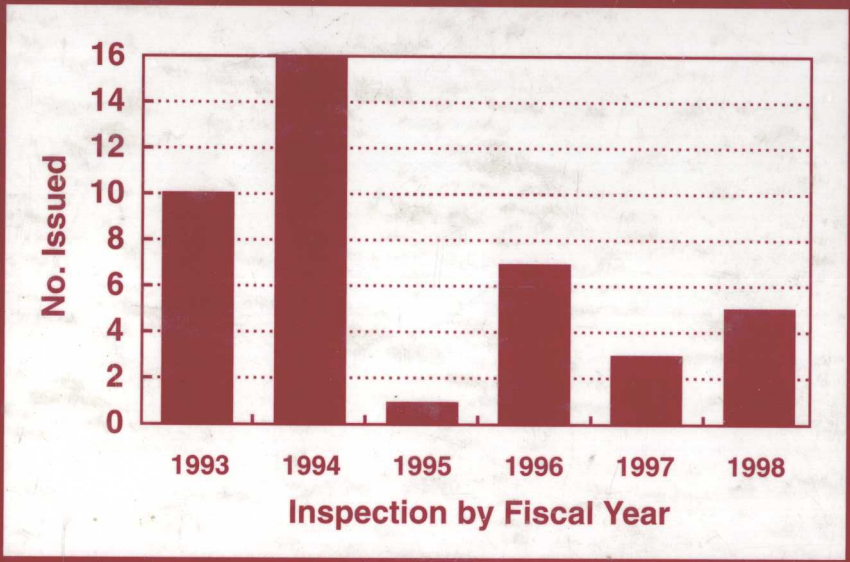
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 104

The Clinical Audit in Pharmaceutical Development



edited by
Michael R. Hamrell

The Clinical Audit in Pharmaceutical Development

edited by

Michael R. Hamrell
MORIAH Consultants
Yorba Linda, California

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Preface

Many books have been written on the regulatory process and how to conduct and design clinical trials, how to interpret clinical data, and how to report on clinical data. However, the basis for valid results from a study and their meaningful interpretation is an audit of the data. If an audit of the data reveals inconsistencies, then the validity of the whole study may be in doubt. No aspect of the clinical drug development process has received more focus and attention recently than the clinical audit.

The intention of this book is to gather the collective expertise of a worldwide group of experts to address the current issues and trends in the validation and auditing of a clinical study. Quality assurance audits, whether for a clinical study or any other process, must be built in at the beginning. One cannot add quality at the end simply by doing some audits and declaring the results valid.

The basis for the quality steps in clinical development is the international set of standards for the conduct and monitoring of a clinical trial known as Good Clinical Practice (GCP). GCP, like the other quality practices for manufacturing (GMP) and nonclinical laboratory studies (GLP), is a set of quality standards for the conduct, data integrity, reporting of findings, and documenting of all activities related to a clinical study. For many years, only the U.S. Food and Drug Administration (FDA) had a formal set of guidelines and expectations for clinical research auditing. GCPs have been adopted and implemented internationally in the

past few years. The implementation of a single product registration procedure in Europe has helped to unify practices in clinical research. There has also been much movement toward harmonization of these standards around the world, through the International Committee on Harmonization (ICH) meetings. As with GMPs and GLPs, the need to independently verify and document the compliance, validity, and authenticity of the data is now a part of the clinical development process as well.

A key element of international GCPs is the role of the independent quality assurance audit. These QA audits are conducted by the sponsor of the study to validate the study results. In contrast, the FDA has always relied heavily on the audit of pivotal clinical studies by its own team of inspectors.

This book covers the concepts of clinical studies and data verification and validation, including the general concept of Good Clinical Practices (GCPs), monitoring, auditing, and the role of the regulatory agencies in the review, validation, and auditing process. Each of these important topics is compared and contrasted among countries around the world. The first chapters deal with an introduction to the clinical development process, the regulations in each major country that address clinical development, and the role of GCPs in the conduct of clinical trials.

The next three chapters describe the various steps and methods for establishing quality in the conduct and clinical studies, discussing the roles of monitoring in the clinical trial process and of the Quality Assurance group. The next two chapters discuss the role and significance of the regulatory agency audit, along with some typical findings and outcomes. Although the FDA has been conducting clinical audits of investigators, sponsors, IRBs/ethics committees, and contract groups for years, most European Union countries and Japan only recently have begun audits of clinical information.

The last chapter discusses how failure in complying with the clinical trial process can lead to questionable practices, which may be the result of inadvertent or deliberate misconduct or outright fraud. The ramifications of these findings in a clinical study are discussed as well as solutions for how to prevent or handle fraud.

Michael R. Hamrell

Contributors

G. Ball, Ph.D. Director, Good Clinical Research Practices, Headley Down, England

W. Bohaychuk, Ph.D. Director, Good Clinical Research Practices, Headley Down, England

Michael R. Hamrell, Ph.D. President, MORIAH Consultants, Yorba Linda, California

Arthur M. Horowitz, Ph.D. President, Arthur M. Horowitz & Associates, Rockville, Maryland

Richard Kiernan, A.A.S., B.S. Vice President and World Wide Director of Compliance, Glaxo Wellcome plc, Research Triangle Park, North Carolina

Marijke Korteweg, Ph.D, Ph.D. Principal Administrator, Technical Coordination, Inspections, The European Agency for Evaluation of Medicinal Products, London, England

Diana B. Lee, M.S. Manager Electronic Data Integrity, Genentech, Inc., South San Francisco, California

Douglas R. Mackintosh, Dr.PH., M.B.A. President, GCPA, Inc., Fairfax, Virginia

Vernette J. Molloy, M.B.A. Vice President, GCPA, Inc., Fairfax, Virginia

Jon R. Wallace Vice President of Quality, Cephalon, Inc., West Chester, Pennsylvania

Frank Wells, FRCP Consultant Pharmaceutical Physician, Chairman of Ethical Issues Working Group, Faculty of Pharmaceutical Medicine of the Royal College of Physicians, Ipswich, England

Tammala Woodrum, J. D. Senior Compliance Associate, Genentech, Inc., South San Francisco, California

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Introduction to the Clinical Development Process

Michael R. Hamrell
MORIAH Consultants
Yorba Linda, California

I. INTRODUCTION

The concept of quality in clinical trials has been a concern for a long time. In recent years, the advent of the formal consideration of a standard set of practice for the conduct of clinical trials has given quality a formal position in clinical research.

In a multinational development program a global clinical plan is essential. Despite the recent harmonization efforts of the International Conference on Harmonization (ICH), there is still some disparity in the regulatory requirements between the United States and other countries. Differences in the practice of medicine and therapeutic alternatives for certain diseases also influence the design and implementation of a global clinical program. However, the common thread of all regulatory agencies in the consideration and approval of new drugs is that the clinical trials be of high quality and that the data can be demonstrated to be valid and reliable (1).

Prior to the initiation of clinical trials, the sponsor must develop sufficient information to show that the proposed clinical studies justify the risk to the subjects involved. In the United States, this information is documented and submitted in the form