DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 25

Pharmaceutical Statistics

Practical and Clinical Applications

Sanford Bolton

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Sanford Bolton
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and Allied Health Professions
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To my dear Phyllis

always present,
always sensitive,
always inspirational

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Pharmaceutical Statistics

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A Series of Textbooks and Monographs

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Preface

This book is intended to serve as a practical reference or as an introductory statistical text for students and scientists in pharmacy, pharmaceutical research, and pharmaceutically related industries. This book may thus appeal to scientists in the clinical sciences, physicians engaged in clinical studies, medical students, and researchers in pharmaceutical and cosmetic formulation. I would hope that this book would stimulate the introduction of formal courses in statistics within colleges of pharmacy at both the undergraduate and graduate levels. In particular, it should be immediately useful as a reference and text for scientists in the pharmaceutical industry.

This is not a work on theoretical statistics. For the most part, theory is avoided so that the reader can concentrate his or her energies on applications. Real-life examples are presented with direct application to areas such as quality control, analytical development, biological testing and assay, clinical testing, consumer testing, and pharmaceutical development. I do not mean to imply that theory is not important, but there are many excellent books dealing with statistical theory, and none which are addressed specifically to practical pharmaceutical problems. I hope that this will be a first step in filling that gap.

Most of Chap. 1 through 9, and Chaps. 11 and 15 can be used for an introductory college level course. More or less may be included, depending on the background of the students. The remaining chapters cover specialized topics, and are often more advanced. These chapters are for interested readers and may be used as a reference. Those sections and chapters which cover material of a more advanced nature are designated by a double asterisk (**). Every effort has been made to present these ideas as simply as possible.

No previous statistical education or extensive mathematical background is required. All that is needed is effort and an ability to perform arithmetical calculations (adding, subtracting, multiplying,

dividing, etc.). The use of a pocket calculator or a home computer is highly recommended.

The exercises are an integral part of the book; most of them are meant to give the student practice with the material presented herein. Some exercises, also identified by double asterisks, make use of the material presented, but also attempt to bring forth ideas not explicitly or completely presented in the text. These more difficult exercises should expand the scope of the book.

I would like to thank those who helped make this work possible. In particular, thanks go to Guy Cohen, who carefully reviewed and critiqued my first draft; to Bharati Sanghvi and Mohan Sondhi, who reviewed parts of this book and gave me many helpful suggestions; to the anonymous reviewers whose comments were taken to heart; and to those students who discovered many little ways to improve the book. Peter Cipolla deserves special mention in this regard. A debt of gratitude is owed to Dr. John Fertig, my first mentor, who has always encouraged me in my efforts as a statistician. And to my young artist friend, Lisa Mahmarian, a well-deserved thank-you for the fine illustrations that so charmingly enhance the text.

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Introduction

Statistical techniques have been widely used in many diverse areas of scientific investigation. Although the need for statistical input in the pharmaceutical sciences has always been evident, 20 or 30 years ago its absence posed no immediate or tangible problems. There was no review process to criticize possible poor design or possible lack of optimality. The consumer or the "marketplace" was the final judge of product development. Also, to assign a cost/benefit parameter in terms of dollars to the "abstract" contribution of statistics and statisticians to pharmaceutical development is a difficult concept.

Before proceeding, a few words are needed to describe what is meant by "statistics" in the context of this book. Statistics mean different things to different people. Some persons visualize a statistician as a type of accountant—a caretaker and manipulator of figures. Others think of statisticians as spending their time compiling tables of numbers—as actuaries. Still others view statistics as a way of helping to make decisions, creating order out of a chaos of numbers, often a savior of otherwise uninterpretable data. Actually, all of these concepts contain some truth. Statistics encompass a wide range of endeavors and applications. We will restrict our presentation to a limited view of this field, concentrating on topics which find particular application to pharmaceutical research. These topics include estimation and decision making, and testing of hypotheses. Also, we will describe frequently used statistical experimental designs. Another somewhat advanced topic which will be introduced is formulation optimization.

The statistical process depends on the degree to which uncertainty follows laws of probability. We call the uncertainty "variability." When a new drug is said to be proven superior to previous treatments, based on a series of clinical studies, we have our "fingers crossed." What is meant by "proven" is really based on a belief. The "belief" is not founded on intuition, but is based on objective statistical criteria, which are based on probability. Thus, when we say that the new drug

is more effective than previous treatments, we are really saying that the new drug is "most probably" more effective. The drug development process consists of many separate steps, which eventually lead to the use of the drug in many patients in many clinical locations. The slow and methodical development of new drug entities in today's consumer-oriented environment ensures that the probability is very high that the final product is safe and effective. The process of making predictions based on observations of a small portion of the population (a sample) and applied to a larger population is known as statistical inference. It is this aspect of statistics which will concern us to a great extent.

Statistical applications have gradually become integrated in diverse areas of the great "diversity" of the drug development process. Pharmaceutical research, in its broadest sense, provides one of the most fertile areas for statistical research and applications. The development of drugs is eventually dependent on their safety and effectiveness in living material, particularly in humans. The incredible variability of human response, including the well-known placebo effect, makes the use of statistical input a necessity when assessing drug efficacy and safety in the present scientific environment. Applications of statistical methods are now routinely found not only in clinical studies, but also in the endeavors of pre-clinical, quality control, and pharmaceutical development laboratories, as previously noted. The scientific personnel in these areas are those who now confront and use statistical techniques every day in the pharmaceutical industry.

To precisely identify the reasons for the relatively recent surge and popularity of statistics in the drug development process, as well as to account for the respect which it now commands, is difficult. One could easily pinpoint one major impetus, the close connection between industry and government, particularly the FDA. The FDA now has a well-established statistical group which has made its voice heard loud and clear. No longer are "testimonials" sufficient to get a drug to market. Results from clinical trials, quality control, and pre-clinical studies are usually statistically designed, analyzed, and documented, as evidence of good scientific practice.

With regard to clinical studies, Dr. S. Dubey of the FDA has discussed the statistical documentation for protocols, which include the design, the "hypothesis" to be tested and the patient sample size [1]. He notes that "quantitative" measurements should be used whenever possible and that less objective measurements deserve to be clearly specified. Dr. Dubey states that design factors should be accounted for, and pooling of data from different sources justified, particularly when combining data from multiclinic studies. Statistical methods to be used in data analysis should be documented and clearly presented, and should include a statement of the assumptions necessary for the validity of the analysis. A power analysis, useful for determining sample size, is also

desirable. Finally, he emphasizes the use of summary tables and graphs as an aid in explaining and presenting the experimental results. This attests to the FDA's concern for the quality of data and analysis in FDA submissions.

Although the need for a lucid presentation of data may seem self-evident and, perhaps, not such a great challenge, it is a crucial part of transmitting the message culled from any experiment to a third party. How to best present summaries and "pictures" of the data which clearly relay the intended message is not always immediately apparent. FDA statisticians have made some recommendations in this respect. They also understand the importance and challenges of presenting well thought out, clear data displays [2].

The proper statistical analysis is dependent on study design as well as the nature of the data. The statistical methodology should be clearly documented for clinical studies according to Dr. R. O'Neill of the FDA [3]. He notes, for example, that averaging data may obscure both individual results and time trends, often very relevant to experimental conclusions. He also emphasizes that the statistical model, assumptions, and calculations be clearly presented as part of the statistical documentation of clinical studies. Statistical contributions to protocol design and data analysis will be presented in the discussion of clinical trials in this book.

The above recommendations by FDA statisticians are noted here, not only because such procedures represent good scientific practice (generally accepted by scientists everywhere, including those in the pharmaceutical industry), but to highlight the increased awareness of statistical input into scientific experimentation, particularly where considerable variability exists.

Statistical applications have always been recognized as crucial to quality control procedures, tests, specifications, and definitions. Also in recent years, the application and need for statistical procedures in pre-clinical experiments has been much publicized and researched. Some more far-seeing pharmaceutical companies have been applying statistical methods in these areas for many years. More recent regulatory stimulation as well as increased exposure of the drug development process to the scrutiny of outside public and government interest groups, have stimulated the growth of statistical applications in these areas. Statistics often substantiate, in a quantitative way, the "gut" feeling of the scientist, lending objective documentation to sometimes intuitive insight of experimental results.

Pharmaceutical development and technology is another area which is receiving more attention for statistical applications. In addition to being useful as aids to the decision-making process, statistically derived optimization designs are now being used to find the "best" combination of ingredients with respect to some formulation attribute. Hence, statistics now pervade almost all areas of drug development.

One concept which deserves mention can be thought of, in a sense, as the ethical aspect of statistics. Most of us, especially statisticians, are tired of the cliché concerning the three kinds of lies: "lies, damn lies, and statistics." However, one cannot deny that there are many ways of looking at data. It is not uncommon to find experts disagreeing on the best way to analyze or interpret a set of experimental data. Often, there is no one correct method. Judgment and experience are essential ingredients of the analysis. It would be disturbing, however, if disagreement on the approach or interpretation resulted in disparate and conflicting conclusions. Fortunately, when alternate methods are sound, this is rarely the case. The misuse of statistics, which consists in part of (a) coming to a firm conclusion with poor data due to design or observational flaws, or (b) *selecting* only the data which proves a pre-determined hypothesis, is to be condemned. The statistician is a scientist, and as is the case with all scientists, integrity is key to success, both inward and outward. Data maneuvering or falsification will satisfy only very immediate and temporary objectives.

This book is an attempt to acquaint the student and pharmaceutical scientist—from clinical monitor, to the analytical chemist, to all members of the pharmaceutical research community—with some basic concepts and analyses. The approach is strictly heuristic, and is by no means a systematic theoretical approach. Most examples of problems and data analysis which arise in practice are not simple, often having unexpected wrinkles which invalidate the hoped-for simple analysis and interpretation promised by the elegant experimental design. Most of the time, professional statisticians should be consulted before proceeding with an analysis or publishing the results and conclusion of a study.

To summarize, the aim of this book is to educate the medical and pharmaceutically oriented scientist in statistical usage. If those who read and learn from this book are able to understand and intelligently incorporate some of these statistical ideas into their experimental toolbags, this objective will have been achieved.

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