DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 8

Prescription Drugs in Short Supply

CASE HISTORIES

Michael A. Schwartz

PRESCRIPTION DRUGS IN SHORT SUPPLY

DRUGS AND THE PHARMACEUTICAL SCIENCES

A Series of Textbooks and Monographs

Editor

James Swarbrick
School of Pharmacy
University of Southern California
Los Angeles, California

Volume 1. PHARMACOKINETICS, *Milo Gibaldi and Donald Perrier*

Volume 2. GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICALS: A PLAN FOR TOTAL QUALITY CONTROL, *Sidney H. Willig, Murray M. Tuckerman, and William S. Hitchings IV*

Volume 3. MICROENCAPSULATION, *edited by J. R. Nixon*

Volume 4. DRUG METABOLISM: CHEMICAL AND BIOCHEMICAL ASPECTS, *Bernard Testa and Peter Jenner*

Volume 5. NEW DRUGS: DISCOVERY AND DEVELOPMENT, *edited by Alan A. Rubin*

Volume 6. SUSTAINED AND CONTROLLED RELEASE DRUG DELIVERY SYSTEMS, *edited by Joseph R. Robinson*

Volume 7. MODERN PHARMACEUTICS, *edited by Gilbert S. Banker and Christopher T. Rhodes*

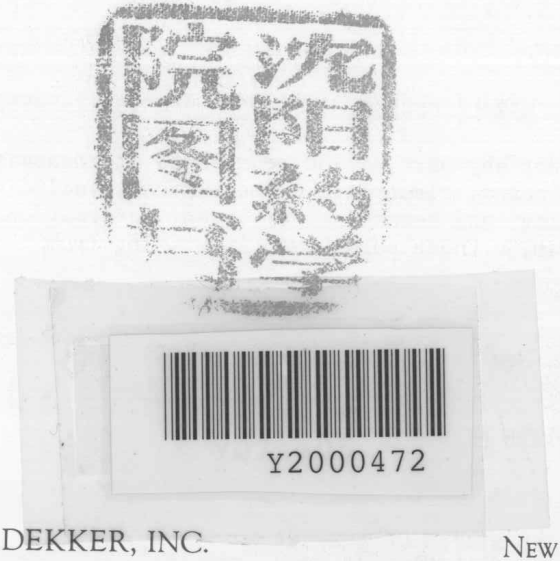
Volume 8. PRESCRIPTION DRUGS IN SHORT SUPPLY: CASE HISTORIES, *Michael A. Schwartz*

Other Volumes in Preparation

PRESCRIPTION DRUGS IN SHORT SUPPLY
CASE HISTORIES

MICHAEL A. SCHWARTZ

College of Pharmacy
University of Florida
Gainsville, Florida



MARCEL DEKKER, INC. NEW YORK AND BASEL

Library of Congress Cataloging in Publication Data

Schwartz, Michael A.
Prescription drugs in short supply.

(Drugs and the pharmaceutical sciences ; v. 8)
Bibliography: p.
Includes index.
1. Drug trade--United States. 2. Drugs--United States--Case studies. I. Title.
HD9666.5.S37 338.4'7'6151 79-24783
ISBN 0-8247-6910-4

MARCEL DEKKER, INC.

270 Madison Avenue, New York, New York 10016

Current printing (last digit):

10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

PREFACE

A shortage in the supply of a life-saving drug can obviously have serious consequences and it was difficult for me to accept the fact that such shortages could occur in the United States. Thus when I was asked to study this situation my initial reaction was "what is there to study?" A little reading and discussions with some colleagues convinced me that it would indeed be worthwhile to investigate the reasons why certain shortages did occur with the hope that doing so would reveal some steps which could be taken to prevent similar occurrences in the future.

The stories behind some of the major supply shortages, or threatened shortages of important drugs are told in these pages.

In doing so I have attempted to keep technical detail to a minimum so that those readers not technically trained may easily understand each situation. Those with more direct concern, pharmacists, physicians and people in the pharmaceutical industry and government will, I hope, appreciate the fact that they can now find these stories in one place for convenient reference. It is also to this latter group that the recommendations are addressed.

Comprehensive coverage of all the shortages which occurred would not have been possible and it was necessary to exercise some selectivity. In fact the case stories included exemplify very well the

important reasons for shortages and the addition of others would have added little to the conclusions.

For suggesting that I undertake this work and for its support, I am most grateful to Dr. Louis Lasagna and the Center for the Study of Drug Development.

A whole host of individuals were extremely helpful in providing factual information or contributing their candid views. Some requested that they not be identified and, while respecting their wishes, I hope they know that their contributions added much to this work. I would like to note the assistance of Dr. John Jennings and his associates at the Food and Drug Administration, Dr. John Adams and Howard Binkley of the Pharmaceutical Manufacturers Association, Jane McGrew of Washington, D.C., Edward Johnson, Chairman of the Opium Policy Task Force, Dr. Michael Stolar of the American Society of Hospital Pharmacists, Dr. Kenneth Barker, Chairman of the National Coordinating Committee on Large Volume Parenterals, Clealand Baker of Burroughs Wellcome, Raymond Chiostri of Inolex Corporation, Dr. Cornelius Pettinga and his associates at Eli Lilly and Co., Dr. Robert Willette of the National Institute for Drug Abuse, Delbert Konner and Tom Gitchell of the Drug Enforcement Administration, Malcolm Lawrence of the Department of State and Donald Kaplan of the Department of Justice. Many hospital pharmacists throughout the country must also be included in this group.

For allowing me the use of the publications and facilities, I must acknowledge the kind cooperation of Eliana Saxton and Cole Werble of F.D.C. Reports and Dr. Richard Hampton of IMS America.

For their patience in deciphering my handwriting, and typing the manuscript, I am grateful to Miss Kristine Merritt and Mrs. Patricia Poczkalski. I must also acknowledge the helpful suggestions of my good friend and colleague, Dr. Daniel H. Murray, and Marilyn Schwartz, both of whom reviewed the manuscript.

Michael A. Schwartz

CONTENTS

Chapter 1

ARE WE RUNNING OUT OF CERTAIN DRUGS?

On December 5, 1974, a U.S. Senate hearing, chaired by Senator Edward M. Kennedy, examined shortages of prescription drugs, both current and impending, in the United States. During the previous year the American public had become accustomed to the word "shortage" as a result of the international oil situation, but this hearing was the first public exposure to similar problems with prescription drugs. It is doubtful that most citizens would have even suspected that this nation, with its large pharmaceutical manufacturing capacity and high standards of quality health care, might be forced to ration certain critical drugs or to use less desirable substitutes because of limited supply. Yet, that is exactly the prospect we faced. As stated by Senator Kennedy in introducing the hearing:

> The consequences and potential consequences are grave. What is lacking is an early warning system that would enable prediction of shortages early enough to allow preventive measures to be taken. It is my hope that today's hearing will spur the development of such a system and a solution to these problems. The alternative is to react only after shortages occur, and the consequences of that may be measured in terms of lives.

Testimony of witnesses from the pharmaceutical industry and government revealed that:

...the inventory of opium in the hands of U.S. processors had fallen to precariously low levels, threatening a shortage of the important analgesic drug codeine.

...the price of quinidine, a drug used in treating heart disease, had doubled over the previous summer allegedly due to a shortage, which, it was speculated, might have been orchestrated by an international cartel.

...a shortage of heparin, an inhibitor of blood coagulation obtained from a pig intestinal lining and for which there is no substitute, had resulted from economic factors in the meat packing industry.

...injectable forms of ampicillin, a penicillin derivative in wide use, had been in short supply for some time because the firm producing most of it had been forced to close down its manufacturing facility for a longer-than-expected time.

Since 1974 additional shortages have occurred. In 1976, injectable penicillin G was in short supply, again because the major producing firm had closed its plant and could not reopen in a new location at the expected time due to unforeseen circumstances. There has also been a rash of shortages of parenteral products due to what have generally been termed "production problems" in the pharmaceutical industry, but which also involved more intensive federal government regulation of manufacturing practices.

Virtually all of the identified shortages have been temporary, and in almost every case (heparin being a notable exception) adequate supplies of substitute drugs have been available. Also, there is no evidence that a single patient died or was significantly harmed because of a shortage of any drug.

On the other hand, there have been instances which suggest that in some cases less than the best possible care was given because a substitute drug was used when the best drug was not available.

Thus, it seems reasonable to raise questions concerning both our current ability to prevent drug shortages and to deal with them should they occur. Do we have an adequate early warning system? Do we have the information needed to project future demand for and

supply of critical drugs? Do we have mechanisms for applying this information? What has been done since the 1974 hearings? What else should be done? The answers to these questions are the subject of this monograph.

Through a critical analysis of the reasons for those shortages which have occurred, it should be possible to identify the types of situations most likely to lead to shortages in the future. Assessment of those measures which have been taken to relieve past shortages and to prevent future shortages should provide society with guidelines for the future.

In the succeeding five chapters are presented case histories of those shortages which were of the greatest national scope or best illustrate the general types of problems involved. Chapters 2, 3, and 4, covering opium derivatives, quinidine, and heparin, respectively, are concerned with the supply of products from natural sources and exemplify one major area of concern. Chapters 5 and 6, dealing with injectable penicillins and other parenteral products, illustrate the general problems involved in producing these particular products and the role of the federal government in regulating their manufacture.

The final chapter presents an analysis of measures taken to gather pertinent information on future projections of drug supply and demand and to monitor shortage situations as they occur. There follows an assessment of our current ability to prevent and deal with shortages and recommendations for further steps which might be taken.

Before turning to the specific cases, it is useful to define the terms of reference and to provide some background on the U.S. pharmaceutical industry and the Food and Drug Administration, which is the primary federal agency regulating the industry.

WHAT IS A SHORTAGE?

Webster defines a shortage as "deficiency in the amount required, a deficit." This definition cannot, however, be applied to prescription drugs in a completely straightforward manner. It seems

clear that where a single drug is the only treatment for a particular condition, and the amount of drug is less than required to treat all of the patients, there would exist a well-defined shortage of that drug. Such unambiguous cases are rare, however. In most instances, although a particular entity may be the "drug of choice," i.e., the most desirable treatment, other drugs can be substituted. In some cases the use of the substitute may entail greater risk or may cost several times more than the unavailable drug. Should these situations also be designated as shortages?

Even less clear is the case where a particular dosage form of a drug is in short supply. For example, the injectable form may become unavailable while the oral form is plentiful. Should this be considered a shortage if the oral form can be substituted? Consider also the situation where the shortage is apparent only at the manufacturer level, e.g., shortage of a particular raw material, but for the moment a plentiful supply of marketed drug for the patients who need it; while this situation may pose a threat of shortage at some future time, should no new supply of raw material become available, it might not be considered a shortage in the same light as the cases mentioned earlier.

A particular drug may be in short supply in one part of the country but be plentiful in another during a particular period. Is this a real shortage?

For the purposes of this monograph, all of these cases will be considered as shortages by applying the general criteria that a shortage of a drug exists when a physician cannot have immediately available his choice of therapy for a patient in the dosage form and quantity desired and that a shortage is threatened when a manufacturer has insufficient inventory of either raw materials or finished product to meet projected demand.

Since the ultimate purpose of this monograph is to focus attention on the prevention of future shortages, it is necessary to review those cases which have posed a threat of shortage even though the shortage never reached the patient care level.

THE PHARMACEUTICAL INDUSTRY

The manufacture of drugs and drug products in the U.S. is carried on by some 700-800 companies, of which only about 300 have twenty or more employees. Included in this number are many firms that produce only proprietary products (nonprescription drugs). The ethical pharmaceutical industry producing prescription drugs is much smaller and more concentrated. In 1973, for example, only 18 companies (with sales over $100 million each) accounted for 73% of the ethical drug domestic market. The industry is represented by the Pharmaceutical Manufacturers Association (PMA) which has 130 members.

Worldwide sales of ethical pharmaceuticals by U.S. firms totaled $10.5 billion in 1974, an increase of over 14% from the previous year. The growth rate of U.S. sales exceeded the growth of the Gross National Product by an average of 15% between 1967 and 1974, with little of the increase being the result of inflation, since manufacturers' prices for prescription drugs remained essentially constant during that period.

International sales of ethical drugs by U.S. companies showed much greater percentage increases over the same seven-year period. Whereas foreign sales accounted for 29% of the total in 1967, they reached 38% in 1974. Industry representatives believe, however, that in the future differences in growth rates between foreign and domestic sales will diminish.

It has been estimated that annual U.S. ethical pharmaceutical expenditures will be $14.4 billion by 1980 and $17.5 billion by 1985, compared with $11 billion in 1975.

The pharmaceutical industry is considered to be highly profitable. In 1974 drugs ranked first out of 40 manufacturing industries in profits as a percent of sales and second in return on net worth.

The industry is among the most research intensive, having the highest ratio of research and development (R&D) expenditures to sales of any industry not linked to the defense-space sector. In 1975 the industry spent about $1 billion on R&D, and for the past decade R&D

expenditures have remained consistently between 8% and 9% of global sales. About two-thirds of the new drug entities introduced worldwide since 1941 have originated in the U.S.

The pharmaceutical industry is also one of the most highly regulated. Its research efforts, particularly clinical testing of potential new drugs, manufacturing processes, quality control and marketing practices, are all subject to close scrutiny by government agencies. According to PMA, in 1973 selected member companies spent $100 million for quality control activities, and 82% of this expenditure was made by companies with sales of at least $100 million.

FOOD AND DRUG ADMINISTRATION (FDA)

The Food, Drug and Cosmetic Act of 1938 required that before a drug product could be marketed there must be approval of a New Drug Application by the FDA. The requirement at that time, and until 1962, was that the safety of the product for human use be demonstrated. In 1962 amendments to the law added the requirement that the drug product be proven efficacious as well as safe. Also added to the law at that time was a section on "current good manufacturing practices" (CGMP).

Regulations implementing the CGMP first appeared in June 1963 and were revised substantially in 1971. Further revisions were proposed in the Federal Register on February 13, 1976 for comment and have not been finalized at the time of this writing.

Prior to the 1962 amendments FDA could declare a drug product to be adulterated only if it lacked the identity, strength, quality, or purity it purported to possess. The new law and implementing regulations enabled the FDA to apply the adulteration sanction if the conditions under which the drug was manufactured, processed, packaged, or stored were inadequate, even when there was no defect in the product itself.

The CGMP regulations have grown in length over the years, but, more important, have had an impact in some of the recent drug shortages. This influence will be considered in the specific cases.

In carrying out its responsibilities, the FDA conducts inspections of manufacturing plants, tests production samples, and may seize products considered to be adulterated. The agency works with manufacturers in recalling products found, after shipment, to be adulterated. While the FDA itself may not order a manufacturer to recall a product, when there has been shown to be a clear cut problem, the manufacturer usually initiates the recall voluntarily.

For certain classes of drugs each batch must be "certified" by the FDA prior to marketing. This provision applies to antibiotics, vaccines, and insulin products. The FDA maintains extensive laboratory facilities in which these products as well as samples from inspections and other materials are tested.

An understanding of the nature of the industry and its interaction with the FDA is critical to appreciation of the respective roles each has played in relation to drug shortages and will continue to play in the future. This will become clearer as the individual case histories are presented and will be seen as an important factor in assessing our current status and future prospects.

Chapter 2

LICIT OPIUM

Illegal traffic in, and use of, opium and drugs derived from it, particularly heroin, has been well publicized. Less well appreciated is the fact that relatively large amounts of morphine and codeine, both derived from opium, are used throughout the world and are generally considered to be essential drugs in the treatment of pain.

In 1972 it became apparent that the U.S. faced a potentially critical shortage of these drugs. The inventory of opium in the warehouses of the three firms that process it had dropped from the normal 12-month level to less than a five-month supply. Demand for codeine had been increasing rapidly in the U.S.; poor crops in India, the major supplier of opium, had reduced the amount available for import. Turkey had banned cultivation of the opium poppy to prevent diversion into illegal channels. The Soviet Union, normally producing enough opium to meet its own needs, suddenly began buying on the world market. All these factors contributed to the reduced inventory in the U.S., and it was forecast that we could run out of opium drugs within two years.

Fortunately, steps were taken to relieve the shortage, and it is now projected that future demand for at least the next few years will be easily met. The opium shortage, however, is a good example