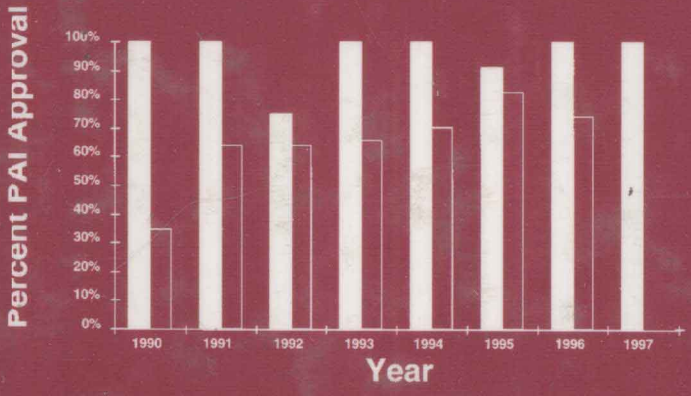
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 93

Preparing for FDA Pre-Approval Inspections



edited by
Martin D. Hynes III

Preparing for FDA Pre-Approval Inspections

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Eli Lilly and Company
Indianapolis, Indiana

MARCEL DEKKER

MARCEL DEKKER, INC. NEW YORK • BASEL

Library of Congress Cataloging-in-PublicationData

Preparing for FDA pre-approval inspections / edited by Martin D. Hynes, III.
p. cm.— (Drugs and the pharmaceutical sciences; v. 93)
Includes index.
ISBN 0-8247-0218-2 (alk. paper)
1. Drugs—Research—Standards—United States. 2. United States. Food and Drug Administration. I. Hynes, Martin D. II. Series.
RM301.27.P74 1998
615'.19—dc21 98-27750
CIP

This book is printed on acid-free paper.

Headquarters
Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution
Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 44-61-261-8482; fax: 44-61-261-8896

World Wide Web
http://www.dekker.com

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above.

Current printing (last digit)
10 9 8 7 6 5 4 3

PRINTED IN THE UNITED STATES OF AMERICA

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To my wife Lynn
and my children Amy and Katie
for their love and support

Preface

During the 1989 generic-drug scandal, the Food and Drug Administration (FDA) discovered that a number of firms had committed fraud in the conduct of bioavailability and bioequivalence studies. It was further found that generic firms had misrepresented study data, facilities, and manufacturing processes. The FDA also concluded that production problems could be traced to inadequate product development. As a result of these findings, the FDA significantly increased its focus on product development activities.

Evidence of this increased focus on the part of the FDA first emerged in the mid-Atlantic region in the form of the 1990 mid-Atlantic Regional Drug Inspection Program authored by Henry Avellon. This regional inspection program led to the development of an FDA-wide pre-approval inspection program that applied to both generic and ethical firms. This program was summarized in the FDA Compliance Program Guidance Manual (7346.832) on Pre-Approval Drug Inspections/Investigations that was officially issued in 1990. This inspection manual for human drugs was revised in 1994. The program was expanded in 1991 to cover animal drugs as well as human drugs.

Introduction of this pre-approval inspection program represented significant change in the approval process for new chemical entities (NCEs) and generic drugs, in that for the first time the field/district compliance branch of the FDA was directly involved in the process of approving drugs for commercial use. Prior to this FDA initiative, only the Center for Drug Evaluation and Research (CDER) reviewed and approved marketing applications. Thus, a new and second hurdle was introduced to the drug approval process. The imposition of this additional hurdle resulted in numerous (and at times lengthy) delays in drug approvals. In the 12-month period ending in March 1991, approval was withheld on 65% of the applications reviewed by the FDA field offices. The rate at which approvals have been withheld has declined over the past several years to approximately 30% in

1997. Although this represents marked improvement over the early years, the rate is still disturbingly high. These delays not only are costly to the firms bringing new drugs to the market but they slow the availability of new therapies to patients in need. It is therefore important to further decrease the rate at which the field offices are recommending delay in approval.

The aim of this book is to help those involved in product development understand FDA requirements for the manufacture of clinical trial material and product development activities. Additionally, it describes what the FDA will look for during the conduct of the inspection.

The book also outlines strategies that various firms have utilized to successfully prepare for pre-approval inspections. These strategies range from activities that can take place in the weeks and months prior to an inspection to longer-term approaches to product development during the years prior to an inspection. The goal of these strategies is to minimize delays in approval.

I am indebted to my quality colleagues at Eli Lilly and Company for their collaboration and dedication. In particular, I wish to acknowledge the contributions of Bill Chiasson, Rick Justice, Jole Rodriguez, and Irv Taylor.

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I. DEFINITION OF A PRE-NEW DRUG APPLICATIONS APPROVAL INSPECTION

A. Inspection History

A pre-approval inspection is a visit by one or more food and drug investigators to review the adequacy and accuracy of the information provided in a regulatory submission (*Compliance Program Guidance Manual, Program 7346.832*). The program was first implemented in the Food and Drug Administration's (FDA's) mid-Atlantic region, which has the largest number of pharmaceutical manufacturing plants in the United States. Leadership for the program during its formative years was provided by Henry Avallone, Joe Phillips, and Richard Davis of the mid-Atlantic office. The first formal communication of the program was in a 1990 publication authorized by Henry Avallone entitled "Mid-Atlantic Region Pharmaceutical Inspection Program."

Shortly thereafter, a formal compliance manual was issued by the agency. This manual, entitled *The FDA Compliance Program Guidance Manual on Pre-Approval Inspections/Investigations* (*Program 7346.832*), was formally published in October 1990. The manual outlined a role for both the Center for Drug Evaluation and Research (CDER) and the Field or District Offices in the drug approval process, thus adding an additional review step to the new drug approval