that generated such entities from the data. Again, all of this is more pressing for the highly regulated pharmaceutical industry.

For all of the foregoing reasons, the pharmaceutical industry has become interested in "enterprise" statistical and information systems. Such systems allow users to store and track information across various groups within an organization. Examples of such systems are the *Statistica Enterprise wide SPC system* (StatSoft, Inc.), the *SAS<sup>®</sup> Enterprise Guide<sup>®</sup> 4.1 for Statistical Analysis* (SAS Institute Inc.), and

the *Minitab Quality Companion* (Minitab Inc.). Such systems provide electronic venues for developing add-on modules for analyses particular to the pharmaceutical industry. But such systems also call for greater due diligence in software validation across a large group of company subunits that are in a regulated environment.

Despite the need for reliable software validation, increasing sophistication in technology is driving the need for increasing sophistication in statistical analyses and algorithms (Steinberg et al. (2008)). Many younger statisticians (particularly recent graduates) in both the pharmaceutical industry and associated regulatory agencies (e.g., the FDA) have learned their applied statistics using the R (open source) computing environment (Bell et al. (2006)). Consequently, these statisticians want to use R because it is familiar and often has relatively recent statistical methods that are not yet available in commercial packages. In fact, the Drug Information Association and the FDA cosponsor an “Open Toolbox Initiative Forum” to support vendor-neutral software products in an integrated environment.

Interestingly, there are no federal regulations prohibiting the use of open-source statistical software (Bell et al. (2006)). Instead, the FDA rightly supports good software validation that produces a “level of confidence” in the results. Further, the choice of statistical software should not alter the results (Bell et al. (2006)). Given the growing complexity of statistical software, this appears to imply that identical (or possibly similar) analyses using two or more different software applications may be needed to help provide such a level of confidence. Of course, such “level 1” validation exercises may not be considered sufficient for many statistical analyses subject to regulatory oversight. For a discussion of unmet software needs for industrial statistics, see the authors’ technical report, Peterson et al. (2009).

## The Changing Role of Statisticians

As the foregoing discussion makes clear, the utilization of statistical thinking and methods has made significant contributions to the success of the pharmaceutical industry. Undeniably, statistical methods now play an integral part in the industry—in discovery by chemists and biologists, in drug development and manufacturing by chemists, engineers, and pharmaceutical scientists, and in regulatory compliance and quality control.

But what of statisticians themselves? Certainly, they have played a major role in providing the infrastructure as well as in solving important problems and expanding the use of statistics in the pharmaceutical industry. However, as statistical thinking and methods become even more critical for success in the industry, statisticians will need to acquire new skills, particularly leadership skills, to move from their traditional role as passive advisor to a more dynamic role as creator of value. Statisticians in the pharmaceutical industry can provide leadership in three basic, and synergistic, areas: (i) within their own company, (ii) within the pharmaceutical industry (e.g., the Pharmaceutical Research and Manufacturers of America (PhRMA)), and (iii) in collaboration with statisticians at the FDA (e.g., the annual FDA/Industry Statistics Workshop).

### From Consultant to Collaborator to Leader

As statistics originally evolved with scientific management, statisticians became highly specialized functionaries in large organizations. They analyzed data that other people had created and passed along their analysis to engineers and business leaders who used the analysis in making decisions. In the pharmaceutical industry, as in other industries, statisticians first served in that consultative role, typically working one-on-one with internal “clients,” designing studies, analyzing data, and providing training. They provided methods for data collection, strategies for design of experiments, and provided guidance on the most effective use of the concepts, methods, and tools of statistics. When statistical software emerged, they added that expertise to their portfolios.

A confluence of several powerful trends in recent years is requiring new roles for the statistician. First, the internet now makes many data sets accessible to anyone instantly, undermining the statistician’s “ownership” of data. Second, the ubiquitous commercial statistical software described above enables nonstatisticians to perform many of the statistical operations that were formerly the province of specialists. Third, statistics classes are now commonplace in academia, including in business, engineering, economics, and social-science curricula; and the widespread use of statistics-intensive methodologies, like Six Sigma, has provided mass statistical training for nonstatisticians in many organizations.

But more positively, and perhaps most importantly, pharmaceutical industry scientists and engineers began to recognize the value that statisticians

TABLE 4. Expanded Role of Statisticians

Consultant (Old)	Leader (New Expanded)
Analyze data and design experiments	Determine the appropriate strategy and approach
Teach statistical tools	Design training systems, coach, mentor, and train
Work with technical people	Work with managers and technical personnel
Consult on other people's projects	Lead cross-functional projects
Narrow expertise and accountability	Broad expertise and accountability
Follow simple regulatory guidelines	Collaborate with regulatory agencies to influence new guidance
Reactive	Proactive

could provide. As statisticians were assigned to more and more project teams, their role changed from consultant to collaborator. They made unique contributions in their capacity as the primary interpreters of data, guiding interpretation and determining the most effective use of tools and methods. Today, in many industries, statisticians serve as team leaders, providing guidance and oversight of programs from beginning to end. While this role is less common in the pharmaceutical industry, it is a model that can work effectively and should be considered.

### New Skills Needed

One index of the increasing value that the industry places on statistical methods may be found in the number of industry organizations devoted to addressing statistical issues. Those organizations include:

- PhRMA Chemistry, Manufacturing, and Control (CMC) Statistics Expert Team comprised of ~30 statisticians from ~20 PhRMA member companies;
- Informal Nonclinical Statistics Forum, a colloquium of nonclinical statistical managers who meet yearly to share experiences;
- Midwest Biopharmaceutical Statistics Workshop and the FDA/Industry Statistics Workshop, which has been including an increasing number of CMC-related statistics topics on their program list.

The role of statistics and statisticians will grow even more central as regulators move toward the risk-based approach to compliance embodied in PAT and QbD. With the door thus open for even broader and deeper use of statistical thinking and methods, industry statisticians and their employers will need not only to rethink their technical skills but also to learn to deploy PAT and QbD. As statisticians take on

their expanded roles, they will need to expand their skills dramatically (See Table 4).

Many of these leadership skills are new to statisticians, and they will have to work to acquire them (Snee and Hoerl (2004)). Other new skills may play into some of the traditional strengths of statisticians. Among the most important leadership skills are the following:

- *Effective leaders not only know how to lead, they also have substantial business and regulatory knowledge.* In their new role, statisticians will need to understand how business works in general, how it works in the pharmaceutical industry, and how it works specifically for their companies. They will therefore need to understand strategic planning (the process for arriving at change objectives) and strategic deployment (the process of implementing strategy).
- *Leaders are comfortable with process and systems thinking.* In many ways, this is the easiest aspect of leadership for statisticians. After all, improving the way work gets done inevitably entails improving processes. Statisticians, steeped in analytic rigor, are uniquely positioned in that regard. Because leaders are also familiar with the proven, structured improvement methods, such as Six Sigma or Lean Sigma, that provide the practical means for improving processes, statisticians have a head start in these statistics-intensive methods. Statisticians are also most strongly positioned to develop sound statistical approaches and cogent quantifications relative to ideas put forth in new regulatory guidance documents, such as the “design space” concept. But it should be remembered that those methods also include such management and leadership skills

as project selection, project management, and results-tracking with clear metrics and milestones.

- *Leaders possess the so-called soft skills in abundance* (Snee (1998)). To be real leaders of critical projects, statisticians must know how to create stakeholders in a project, including those executive stakeholders and champions who are necessary for success. They must become adept at reviewing, coaching, and communicating. They must understand group dynamics, know how to lead teams, and know how to design and facilitate meetings. Projects, no less than grand strategy, require vision and direction for success. Statisticians must not only know how to set such direction but also communicate it concisely and clearly to their teams. In addition, they should be adept at removing barriers, like insufficient resources, lack of training, and inadequate time, that impede success. And they should remember some of those barriers lie in people's psyches—especially in their fear of change—and that the best way to overcome them is through coaching and counseling, not criticism.

With these leadership skills, coupled with technical expertise, statisticians should be ideally positioned to help deploy new risk-based compliance initiatives, to show their organizations where statistical methods can create value, and to create and sustain statistically driven continuous improvement with the aim of cutting costs, speeding time to market, and

lightening regulatory burdens. The challenge is convincing others that statisticians are capable of being in these leadership positions. In a sense, current leaders are being asked to allow some newcomers into the game. This is not easy.

## Pharmaceutical Case Studies

The four case studies discussed below provide a small sample of the types of problems encountered in the development and manufacturing of pharmaceuticals.

### Case 1: Improving Yield for a Pharmaceutical Synthesis

As described in Aggarwal (2006), the yield from the synthesis of a small-molecule pharmaceutical (the API) was lower than desired (~40%). The laboratory decided to optimize the process using DoE. In a sequential experimental design, the initial design (a full factorial) was used to screen for significant factors. A follow-up experiment (a response surface study) was performed over the appropriate region to optimize the process, using factors suggested by the initial experiment. The factors studied in the screening experiment are illustrated in the following half normal plot of experimental results (Figure 5).

Solvent volume, the catalyst loading, and reaction temperature were clearly identified as having an impact on yield. Interaction plots (Figure 6) revealed some of the nature of the effects.

The labs used this information to generate a response surface design (a face-centered central com-

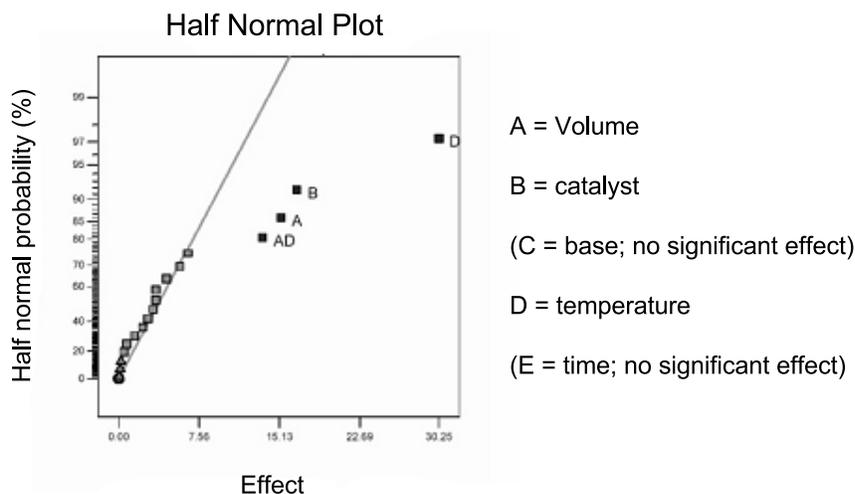


FIGURE 5. Half-Normal Plot of Effects from Pharmaceutical Synthesis Experiment.

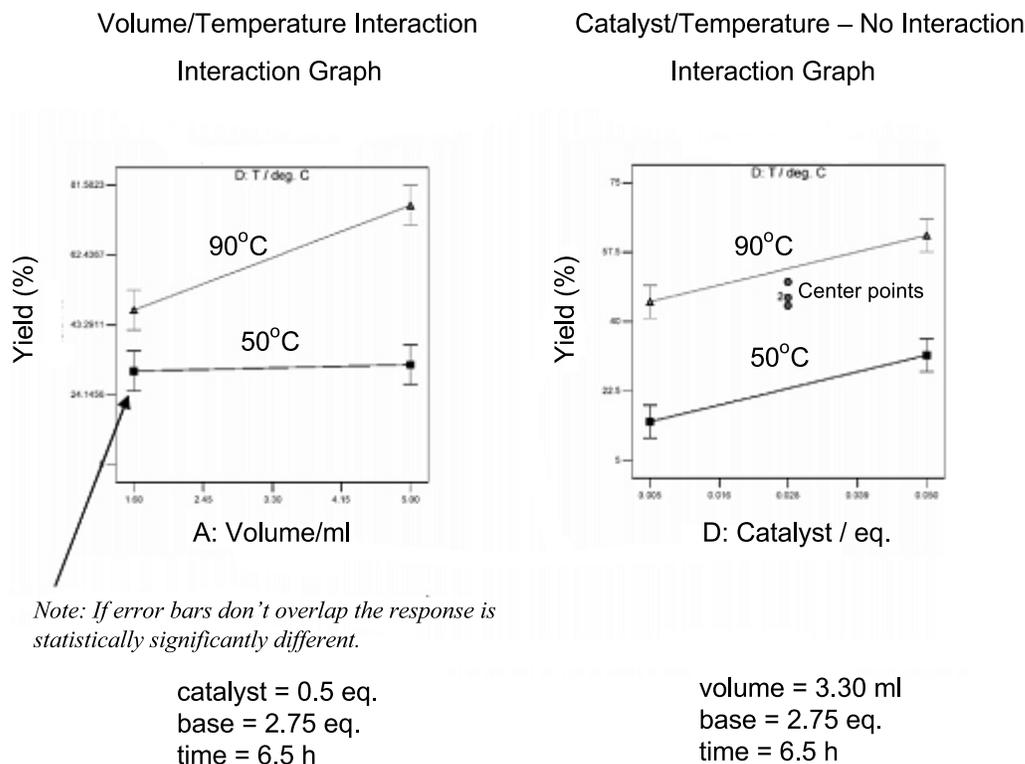


FIGURE 6. Plots for Volume–Temperature and Catalyst–Temperature Interactions.

posite design, to avoid setting levels in excess of the capability of the reaction), using the factors identified in the screening design. The labs also hoped to discover how to manage catalyst load using some of the other factors because the catalyst was expensive. The resulting response surface revealed that yield could be optimized with increases in temperature and solvent volume, while the amount of catalyst could be decreased due to the synergistic impact of these two factors. Final yields were confirmed to be in excess of 90% compared with average yields of approximately 40% that were observed prior to employing DoE. Thus, the lab doubled its capacity, while saving in cost by using less catalyst.

### Case 2: Leadership for Design-Space Issue

As stated previously, the new regulatory concept of “design space” involves creating a multidimensional process capability region that has been demonstrated to provide “assurance of quality”. Recently, in a large, multinational pharmaceutical company, various scientists (process chemists, pharmaceutical scientists, chemometricians, etc.) were meeting to formulate ideas about how to develop an approach to

design-space construction within their company. Seeing this as an opportunity, some statisticians within the company decided to develop a probabilistic risk-based approach to design-space construction to address, in particular, the need to demonstrate “assurance of quality” as required by the ICH Q8 guidance.

The statisticians involved (in both the United States and Europe) worked together as an informal team and separately as individual consultants and members of matrix teams to formulate and build example Bayesian design spaces as defined in (1) in the Emerging Statistical Methods section. This approach was applied to problems in both (small-molecule) pharmaceutical and biopharmaceutical projects. Some prototype programs were written in R and SAS/IML, and then data from experiments were analyzed and presented to scientists and their management. Some external presentations and papers were generated. Eventually many in-roads were made to acceptance by the company scientists of this creative formulation of a design space. A simplified example of one of their reliability-based design spaces is shown in the probability surface plot in Figure 7.

Further progress toward company-wide accep-

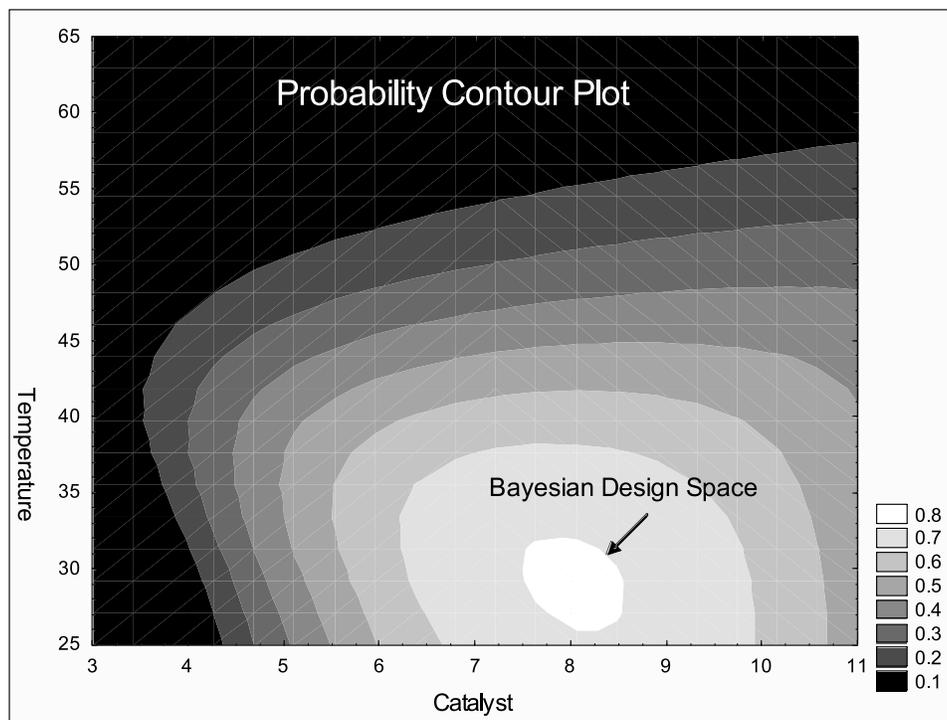


FIGURE 7. Reliability Contour Plot (See Level Scale on Right). The elliptical region in white is a prototype design space. This region has higher relative probability of simultaneously meeting all product-release specifications as a function of the temperature and catalyst factor levels. (Plot obtained from Stockdale and Cheng (2009). Used with permission from the Association for Quantitative Management.)

tance is still ongoing. Some future hurdles remain (e.g., addressing functional data). A definitive measure of success would be for such a design space to be submitted by the company, approved by regulatory authorities, and implemented in the manufacturing plant.

### Case 3: Validation of a Complex Tedious Biological Assay

Validation of biological assays, particularly assays using large numbers of animals, is a tedious and expensive prospect. It's particularly important, as well, to make sure that a minimum number of animals are utilized for these purposes. An animal potency assay was developed for a vaccine product that uses 120 animals per run and takes 6 weeks to perform. The challenge was to obtain the maximum amount of information with minimum use of mice and time. The laboratory chose to include an assessment of the product distribution together with the assay validation and thereby gain valuable information about both assay and product variability. Ten lots of product were strategically identified, which were manu-

factured across a range of processing conditions, in order to best simulate the product distribution. Each lot was assayed twice in the bioassay, in a manner that would allow for independent estimates of inter-run variability throughout the experiment using the design shown in Figure 8.

A reference (Ref) was included in each run to calibrate bioassay results, while a clinically relevant lot (Clin) was included in order to set a specification for commercial materials tested in the bioassay. The reference was tested in duplicate in order to derive a criterion for "parallelism" in the bioassay according to Hauck et al. (2005). The validation results are illustrated in Figure 9.

Excellent precision was observed between replicate runs of the bioassay for all lots, while commercial materials performed as well as or better than lots tested in clinical trials (POC Lots 1–3 in Figure 9). The precision estimated from these data was used together with a minimum threshold to derive a release potency limit for lots of commercial material according to Apostol (2008).

Run									
1	2	3	4	5	6	7	8	9	10
Ref	Ref								
Lot 1	Lot 1	Lot 2	Lot 4	Lot 4	Lot 5	Lot 7	Lot 7	Lot 8	Lot 9
Lot 2	Lot 3	Lot 3	Lot 5	Lot 6	Lot 6	Lot 8	Lot 9	Lot 10	Lot 10
Clin	Ref	Clin	Ref	Clin	Ref	Clin	Ref	Clin	Ref

FIGURE 8. Design for Biological Assay Validation.

#### Case 4: Regulatory Action and Use of Statistical Methods

A brief conceptualized version of a recent incident illustrates the leverage exercised by regulatory authority. A pharmaceutical company manufactures a tablet with two active ingredients. One of the ingredients is present in a very small absolute amount by weight. Small absolute deviations in the actual weight of this ingredient produce large relative (percent) deviations from the targeted dosage. As with most drug products, the specifications for this active ingredient are expressed as an allowable range of percentage of target dose. These ranges are typically 90 to 110% of target dose.

More important for this discussion, the manufacturer is required to report all OOS events to the FDA. These events are monitored and the agency has a series of escalating remedies to enact. Early among these is the right to send inspectors to the manufacturing facility at any time, announced or unannounced. The inspectors must have a stated purpose, but once an inspection begins, their audit trail may lead in many directions, particularly if irregularities are encountered along the way. In the example here, a series of OOS lots of product occurred over the course of a number of months—not every lot failed, but there were enough failures to cause notice. The facility was inspected; the OOS reports were audited, and the conclusion was reached by the FDA that the manufacturer did not understand the root cause of the failures and was therefore presenting an unmitigated risk to the public. Note that this is not a case of direct contamination or of an immediately harmful level of active ingredient. The regulator was principally concerned about the lack of apparent understanding demonstrated by the manufacturer.

The manufacturer's responses to the regulatory concerns were deemed unsatisfactory and the FDA

determined to use its ultimate stricture—seizure of product at the manufacturing site. Federal marshals entered the manufacturing site and seized all lots of the particular product. Manufacturing of the product was halted. The FDA appointed a third party “monitor” to oversee the investigation of root cause, the implementation of process changes, and the assessment of new manufacture postimprovement. The third-party monitor was hired at the expense of the product manufacturer. Additionally, the manufacturer was required to post a substantial bond that would be forfeited in the event of insufficient cooperation and progress.

Where were the statisticians? The ultimate questions in this incident regarded patient safety. One slightly underdosed tablet may not be harmful, but when a medicine is taken daily to treat a chronic ailment (e.g., asthma or diabetes), the potential long-term effects are of chief concern. Therefore, the statisticians were asked to calculate probabilities such as, “How many defective tablets were likely to occur in a monthly supply of 30?” or “How many defective tablets might a patient obtain in a year's supply?” These probabilities depend on the failure rate in the manufacturing process. The underlying statistical questions then become “the best estimate of the tablet failure rate” and “the upper bound on the failure rate.” The data suggest that the tablet failure rate,  $\pi$ , varies from batch to batch. Binomial mixture models are suggested, where  $\pi$  is a random effect associated with variations in the set-up, inputs, and conditions of each manufacturing run.

In terms of uncovering root causes for the failures, a primary question is “When did the problem begin?” This means extensive examination of time-series manufacturing data. An element of statistical interest is that the batch sizes vary and range from hundreds of thousands to millions of tablets,

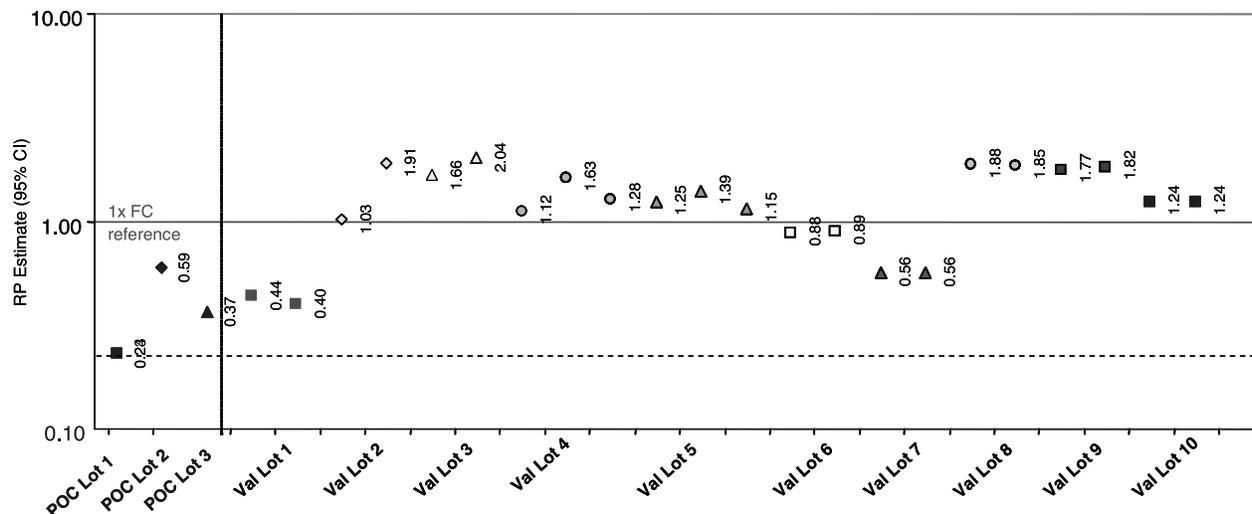


FIGURE 9. Results for Biological Assay Validation Study. (Note: run 4 of the design was repeated due to a performance issue related to the duplicate of the reference; thus, three replicates of lots 4 and 5 appear in the figure.)

and the number of tablets sampled from batches also varies—ranging from 20 to a few hundred. Control-chart techniques were heavily utilized. In addition, a variety of graphical techniques, including box plots and cusums, were helpful in explaining statistical conclusions to both regulators and company senior managers. Identification of a starting point allowed the manufacturer to identify process changes or incidents that occurred in the specified time frame. This generated hypotheses regarding ultimate causes. The statisticians were again involved in helping design experiments that would test those hypotheses. Resolution and prevention were largely engineering considerations. However, an extensively revised monitoring system was put in place—again with heavy emphasis on the use of control-charting techniques, including appropriate training and interpretation. Ultimately, the manufacturer was successful in reinstating their product in the marketplace.

### Summary

Throughout most of the 20th century, pharmaceutical regulation was largely a matter of reactive legislation, but this century has seen the rise of science-based regulatory initiatives, including ICH guidelines on pharmaceutical development, pharmaceutical quality, the pharmaceutical quality system, and the FDA's guidance on Good Manufacturing Practice (GMP), Process Analytical Technology (PAT), and Quality by Design (QbD). These initiatives have brought a new emphasis on process understanding

and quality and the use of statistical methods for both. These regulatory trends, as well as the inherent complexity of pharmaceutical manufacturing, economic pressures, and the increased need for technology transfer, will continue to accelerate the industry's need for sophisticated, statistics-driven approaches to quality and process understanding as well as the statisticians to apply them.

Today, pharmaceutical development, following the discovery of an active pharmaceutical ingredient (API), typically proceeds along several parallel paths, each requiring particular statistical techniques. These tools and statistical methods include Design of Experiments (DoE), screening experiments, optimization studies, regression modeling, process optimization, and robustness studies. Analytical-method development employs such tools as analysis of variance (ANOVA), variance-component studies, method ruggedness studies, and basic statistical techniques, including graphics. In manufacturing, statistical process control (SPC) is used extensively to monitor and improve processes. Statistical techniques found in Six Sigma, Lean Manufacturing, PAT, Design for Six Sigma, and QbD are also increasingly being used to improve processes.

The FDA's encouragement of the pharmaceutical industry to achieve better understanding of manufacturing processes and to quantify the risks associated with out-of-specification product has widened the set of statistical tools to include the use of multivari-

ate mathematical approaches, such as response surface methodologies, process simulation, and pattern recognition tools, in conjunction with knowledge-management systems. These emerging statistical methods are also driving the development of more powerful commercial statistical software, which is enabling nonstatisticians to do their own statistical analyses. Information technology is also making contributions to data mining, database management, and knowledge management, increasing the industry's interest in "enterprise" statistical software that can be used across an organization.

As statistical thinking and methods become even more critical for success in the industry, statisticians have begun to move from their traditional role as passive advisor to a more dynamic role as creator of value. Their role is becoming even more central as regulators move toward the risk-based approach to compliance embodied in PAT and QbD, requiring industry statisticians to rethink their technical skills, learn to deploy PAT and QbD, and acquire new leadership skills commensurate with the increased importance of their discipline within the industry. With those new skills and methods, they can become catalysts for both process-development understanding and product-quality improvement.

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### Appendix

#### Key Abbreviations and Acronyms

Abbreviations/ acronyms	Meaning
API	Active pharmaceutical ingredient
cGMP	Current Good Manufacturing Practice
CMC	Chemistry, manufacturing, and control
DCU	Dose-content uniformity
EMA	European Medicines Agency
FDA	Food and Drug Administration

#### Key Abbreviations and Acronyms (*Continued*)

GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
LC	Label claim
LOA	Limit of agreement
NDA	New drug application
OOS	Out of specification
PAT	Process analytical technology
PhRMA	Pharmaceutical Research and Manufacturers Association
QbD	Quality by design
QC	Quality control
RSD	Relative standard deviation
USP	<i>United States Pharmacopeia</i>

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