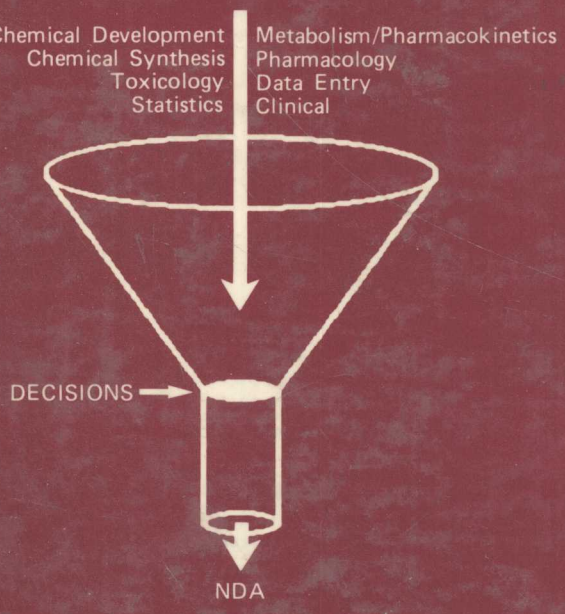
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 34

Clinical Drug Trials and Tribulations



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Clinical Drug Trials and Tribulations

DRUGS AND THE PHARMACEUTICAL SCIENCES

A Series of Textbooks and Monographs

Edited by

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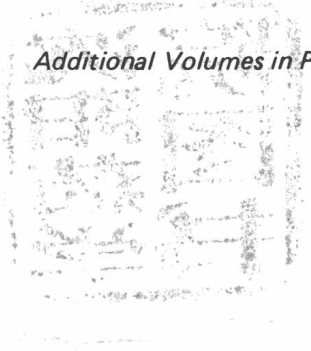

To my wife, Adrian, and my three sons, Jo, Mike, and Dan, who tolerated my absence from our family life when I was out of town in the fascinating pursuit of clinical drug development.

The book is also dedicated to all patients, past, present, and future, who volunteer for participation in clinical drug trials. Without them no drug could ever be shown to be safe or efficacious. These patients are the silent heroes behind every advancement in drug therapy.

Preface

For those individuals fortunate enough to be engaged in it, clinical drug development is a fascinating endeavor. Within the scope of drug development is all the sleuthing of a mystery novel, all the politics of a race for political office, all the power of Wall Street dollars, all of the intrigue of scientific mystery, and all the pathos of a Greek tragedy.

This book is not a "how-to" book. There are already many of those in existence. Rather, this book is meant to address the "whys" -i.e., why certain decisions were made, and what were the consequences of those decisions. In the process, the intriguing tribulations of clinical drug trials emerge.

The number of difficult decisions that must be made during the course of clinical drug development seems endless. In 17 years in the business, I am still faced daily with new tribulations and challenges I have never before encountered. The one rule of clinical drug development must be that things never turn out as designed or expected.

One other aspect of clinical drug development involves teamwork. Despite the significant contribution to alleviate the ills that befall mankind, individual stars seldom emerge from the clinical development team. The tribulations faced in the microcosm of the project team operating within the pharmaceutical industry are evident throughout many of the chapters in this book. In a more macrocosmic sense,

the team becomes industry working with academia and the regulatory authorities. There are highly dedicated individuals working together in each of these areas.

As with any book, several people were instrumental in its production. Linda Cook (who, by marrying during the production of this book, acquired the much more difficult-to-spell name Cocchetto) provided important advice and encouragement throughout. Robert Sutton during the early stages and Paul Stang later on provided the glue that held together all the authors and the editor. My everlasting thanks to all of them. They could write about their own tribulations on the production of a book. Lastly, my thanks to all the authors who delivered chapters . . . it was an imposition on their time and energy, but I believe the result in this case is greater than the sum of the parts.

Allen E. Cato

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Contents

1

The Challenge of the Clinical Development of Drugs

ALLEN E. CATO *Cato Research Ltd., Chapel Hill, North Carolina*

It would be easier for a camel to go through the eye of a needle than for a new chemical entity (NCE) to make its way from synthesis through the tortuous pathway of development to emerge as a marketed new drug. The process involves a steady progression through multiple stages, with treacherous decision points along the way. It is a long, costly, and extremely risky process. Most of all, it is a process that involves the constant percolating of data through rigorous filters strewn with tribulations complicated by the difficulty of making decisions that affect human health when all the facts are not known.

In order to comprehend the magnitude of drug development, it is useful to consider the many different areas that constitute the drug development process. Figure 1 depicts some of the key disciplines that contribute to the process. Information from each of these areas feeds into a common funnel with a filter, where multiple decisions must progressively be made in order for the compound to survive.

Figures 2 and 3 show the process broken down into preclinical and clinical segments. Keep in mind that the process is a dynamic one. The various disciplines listed are constantly interacting with one another. The entire flow of data requires constant feedback and fine tuning. For example, a compound may be considered slightly too toxic for the amount of pharmacological effect it has. This information would be given by the toxicologist to the chemist, who would make