Introduction to Statistics in Pharmaceutical Clinical Trials

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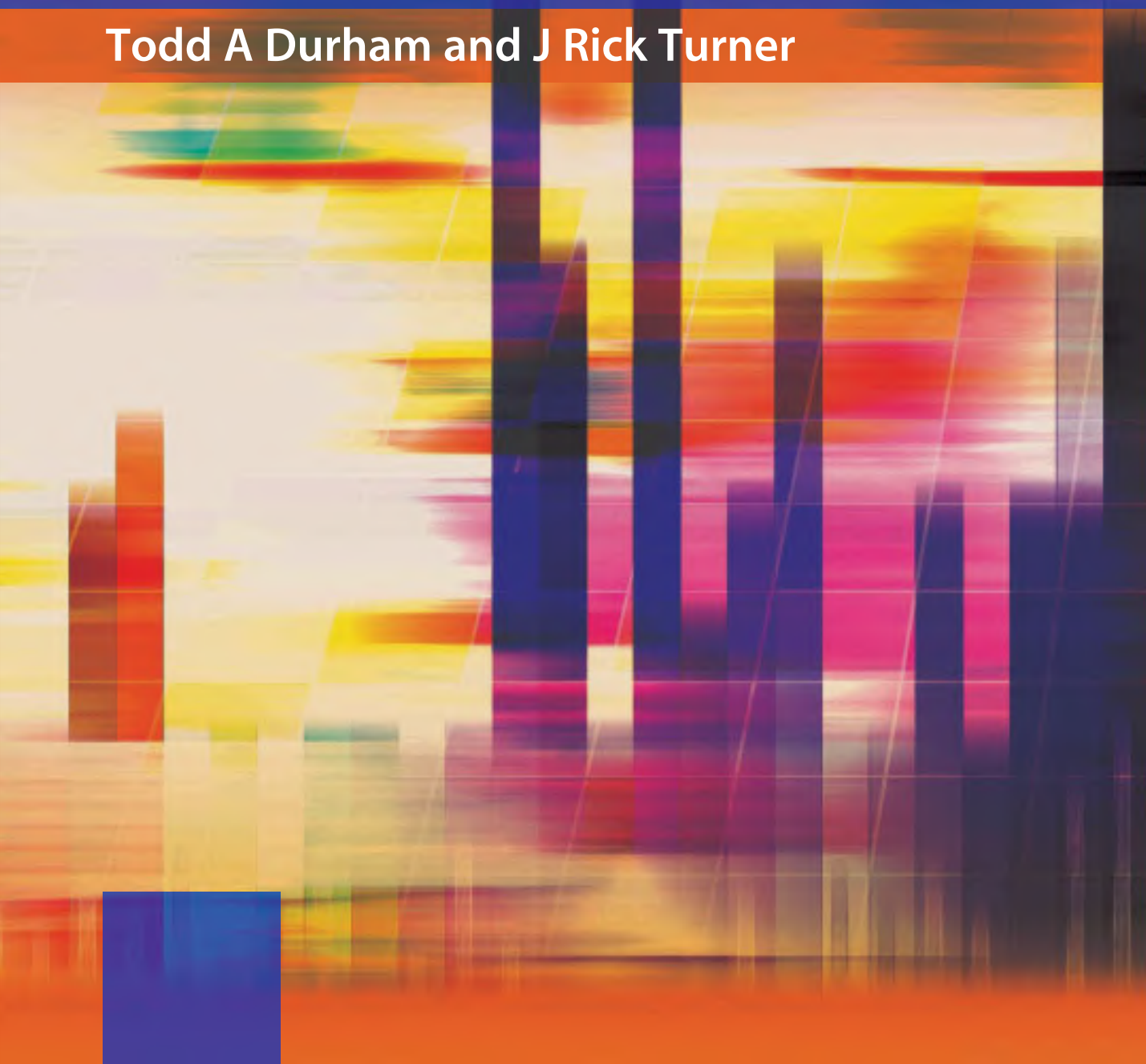

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The drug selections and doses given in this book are for illustration only. The authors and publishers take no responsibility for any actions consequent upon following the contents of this book without first checking current sources of reference.

All doses mentioned are checked carefully. However, no stated dose should be relied on as the basis for prescription writing, advising or monitoring. Recommendations change constantly, and a current copy of an official formulary, such as the British National Formulary or the Summary of Product Characteristics, should always be consulted. Similarly, therapeutic selections and profiles of therapeutic and adverse activities are based upon the authors' interpretation of official recommendations and the literature at the time of publication. The most current literature must always be consulted.

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Foreword

With this introductory text, the authors have managed to de-mystify Statistics for students of pharmacy and clinical research who may be taking their first, or one of their earliest, courses in the subject. Three fundamental departures from the standard treatment of statistics are evident from the start – the way in which "Statistics" is defined, the organization of the book itself, and the use of a single, unifying disease area for illustration throughout the book. The reference to Statistics as "an experimental approach to gaining knowledge" at the start of the first chapter sets the tone for the rest of the book. Statistical concepts are defined and explained relative to their usefulness in clinical decision making. A unique operational definition of the discipline of Statistics is presented that consists of six components, beginning with the posing of a research question and concluding with both a regulatory submission and peer-reviewed publication. This is a far cry from the standard definitions used in most Statistics texts and alerts the reader to the fact that applications and discussions of utility will be intertwined with mathematical concepts and methodologies for the duration of their reading.

Rather than simply providing an exposition of mathematical terms and operators followed by a canvassing of the usual array of statistical tools and techniques, the authors choose instead to follow the product development pathway in organizing their book, showing how statistics plays an important role in providing the ability to move from step to step with objectivity and sound decision making. After an overview of the drug development paradigm that includes the nonclinical, manufacturing, and marketing aspects, the reader is introduced to the fundamentals of experimental design, probability distributions, and hypothesis testing. The reader is then guided through each phase of pharmaceutical clinical trials. From early phase to confirmatory trials, the questions that need to be addressed and the types of data and statistical tools needed to address them are explained and fully illustrated with an antihypertensive treatment example. Note, however, that the straightforward nature of the exposition does not equate to simplicity of subject matter. Nonparametric statistics, noninferiority trials, and adaptive designs all receive mention as the text covers the majority of situations these future researchers are likely to encounter. And unlike many basic statistics texts with a focus on efficacy occupying the majority of the pages, safety analyses receive nearly equal treatment here. Timely safety topics of particular clinical interest, such as QT/QTc interval prolongation and how to design a study to test for this adverse effect, are covered.

Focusing on a potential treatment of hypertension for illustration throughout the book provides consistency and really makes the product development pathway come alive. The reader has the sense of helping move this product from phase to phase, and the example serves to not only illustrate the statistical methods, but also the clinical decision making surrounding the product's development. In addition, the reader is able to accumulate the medical background required to appreciate the data examples in a minimum number of pages, and the example is rich enough so as to not afford any loss of generality with this singular focus.

The dialogue between clinician and statistician is of the utmost importance in the successful execution of a product development program today. The need for strong communication skills, verbal and written, among those involved in this

complex process has never been greater. The authors have provided a text that fully equips students to engage in clear and meaningful dialogue with their clinical colleagues and regulatory counterparts. By focusing on the common goal of learning essential information about experimental products through well-designed and well-conducted studies, and accurately collected and appropriately analyzed data, the reader never loses sight of the fact that statistics are the means to the end, and not the end in themselves. As the authors note on page 191, "Our interest in Statistics, then, is a pragmatic one: The discipline provides the best way currently available to conduct clinical development programs."

I have had the pleasure of working with Todd Durham for over 10 years and I am not surprised in the least with his clear and concise treatment of Statistics in this text. He is known among friends, colleagues, and students for his thoughtful approach to study design and analysis problems, his excellent communication skills, and his great capacity for mentoring and tutoring others. His contributions through this text will enable other classrooms to benefit from his winning style of teaching even when he is not present to lead the discussion himself. Todd is an Adjunct Professor of Clinical Research at the Campbell University School of Pharmacy, and teaches Statistics to students in the Master of Science in Clinical Research program. I am delighted that this collaboration with Rick Turner, the Chairman of the Department of Clinical Research, has proved so successful.

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Preface

This book is an introductory statistics textbook designed primarily for students of pharmacy, clinical research, and allied health professions. It takes a novel approach by not only teaching you how to conduct individual statistical analyses, but also placing these analyses in the context of the clinical research activities needed to develop a new pharmaceutical drug. By taking this approach, we are able to provide you with a unified theme throughout the book and, in addition, to teach you the computational steps needed to conduct these analyses and provide you with a powerful conceptual understanding of why these analyses are so informative. This approach also makes the book well suited to professionals entering the pharmaceutical, biotechnology, and contract research organization (CRO) industries who wish to gain a broader understanding of study design and research methodology in clinical trials. Both target audiences will find this book a useful introduction to the central role of the discipline of Statistics in the clinical development of pharmaceutical drugs that improve the human condition. Important concepts are reinforced with review questions at the end of chapters.

By focusing on the statistical analyses most commonly used in drug development and employing an organizational structure that follows the order in which these statistical analyses are commonly used in clinical drug development, the book shows you how the discipline of Statistics facilitates the acquisition of optimum quality data, that is, numerical representations of relevant information, which form the basis of rational decision-making throughout the drug development process.

Although this book meaningfully integrates the computational aspects of statistics with the overall conceptual objectives for which they are used, we have not included some topics that are traditionally included in introductory statistics textbooks, including linear regression and correlation. We believe that the selected topics and the depth at which they are discussed are appropriate and unique for our intended audience. While we are very happy with the title of the book as it is, the title *The Statistical Basis of Decision-making in Pharmaceutical Clinical Trials* would capture one of the book's major themes extremely well.

The motivation to write this book is directly related to our professional activities. Both of us teach Statistics in the Department of Clinical Research at the Campbell University School of Pharmacy (TD, a professional biostatistician, is also an Adjunct Professor of Clinical Research, and RT is Chairman of this department). The department is located in the heart of North Carolina's Research Triangle Park, one of the world's leading pharmaceutical and biotechnology research centers. Statistics courses in this department are therefore taught in the context of the development of new pharmaceutical and biopharmaceutical products, with the goal of providing a solid knowledge and understanding of the nature, methods, applications, and importance of the discipline of Statistics. It should be emphasized that we are not training our students to be professional statisticians. Rather, we wish them to become familiar with the basics of design, methodology, and analysis as used in the development of new drugs. We aim to convey the following information:

- why, and how, data are collected in clinical studies (to investigate a specific question, using appropriate study design and research methodology)

- how these data are summarized and analyzed (descriptive statistics, hypothesis testing and inferential statistics, statistical significance)
- what the results mean in the context of the clinical research question (interpretation, estimation, and clinical significance)
- how the results are communicated to regulatory agencies and to the scientific and medical communities.

By presenting statistical analysis in a meaningful, integrated, and relevant manner, our students' knowledge and retention of the material is markedly improved. Moreover, their understanding and appreciation of the discipline of Statistics in all of their future scientific endeavors (both academically while studying, and professionally once in the workforce) is considerably enhanced. This book will become the text for the first of two Statistics courses in our Master of Science in Clinical Research program.

It is appropriate to acknowledge here that neither author is a clinician. The first author is a professional statistician and the second a professional educator, medical writer, and research methodologist. We are also both clinical trialists: The first author is experienced in statistical aspects of clinical trials, and the second in writing regulatory clinical documentation. At various points throughout this book, we discuss how the discipline of Statistics provides the rational evidence for making clinical decisions. On several occasions we use hypothetical data, show how statistical analyses of these data and the associated statistical interpretations can form the rational basis for clinical decision-making, and illustrate what the hypothetical clinical decision might be. This is done for educational purposes. Please remain aware, when reading our hypothetical clinical interpretations, that we are not clinicians: We are conveying the logic and importance of incorporating statistical information in the process of clinical decision-making. The crucial role that the discipline of Statistics plays in clinical practice is to provide the information upon which evidence-based clinical practice is based. The most effective drug development programs, one facet of the larger field of clinical research, result from the collaboration of many specialists, including statisticians and clinicians. Actual clinical decisions are, of course, the province of clinicians.

We express our thanks to professional colleagues and students who have supported and informed us during the preparation of this book. Christina De Bono and Kevin Tuley at Pharmaceutical Press have provided constant support and assistance throughout this project, and we are very grateful. Richard Zink provided detailed reviews of several drafts of the manuscript. Finally, our previous students have provided invaluable feedback on lecture material and initial drafts of this book.

Views expressed in this book are those of the authors and Turner Medical Communications LLC, and not necessarily those of Inspire Pharmaceuticals and/or the Campbell University School of Pharmacy.

Todd Durham and Rick Turner
Research Triangle Park, NC, USA
August 2007

Dedications

This book is dedicated to Heidi Durham and Karen Turner, who have been there for us every step of the way. We also thank Rachel, Daisy, Misty, and Mishadow for their wonderful companionship.