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Sarfaraz K. Niazi



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Dedication

To August P. Lemberger

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

Liquid products, for the purpose of inclusion in this volume, include nonsterile drugs administered by any route in the form of solutions (monomeric and multimeric), suspensions (powder and liquid), drops, extracts, elixirs, tinctures, paints, sprays, colloids, emulsions, aerosols, and other fluid preparations. Sterile liquid products are presented in another volume. Whereas liquid drugs do not share the compression problems of solid dosage forms, the filling problems of powder dosage forms, and the consistency problems of semisolid dosage forms, they do have their own set of considerations in the formulation and manufacturing stages. The considerations of prime importance for liquid drugs include solubility of active drugs, preservation, taste masking, viscosity, flavoring, appearance, and stability (chemical, physical, and microbiological), raw materials, equipment, the compounding procedures (often the order of mixing), and finally the packaging (to allow a stable product to reach patients). Suspensions present a special situation in which even the powder for reconstitution needs to be formulated such that it can be stable after reconstitution; therefore, limited examples are included here.

Chapter 1 in Section I (Regulatory and Manufacturing Guidance) describes the practical details in complying with the current good manufacturing practice (cGMP) requirements in liquid manufacturing. This chapter does not address the specific cGMP parameters but deals with the practical aspects as may arise during a U.S. Food and Drug Administration (FDA) inspection. This includes what an FDA inspector would be looking into when auditing a liquid manufacturing facility.

Chapter 2 describes the stability testing of new drugs and dosage forms. Drawn from the most current International Conference on Harmonization (ICH) guidelines, this chapter describes in detail the protocols used for stability testing not only for new drugs but also for new dosage forms. The chapter is placed in this volume because stability studies are of greater concern in liquid dosage forms; however, keeping in mind the overall perspective of the series of this title, this chapter would apply to all dosage forms. Again, emphasis is placed on the practical aspects, and the reader is referred to official guidelines for the development of complete testing protocols. It is noteworthy that the ICH guidelines divide the world into four zones; the discussion given in this chapter mainly refers to the U.S. and European regions, and again the formulator is referred to the original guideline for full guidance. Stability studies constitute one of the most

expensive phases of product development because of their essential time investment. As a result, formulators often prepare a matrix of formulations to condense the development phase, particularly where there are known issues in compatibility, drug interactions, and packaging interactions. The FDA is always very helpful in this phase of study protocols, particularly where a generic drug is involved. It is also a good idea to benchmark the product against the innovator product. However, one should understand clearly that the FDA is not bound to accept stability data even though it might match that of the innovator product. The reason for this may lie in the improvements made since the innovator product was approved. For example, if a better packaging material that imparts greater safety and shelf life is available, the FDA would like this to be used (not for the purpose of shelf life, but for the safety factors). In recent years, the FDA has placed greater emphasis on the control of Active Pharmaceutical Ingredient (API), particularly if it is sourced from a new manufacturer with a fresh DMF. Obviously, this is one way how the innovator controls the proliferation of generic equivalents. The original patents that pertain to synthesis or manufacturing of the active raw material may have been superseded by improved processes that are not likely to be a part of a later patent application (to protect the trade secret because of double-patenting issues). The innovator often goes on to revise the specifications of the active pharmaceutical ingredient to the detriment of the generic manufacturer. However, my experience tells me that such changes are not necessarily binding on the generic manufacturer, and as long as cGMP compliance in the API is demonstrated and the impurities do not exceed the reference standard (if one is available), there is no need to be concerned about this aspect. However, manufacturers are advised to seek a conference with the FDA should this be a serious concern. At times, the manufacturer changes the finished product specification as the patents expire or reformulates the product under a new patent. A good example of this practice was the reformulation of calcitriol injection by Abbott as its patent came to expiry. The new specifications include a tighter level of heavy metals, but a generic manufacturer should have no problem if the original specifications are met because the product was approvable with those specifications.

Chapter 3 describes the container closure systems; again, this discussion would apply to all dosage forms. It is noteworthy that the regulatory agencies consider containers and packaging systems, all those components that

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