HANDBOOK OF
Pharmaceutical Manufacturing Formulations

Over-the-Counter Products

VOLUME 5

Sarfaraz K. Niazi

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Dedication

Dedicated to the memory of Dean Allen I. White

Preface to the Series

No industry in the world is more highly regulated than the pharmaceutical industry because of the potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity to final regulatory approval is a staggering $800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. It is anticipated that the industry will spend about $20 billion on research and development in 2004. Because patent protection on a number of drugs is expiring, the generic drug market is becoming one of the fastest growing segments of the pharmaceutical industry with every major multinational company having a significant presence in this field.

Many stages of new drug development are inherently constrained by time, but the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced 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 into a comprehensive and, by nature, 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 over-the-counter (OTC) products. Although they may easily fall into one of the other five categories, OTC products are considered separately to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of the product; 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 pharmaceutical products into these six categories. Each volume includes a description of regulatory filing techniques for the formulations described. Also included are regulatory guidelines on complying with Current Good Manufacturing Practices (cGMPs) specific to the dosage form and 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 reduce the time required to file by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a fixed paradigm when it comes to selecting formulations: "Not invented here" perhaps is kept in the back of the minds of many seasoned formulations scientists when they prefer certain platforms for development. It is expected that with a quick review of the formulation possibilities that are made available in this book such scientists would benefit from the experience of others. For teachers of formulation sciences this series offers a wealth of information. Whether it is selection of a preservative system or the choice of a disintegrant, the series offers many choices to study and consider.

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

Preface to the Volume

The *Handbook of Pharmaceutical Manufacturing Formulations: Over-the-Counter Products* is written for the pharmaceutical scientist and others involved in the regulatory filing and manufacturing of new OTC products. Because of the wide variety of products involved, from those bordering on cosmetics to proton pump inhibitors, the OTC products are manufactured by the most sophisticated global manufacturers as well as small one-room makeshift manufacturing houses.

The OTC products comprise a special category of healthcare products in that they can be dispensed without prescription, the rationale being that the use of these products does not expose patients to serious risks associated with side effects even if some misuse or overuse of these products occurs. The OTC category includes three types of products:

- Products that require full filing with the U.S. Food and Drug Administration (FDA) for marketing approval (the NDA/NADA or aNDA/aNADA process) including products or compositions not included in the monographs (see below) or administered in controlled release formulations
- Products that do not require filing with the U.S. FDA because they comply with the monographs issued by the U.S. FDA in its *Code of Federal Regulations* (CFR)
- Products that fall under the category of grandfather products which have been in use prior to the 1960s and have not been specifically excluded by the FDA; not all grandfather products fall under the OTC category — only those that are Generally Regarded As Safe (GRAS)

The U.S. FDA provides excellent support through its OTC website (http://www.fda.gov/cder/otc/index.htm) and formulators are highly encouraged to make use of the information available, particularly the updates in the monograph label requirements and withdrawal of approvals of formulations.

With the safety of consumers in mind, the U.S. FDA is in the process of establishing guidelines for all OTC products. Although the U.S. FDA began this work over three decades ago, much remains to be done. The U.S. FDA process begins with the issuance of Proposed Rules; this notification is like a warning (or advice) to the industry that this category of products is now under U.S. FDA watch. Often years go by before Proposed Rules are published in the *Code of Federal Regulations*. The Proposed Rules include not only identification of approved active ingredients but also inactive ingredients that are deemed compatible with the active ingredients and safe for consumers. The Proposed Rules are subject to criticism by the industry healthcare practitioners and consumers. After receiving these comments over what can be a period of several years, the U.S. FDA issues Final Rules on a specific category of products; these become official on the date of publication in the *Code of Federal Regulations*. In many cases, however, the U.S. FDA issues subsequent rules either to delay application of Final Rules or to modify the Final Rules if new information has become available.

The Final Rule requirements have primarily been applied to products on the market and a newcomer is well advised to study competitor products for market leaders as ample opportunities are available to innovate these products. Examples include the Tylenol® Hot Therapy products and loratidine tablets that dissolve in the mouth and do not require water. I foresee more such products entering into the ever-competitive OTC market.

It is imperative that any prospective entry into the OTC market should begin with a thorough consultation of the Final Rules; an examination of Proposed Rules and notifications to issue Proposed Rules is also helpful in determining what rules are about to become Final Rules. Reviewing the discussions about Proposed Rules that have affected their finalization can be very helpful in understanding the relevant issues of safety, efficacy and labeling. Because the marketing of OTC products requires a large investment in marketing efforts, it is prudent to develop a clear understanding of the legality of formulations and claims made in the initial phases of product development.

A large number of products on the market today are not covered by the U.S. FDA monographs but does that make them legitimate? This is the often-asked question. The U.S. FDA has limited resources to tackle everything that is out there on the market. When emergencies arise, however, the U.S. FDA reacts immediately as it did in the case of phenylpropanolamine, pseudoephedrine and recently, kava kava. Here are some broad guidelines adopted by the U.S. FDA for the most commonly abused categories of products:

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