BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY

Fifth Edition

Volume I: Principles and Practice

Edited by

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ImmunoPharmaceutics, Inc.
San Diego, California

A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS, Inc., New York · Chichester · Brisbane · Toronto · Singapore

Library of Congress Cataloging in Publication Data:

Burger, Alfred, 1905–
[Medicinal chemistry]
Burger's medicinal chemistry and drug discovery. -- 5th ed. / edited by Manfred E. Wolff.
p. cm.
"A Wiley-Interscience publication."
Contents: v. 1. Principles and practice
Includes bibliographical references and index.
ISBN 0-471-57556-9
1. Pharmaceutical chemistry. I. Wolff, Manfred E. II. Title. III. Title: Medicinal chemistry and drug discovery.
RS403.B8 1994
615'. 19--dc20 94-12687

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

Apotex Ex. 1022

CHAPTER NINE

From Discovery to Market: The Development of Pharmaceuticals

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ISBN 0-471-57556-9

1 INTRODUCTION

Through the early years of this century, most drugs or medicines that were sold to the public were little more than home remedies or extracts of various natural products including barks and flowers, that owed their activity more to the alcoholic content of the elixir than to the actual activity of the product. With the advent of modern drug discovery technology and the ability to synthesize chemicals with specific pharmacologic activities, drug development has evolved considerably from that point.

This chapter addresses the process of modern drug development from the point where a candidate drug has emerged from the drug discovery process, up through regulatory approval, and beyond into periapproval and post-marketing activities. Although the development of drugs is becoming an increasingly global endeavor, the focus of this discussion is the U.S. Food and Drug Administration (FDA) and the associated steps in drug development necessary to satisfy the FDA, the regulatory body that holds the power of approval or disapproval for drugs on the U.S. market. The FDA also has statutory authority for approval of other therapeutic/diagnostic modalities such as biologics and devices; however, this chapter will focus exclusively on drug development even though there are many concepts of drug development that are applicable to both biologics and devices.

During drug development, not only does the FDA evaluate the scientific merit of the data presented in support of approval of a drug, but also the labeling or package insert which contains the directions for use of the approved drug. The labeling in-

structs physicians about the mechanism of action of the drug: the specific indication(s) approved for the drug; any special precautions that patients should be advised to take when using the drug; any safety issues that have arisen in animal or human testing with the drug that physicians and patients should be aware of; potential adverse effects and their incidence that have been known to occur in clinical studies and could therefore occur in clinical use; any potential for abuse or addiction; and dosing recommendations (see Table 9.1). The content of this labeling determines how the approved drug can be marketed and promoted. As such, labeling becomes a crucial document that can ultimately define the commercial success of the drug and the blueprint upon which drug development should be planned and executed. The evolution of that drug development process is the starting point of this chapter.

1.1 Evolution of Drug Development

Three factors have played a major role in shaping the evolution of drug development. They are: Regulatory Environment, Scientific Environment, and Industrial/Commercial Environment. Each of these environments has had an impact, but not necessarily at the same time or to the same degree. They have evolved at their own pace.

Table 9.1 Standard Sections of a Package Insert

- Description
- Clinical Pharmacology
- Indications and Usage
- Contraindications
- Warnings
- Precautions
- Adverse Reactions
- Drug Abuse and Dependence
- Overdosage
- Dosage and Administration
- How Supplied

1.1.1 REGULATORY ENVIRONMENT. During drug discovery, only general federal laws, regulations, or guidelines regarding environmental protection, animal care and scientific misconduct govern the basic research process. However, once a chemical becomes a candidate for development to ultimate commercialization, the company developing this product must be aware of the specific laws, regulations, and guidelines that are appropriate to the development of such products so that the results of the investigations conducted will be acceptable to the Food and Drug Administration (FDA) and health regulatory authorities in other countries as necessary.

The involvement of the Federal government in the regulation of drugs and the close relationship of this regulation of drugs with foods, dates back more than 100 years. At that time, the practice of medicine in the United States was generally limited to providing advice on the consumption of various herbs, spices, and other food substances that were taken to achieve the desired result; for instance, maintenance of good health or improved health. Because of this differentiation, the U.S. Department of Agriculture has been the federal agency that was initially responsible for monitoring the potential adverse health effects resulting from adulterated food products. Specifically, this responsibility fell to the Division of Chemistry within the Department of Agriculture and this department has been the entity which is the direct forerunner of the present Food and Drug Administration.

The regulation of drugs in the United States has largely been shaped by three major events. First, in the early 1900s, there were widespread abuses in the food industry, especially the meat packing indus-

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