HANDBOOK OF Pharmaceutical Manufacturing Formulations

Sterile Products

VOLUME 6

Sarfaraz K. Niazi

CRC PRESS

Boca Raton London New York Washington, D.C.

Library of Congress Cataloging-in-Publication Data

Niazi, Sarfaraz, 1949–
Handbook of pharmaceutical manufacturing formulations / Sarfaraz K. Niazi.
p. cm.
Includes bibliographical references and index.
Contents: — v.6. Sterile products.
ISBN 0-8493-1751-7 (alk. paper)
1. Drugs — Dosage forms — Handbooks, manuals, etc. I. Title

RS200.N53 2004
615'19—dc21

2003051451

International Standard Book Number 0-8493-1751-7
Library of Congress Card Number 2003051451
Printed in the United States of America 1 2 3 4 5 6 7 8 9 0
Printed on acid-free paper

Dedication

To Professor Shamsuz Zoha, my first pharmacy teacher, who inspired many with his passion for the profession and for science

Preface to the Series

No industry in the world is more highly regulated than the pharmaceutical industry because of potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity (amortized over the cost of all molecules racing) to final regulatory approval is a staggering $800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. In the year 2004, it is anticipated that the industry will spend about $20 billion on research and development. The generic market of drugs as the new entities come off patent is one of the fastest growing segments of the pharmaceutical industry, with every major multinational company having a significant presence in this field.

Whereas many stages of new drug development are inherently constrained with time, the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced with appropriate knowledge by those who have mastered the skills of pharmaceutical formulations. The *Handbook of Pharmaceutical Manufacturing Formulations* is the first major attempt to consolidate the available knowledge about formulations in a comprehensive, and by nature a rather voluminous, presentation.

The book is divided into six volumes, based strictly on the type of formulation science involved in the development of these dosage forms: sterile products, compressed solids, uncompressed solids, liquid products, semisolid products, and OTC products. The separation of OTC products even though they may easily fall into one of the other five categories is made to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of product, and of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of products into these six categories.

Each volume includes a description of regulatory filing techniques for the formulations described. Also included are the current regulatory guidelines on cGMP compliance specific to the dosage form. Advice is offered on how to scale up the production batches.

It is expected that formulation scientists will use this information to benchmark their internal development protocols and cut the race to file short by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a close paradigm when it comes to selecting formulations — "not invented here" perhaps reigns in the mind of many seasoned formulations scientists subconsciously when they prefer to choose only a certain platform for development. It is expected that with the quick review of possibilities available to formulate made available in this book, scientists will benefit from the experience of others.

For the teachers of formulation sciences, this series offers a wealth of information. Whether it is a selection of a preservative system or the choice of a disintegrant, the series offers a wide choice to study and rationalize.

Many have assisted me in the development of this work that has taken years to compile, and I thank scores of my graduate students and colleagues for their help. A work of this size cannot be produced without errors, although I hope that these errors do not distract the reader from the utility of the book. I would sincerely appreciate if readers point out these mistakes for corrections in future editions.

Sarfaraz K. Niazi, Ph.D.
Deerfield, Illinois

Preface to the Volume

The Handbook of Pharmaceutical Manufacturing Formulations: Sterile Products (HPMF/SP) is written for the pharmaceutical scientist and others involved in the regulatory filing and manufacturing of new sterile products. No other area of regulatory compliance receives more attention and scrutiny by regulatory authorities than the regulation of sterile products, for obvious reasons. With the increasing number of potent products, particularly the new line of small protein products, joining the long list of proven sterile products — mainly parenteral and ophthalmic products — the technology of manufacturing sterile products has evolved into a very sophisticated industry. The entry barrier to this technology is much higher compared with those for other dosage forms. Consequently, the cost of production remains high as well. In recent years, regulatory agencies around the world have taken very serious notice of the deficiencies in the manufacturing specifications of the active raw material intended for parenteral administration. New guidelines for the API and aseptic processing of sterile products are the main issues of concern today for manufacturers. This volume of *HPMF/SP* does not delve into details related to starting material issues. Of interest in this issue are formulations of sterile dosage forms, regulatory filing requirements of sterile preparations, and cGMP compliance, all of which are tied together in the final preparation of the Chemistry, Manufacturing, and Control (CMC) sections of regulatory applications.

Chapter 1 describes the specifications of a manufacturing facility to manufacture compliant sterile products. Chapter 2 outlines the New Drug Application (NDA) or ANDA (Abbreviated New Drug Application) filing requirements of sterile products. Chapter 3 describes in detail the layout of formulations provided in the book. This chapter must be thoroughly examined to make the best use of this book. Because the intent of the information provided in this book is to help the formulator develop a product for regulatory filing, boilerplate details are left out. Chapter 3 provides these details and also makes strong recommendations on how the formulator can benefit from the information available from suppliers of components and chemicals used in the formulation.

These three chapters are followed by the body of the book, which provides an alphabetical presentation of formulations of pharmaceutical products based on their generic names. There are three types of formulation entries. In the first type, both the bill of materials and manufacturing directions are provided. This type is further composed of two types, wherein greater detail is provided for some products. This differentiation is intentional because the common details are often omitted in subsequent presentations. The second type of formulations is provided with bill of materials only. This may include products for which the manufacturing directions are obvious to a prospective manufacturer, particularly in light of the details already provided for similar products elsewhere in the book, and also those products for which such information is not readily available. The third category of formulations includes experimental formulations, which may not yet have been commercialized or received regulatory approvals. These formulations are included to show to the formulation scientist unique opportunities that exist for the chemical entity in question.

Formulations of biotechnology-derived drugs are provided with some additional details and remain restricted to declaration of composition, yet they provide a good overview of the complexities involved in such formulations.

In consolidating the details of formulations, efforts have been made to present them in as unified a form as possible; nevertheless, some nonuniformities exist because of the large variety of presentations possible for the wide diversity of formulations presented in the book. A limited number of products intended for veterinary use are also included. These products are subject to cGMP compliance similar to that for human products.

The formulations provided here meet the *4S* requirements:

- *Safety.* This is an important issue for parenteral products; the choice of excipients is limited by this consideration. In most of the formulations, the ingredients are fully approved by the regulatory authorities; in some formulations, the active drug moiety may have been banned in some countries, for example, dipyrone.
- *Sterility.* The compositions presented are fully sterilizable either by terminal treatment or by aseptic processing; where preservatives are added, these are in sufficient quantity to fulfill the dedicated function.
- *Stability.* Besides the rigor of treatment in rendering a product sterile, incompatibility issues may render a sterile product prone to instability.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.