

# Statistics in Drug Development

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## 1.1 Introduction

In the past 50 years, the value of medicine has been clearly demonstrated by a longer life expectancy, a lower infant mortality rate, and the higher quality of life many of our senior citizens have been enjoying. Since the introduction of stomach-acid-blocking H<sub>2</sub> antagonist drugs in the late 70's, the number of surgeries to treat ulcer has been greatly reduced. Childhood vaccination has literally wiped out diphtheria, whooping cough, measles, and polio in the U.S. Deaths from heart disease have been cut by more than half since 1950 and continue to decline. Even though we still face great challenges in combating cancer, great strides have been made in treating childhood leukemia. Early detection has led to successful treatment of some types of cancer such as breast cancer. Treatments for schizophrenia and bipolar disorder have allowed many patients to live almost normal lives. A report (2006) on the value of medicine can be found at the Pharmaceutical Research and Manufacturers of America (PhRMA) website.

The use of statistics to support discovery and testing of new medicines has grown exponentially since the Kefauver-Harris Amendments, which became effective in 1962. The Kefauver-Harris Amendments required drug sponsors to prove a product's safety and efficacy in controlled clinical trials in order to market the product. Since the Amendments, the number of statisticians working in the pharmaceutical industry has greatly increased. This increase took another jump when the manufacturing process came under close scrutiny. As we move into the 21st century, the lure and the promise of genomics and

proteomics will further intensify scientists' reliance on statistics. The need to enhance our overall knowledge about diseases, the need to insert more points into the decision-making process, and the need to bring economics into development strategy considerations will undoubtedly present new opportunities for statisticians.

Even in the face of new opportunities, there are many well-established roles for statisticians in the pharmaceutical industry. The term "well-established" is a relative term since new roles will become more established over time. For example, trial simulation and modeling, viewed as new advancements a decade ago, have now become common practice to help design better trials across the pharmaceutical industry.

Concerned that the current medical product development path may have become increasingly challenging, inefficient, and costly, the U.S. Food and Drug Administration (FDA) issued a document in March 2004 entitled "Challenge and Opportunity on the Critical Path to New Medical Products". The document attempts to bridge the technological disconnect between discovery and the product development process. The disconnect is thought to be largely due to the fact that the pace of development work has not kept up with the rapid advances in product discovery. The document addresses three major scientific and technical dimensions in the critical path of product development. The three dimensions relate to safety assessment, demonstration of a product's medical utility (benefit or effectiveness), and the product's industrialization (scaling up). In addition to understanding the challenges, establishing the right standards and developing better toolkits for each dimension will be key to our ultimate success in overcoming the perceived stagnation in getting new drugs and biologics to the market. Statisticians, with their training in quantification and logics, can play a major role in the preparation and the execution of the action plan.

The call for innovation is nothing new for the pharmaceutical industry. The industry as a whole has made great strides in its basic science research in recent years. Cutting edge techniques are being developed on a daily basis to probe into the biologic origin and genetic connection of diseases. The research on microarrays and genomics has produced more data than could be perceived just a few years ago. With the race to unlock the mysteries of many diseases and finding cures for them, statistical support needs to be broadened in dimensions and increased in depth. Time has never been more right for statisticians to work alongside with their colleagues, being discovery scientists, clinical personnel, manufacturing engineers, or regulatory colleagues. The collaboration should not only help transform data to knowledge, but also help use knowledge for better risk-based decisions.

In this chapter, we will briefly cover some traditional statistical support to show how statistics has been used in many aspects of drug development. Our coverage is by no means exhaustive. It is simply an attempt to illustrate how broad statistical applications have been. We will also highlight some areas where a statistician's contribution will be crucial in moving forward, in view of the FDA's Critical Path initiative and the pharmaceutical industry's collective effort to take advantage of the FDA's call for innovation.

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## 1.2 Statistical Support to Non-Clinical Activities

In an eloquent viewpoint article, Dennis Lendrem (2002) discussed non-clinical statistical support. Traditionally, statistical thinking and approaches are more embraced in areas where regulators have issued guidelines. Examples are pre-clinical testing of cardiac liability, carcinogenicity, and stability testing. Recently, Good Manufacturing Practice has also become a subject of great regulatory interest. The latter captured public attention when manufacturing problems created a shortage of the flu vaccines for the 2004–2005 season. By comparison, statistical input in areas such as high-throughput screening, chemical development, formulation development, drug delivery, and assay development is being sought only when the scientists feel that statisticians could truly add value. This mentality could limit statisticians' contributions since researchers will not know how

statisticians could help unless they have previously worked with statisticians or have been referred to statisticians by their grateful colleagues. For example, scientists who are used to experimenting with one factor at a time won't know the value of factorial experiments. Similarly, even though statisticians well versed in Six Sigma and Design for Six Sigma are well aware of the many applications of the Six Sigma principles, they need to actively sell the applications to potential clients.

The non-clinical support model differs from that in the clinical area because of the usually large client-to-statistician ratio. As a result, after a statistician completes a particular job, he/she often looks for opportunity to consolidate the techniques and institutionalize the tools for the client to use on a routine basis. The automation allows statisticians to focus on opportunities for new collaboration and developing new methodologies for applications.

Non-clinical statisticians often work individually with their clients. Lendrem (2002) described them as "pioneers" because of the frequent needs to venture into unknown areas of new technology. Quantifying gene expression via the microarray technology is one such example. Another is industry's (and government's alike) investment in identifying biomarkers for testing mechanism of action of new molecular or biologic entities. In both cases, the findings will have great clinical implications, but the work starts in the research laboratories and our non-clinical statisticians are the first to deal with the need to measure, to quantify, and to validate the measurements from the technical perspective.

Because of the small number of non-clinical statisticians in many pharmaceutical companies, it is useful for non-clinical statisticians to form an inter-company network to benefit mutual learning. Some of this networking has been in existence for some time. In the U.S., a CMC (Chemistry, Manufacturing, and Control) Statistical Expert Team was formed in the late 60's to focus on the chemistry and control issues related to the manufacturing of pharmaceutical products. Another example is the Pharmacogenomics Statistical Expert Team that was formed in the fall of 2003. Both teams are sanctioned by PhRMA and consist of statisticians from major pharmaceutical companies.

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### 1.3 Statistical Support to Clinical Testing

Clinical testing is typically conducted in a staged fashion to explore the effect of pharmaceutical products on humans. The investigation starts with pharmacokinetic and pharmacodynamic studies, followed by proof-of-concept and dose-ranging studies. Some specialty studies such as drug effect on QT/QTc prolongation and drug-drug interactions studies are conducted at this early stage. Common adverse reactions and early signs of efficacy are the objectives of such trials. The early testings, if satisfactory, lead to the confirmatory phase where the efficacy and safety of the product candidate are more thoroughly investigated in a more heterogeneous population.

Despite common statistical principles, different stages of clinical testing focus on different statistical skill sets. For early proof-of-concept and dose-ranging efforts, study designs could be more flexible and the goal is to learn as efficiently and effectively as possible. Adaptations, in terms of dose allocation, early termination, and study population give great flexibility to such trials. Extensive modeling that incorporates accumulated learning on a real-time basis can lead a sponsor to decision points in a more expedited fashion. Because the purpose of this phase of development is primarily to generate information to aid internal decisions, the developers are freer to use innovative approaches as long as they can successfully defend the decisions that become the basis for later development.

By comparison, statistical approaches for the confirmatory phase need to be carefully pre-planned, pre-specified, and followed in order to give credibility to the results. A pharmaceutical sponsor needs to decide *a priori* study designs, primary endpoints, primary analysis population, success criteria, handling of missing data, multiple comparisons, plus

many others. ICH E9 (1998) gives a very detailed description of all aspects of trial design and analysis that a statistician should consider at this stage. When adaptation is planned, the rule needs to be clearly specified in advance. When interim analysis is anticipated, a sponsor's access to the interim results needs to be tightly controlled.

The confirmatory phase is the place where knowledge about a new molecular or biologic entity is solidified to support a target label. The knowledge, along with the approved label, becomes the basis for recommendations to prescribing physicians and the medical community. The confirmatory trials are also the place where the risk-benefit and cost-effectiveness of a new pharmaceutical product are first delineated. The greater number of subjects studied at this stage gives a sponsor a decent chance to study adverse actions that have a rate between 0.1% and 1%. This phase overlaps somewhat with the life cycle management phase where new indications are being explored and drug differentiation is being sought. If there is a post-marketing study commitment, additional studies will be initiated to fulfill the conditions for approval.

Increasingly, statisticians are participating in promotion review and educational communications to the general public. In addition, many statisticians contribute to activities related to pharmacovigilance and epidemiology.

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## 1.4 Battling a High Phase III Failure Rate

The attrition rate of compounds in the pharmaceutical industry is extremely high. Setting aside compounds that fail the preclinical testing, it is generally recognized that less than 12% of compounds entering into the human phase testing will eventually make it to the market place. The rate is a composite figure formed as the product of the success rates of passing the Phase I testing, passing the Phase II testing, passing the Phase III testing, and passing the regulatory review. Among failures at the various stages, Phase III attrition has the greatest impact. This is so not only because of all the accumulated resources expended up to this point, but it is also because Phase III failure represents a great disappointment to the sponsor, leaving the sponsor short of a defensible marketing application.

In a recent article, Chuang-Stein (2004) conducted a root cause analysis of the Phase III failure rate that was reported to be running at the 50% level. This most recent figure is higher than the 32% rate reported in DiMasi, Hansen, and Grabowski (2003). Chuang-Stein attributed the cause to three major factors: the candidate factor, the sponsor factor, and the environmental factor. While we can't dismiss the pipeline problem, and we have admittedly very little control over the behaviors of some corporate decision-makers at the highest level, many of the causes indeed relate to how clinical development is being conducted and how decisions are made to move compounds through different phases of the development. Chuang-Stein discussed what statisticians could do to help reduce the attrition rate at the late stage. One area where the methodology is well developed and statisticians could make immediate contributions is the judicious use of adaptive designs, or at least group sequential designs, in Phase III trials. The goal of such designs is to give the Phase III trials the best chance for success or to terminate them early if the trials are not likely to meet their objectives. Implicit in such designs is the inclusion of more decision points based on interim results to allow evidence-based decisions. The need to incorporate regular decision points is not limited to Phase III testing. It should be part of every stage of the drug development continuum. These decision points serve as reality checks on the long and costly development journey.

The industry is at a crossroad, and changes are critically needed. Statisticians should take advantage of the challenges and fully engage themselves in looking for better ways to support clinical development of pharmaceutical products.

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## 1.5 Do Statisticians Count?

In a soul-searching article, Andy Grieve (2002) asks whether statisticians count. Even though the number of statisticians working in the pharmaceutical industry has increased by 50-fold since the late 70's, Grieve felt that the influence statisticians had in their respective companies had not increased proportionally. Grieve looked at the barriers that prevented statisticians from contributing as much as they could and offered some solutions.

Particularly noteworthy is the assertion that it is the statistician, and not statistics, that is important. Statistics, as a discipline, does not influence, does not persuade, does not design studies, does not analyze data, does not interpret findings, and does not report results. Statisticians are the ones who make the discipline meaningful by doing all of the above. In other words, statisticians, through their own behavior and communication, spread the statistical principles and promote the statistical thinking. So, when we discuss the successful use of statistics in drug development, we need to bear in mind that as statisticians working in the pharmaceutical industry, we need to be the champions for such causes through our passion for the statistics profession.

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## 1.6 Emerging Opportunities

The Critical Path initiative document describes many opportunities to improve the efficiency of product development. We will mention just a few here. On better tools to assess a compound's safety, FDA states the need for new techniques to evaluate drug liver toxicity, new methods to identify gene therapy risk, better predictors of human immune responses to foreign antigens, new methods to further enhance the safety of transplanted human tissues, and efficient protocols for qualifying biomaterials. On better tools to demonstrate the medical utility of a compound, FDA shares the agency's successful experience with biomarkers in HIV infection and duodenal ulcer healing. FDA states the need for more biomarkers and surrogate markers that can guide product development. In addition, FDA discusses the need for better animal models to combat bioterrorism, more clinically relevant endpoints, better imaging technologies, more innovative designs and analysis methods, and the need for implementing the concept of model-based drug development. The latter involves building mathematical and statistical characterization of the time course of the disease and the drug effect, using available clinical data.

The Critical Path initiative document also discusses the need for better methods to characterize, standardize, control, and manufacture medical products on the commercial scale. Since manufacturing expenses could exceed the research and development investment, there is a need for a better validation process that follows the risk-based inspection paradigm advocated by the FDA in recent months. The latter includes more attention to setting specifications and shifting from detailed data analysis to overall process quality assessment. The same philosophy suggests moving toward acceptance of a probabilistic definition, rather than a pass or fail on the manufacturing process. Most important, FDA wants to encourage the manufacturers to integrate state-of-the-art science and technology into their manufacturing processes.

Following the issuance of the Critical Path initiative document, different centers within the FDA have further identified areas for innovations and have presented opportunities to the FDA's Science Board on November 5, 2004. Since May 2004, many workshops have directed at least part of their agenda towards more efficient and effective ways to test and develop new treatments. Common to many of the discussions are the needs to apply quantitative thinking and techniques. Taking the clinical phase of product development as an example, we see that a major emphasis is to use mathematical and statistical models to help guide drug development and approval. The central idea is to pool data from multiple trials to augment our knowledge base and actively incorporate such knowledge in subsequent studies. Interestingly enough, the concept of pooling data has now been

extended to pooling data of drugs that belong to the same class. The pooling of information across companies, while challenging, will undoubtedly facilitate the collective learning of the pharmaceutical industry.

The opportunities for statisticians to make substantial contributions at the strategic level are beyond what one could have imagined 20 years ago. Along with the opportunities come expectations that statisticians will help solve the puzzle faced by modern-day scientists in the pharmaceutical industry.

## 1.7 Conclusion

Statistics, as a discipline, has broadened its scope significantly over the past 20 years. Wherever there is a need for quantification, statistics has a role. The ability to think in terms of variability, to separate signals from noise, to control sources of bias and variation, and to optimize under given conditions, makes statisticians a valuable partner in the development of new pharmaceutical and biological products.

Mining historical data to add to our cumulative knowledge is a low-cost and high-yield activity. Many companies realize the value of this activity and are actively pursuing it. For example, Bristol-Myers Squibb (Pink Sheet, December 13, 2004) formed a discovery toxicology group and retrospectively analyzed approximately 100 development compounds that failed during a 12-year period. Bristol-Myers Squibb hoped to use the acquired knowledge to decide what assays and technology to implement early to reduce compound attrition. Bristol-Myers Squibb concluded that a combination of *in vitro*, *in vivo*, and *in silico* techniques was needed to improve productivity and reduce attrition. According to the same report in the Pink Sheet (December 13, 2004), other pharmaceutical companies have reached similar conclusions.

Data mining is also expected to help us look for better predictors for hepatotoxicity and cardiovascular toxicity such as Torsade de pointes. Data mining examples can go on and on. I can't think of any scientists who are more poised and qualified to lead this data-based learning endeavor than statisticians!

The challenge is definitely on us, statisticians!

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