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GENERIC DRUG PRODUCT DEVELOPMENT

Solid Oral Dosage Forms

Second Edition

Edited by

Leon Shargel

Isadore Kanfer

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Generic Drug Product Development

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Preface

Since the publication of the first edition of this book, the generic pharmaceutical industry has greatly expanded and has become more competitive. Many generic drug companies have merged, forming large global companies that also manufacture branded drug products. New generic pharmaceutical companies have entered into the marketplace increasing competition. To be successful, generic drug products must be manufactured in a cost-effective manner and on a timely basis. The manufacturer who is first to file a new generic drug product may reap a high financial reward. Even with the successful development of an approvable generic drug product, the manufacturer has financial risks due to possible patent infringement and other legal challenges.

With the expansion of the generic pharmaceutical industry, new approaches have been developed for the manufacture of generic drug products, including the demonstration of drug product performance and meeting regulatory/legal requirements for market approval. Besides patents, costs, and time issues, the manufacturers of generic drug products must develop a product that is a pharmaceutical equivalent and bioequivalent to the reference listed product (usually the brand product) and ensure that the product meets various drug product performance standards such as good manufacturing practices and bioequivalence and also regulatory guidelines. Once approved by the regulatory agency (e.g., FDA), it is assumed that the generic drug product will have the same therapeutic safety, efficacy, and clinical performance as its brand-name counterpart.

This second edition updates each of the previous chapters and includes a new chapter on the US Pharmacopoeia and Pharmacopeia Harmonization. The objectives of this edition are similar to those of the first edition of *Generic Drug Product Development—Solid Oral Dosage Form*. The objectives are to describe, from concept to market approval, the development of high-quality, safe, and efficacious solid oral generic drug products. The revised edition provides a comprehensive account of the scientific, regulatory, and legal considerations for the development of generic drug products from project initiation incorporating the more recent concept of "Quality by Design" to marketing approval. As in the previous edition, the emphasis of this book is the development of solid oral generic drug products. However, much of the material contained in this textbook will have application to the development of other generic drug products.

The audience for this book is the members of the pharmaceutical industry, academia, and health practitioners who are interested in generic drug development and need more information concerning drug product initiation, drug product formulation, biopharmaceutics, drug delivery, bioequivalence, regulatory, and legislative issues. As in the previous edition, emphasis is on practical information for the development of a generic drug product. The text assumes that the reader has basic knowledge of pharmaceuticals and is interested in generic drug product manufacture.

Although the contents of the book emphasize the development of oral generic drug products for the FDA regulatory approval process, much of the information is applicable to other generic pharmaceutical products and approval by other regulatory agencies.

Editors

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Isadore Kanfer, PhD, is professor and emeritus Dean of Pharmacy, and former Head of Pharmacy and Dean of the Faculty (1999–2007), Rhodes University, Grahamstown, South Africa. He has been a visiting professor at the University of California-San Francisco and the University of North Carolina School of Pharmacy, Chapel Hill, North Carolina. Dr. Kanfer spent several years in the pharmaceutical industry in Canada. He earned his BSc in pharmacy and PhD in pharmaceutics from Rhodes University, Grahamstown, South Africa. Having written or contributed to several book chapters and more than 200 research publications and conference presentations, Dr. Kanfer is co-editor of Informa Healthcare's *Generic Drug Product Development* series of books, *Bioequivalent Issues*, *International Regulatory Requirements for Bioequivalence*, and *Specialty Drug Products*. He was awarded honorary life membership of the South African Academy of Pharmaceutical Sciences and is a fellow of the South African Pharmaceutical Society, the American Association of Pharmaceutical Scientists and has recently been elected a fellow of the Canadian Society for Pharmaceutical Sciences. He is associate editor of the *Journal of Pharmacy & Pharmaceutical Sciences* and editorial board member of the *Encyclopedia of Pharmaceutical Science and Technology* and served as chair of the American Association of Pharmaceutical Scientists Bioequivalence Focus Group (2010–2012). Dr. Kanfer was recipient of the Rhodes University Vice Chancellor's Distinguished Senior Research Award for 2007 and was appointed honorary professor, KLE University, Belgaum, India, in 2010.

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Leon Shargel and Isadore Kanfer

CONTENTS

THERAPEUTIC EQUIVALENCE AND GENERIC DRUG PRODUCTS

Multisource drug products are drug products that are marketed by more than one manufacturer, contain the same active pharmaceutical ingredient (API) or drug substance, in the same dosage form, and are given by the same route of administration. Multisource drug products contain identical drug substances and may meet compendial (e.g., United States Pharmacopeia [USP]-National Formulary monograph) standards of strength, quality, purity, and identity. However, multisource drug products should not be considered automatically as interchangeable or therapeutic equivalent, generic drug products. The term "generic product" has somewhat different meanings in different jurisdictions [1]. Regulatory approval for interchangeable multisource products may differ somewhat in each country. To be considered as an interchangeable generic drug product, the product must be approved by the relevant regulatory agency as a therapeutic equivalent. A therapeutic equivalent, generic drug product must have the same performance characteristics and is expected to have the same clinical effect and safety profile as the reference product when administered to patients under the conditions specified in the labeling. Because the reference product (generally the brand's or innovator's product) sold in different countries may not be bioequivalent to each other, each domestic market has regulations that decide which reference product should be used during generic drug product development and approval. International regulatory requirements for generic drug products are discussed in another book in this series [2].

Pharmaceutical Equivalents and Pharmaceutical Alternatives

Pharmaceutical equivalents are drug products that contain the same active ingredient(s), are of the same dosage form and route of administration, and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5 mg capsules). Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring, configuration, release mechanisms, packaging, excipients (including colors, flavors, and preservatives), expiration time, and, within certain limits, labeling [3]. Pharmaceutical alternatives are drug products that contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250 mg capsules vs. tetracycline phosphate complex, 250 mg capsules; quinidine sulfate, 200 mg tablets vs. quinidine sulfate, 200 mg capsules) [3]. The U.S. Food and Drug Administration (FDA) considers tablets and capsules as pharmaceutical alternatives even if the same API in each is bioequivalent. Other countries may accept bioequivalent capsules and capsules of the same drug as interchangeable drug products. Pharmaceutical alternatives may also be different dosage forms and strengths within a product line by a single manufacturer such as extended-release products compared with immediate-release or standard-release formulations of the same active ingredient [3].

Therapeutic Equivalence

In the United States, a therapeutically equivalent drug product must meet certain FDA criteria [3,4], which are as follows:

- Approved as safe and effective
- Pharmaceutical equivalent
  - Contain identical amounts of the same active drug ingredient in the same dosage form and route of administration
  - Meet compendial or other applicable standards of strength, quality, purity, and identity
- Bioequivalent
  - Do not present a known or potential bioequivalence problem
  - Meet an acceptable in vitro standard, or if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard
- Adequately labeled
- Manufactured in compliance with current good manufacturing practice regulations

Economic Savings

Generic drug products are typically sold at substantial discounts from their brand name counterparts. The Generic Pharmaceutical Association (GPhA) recently released an independently conducted analysis showing that the savings to consumers and the U.S. health care system from the use of generic prescription drugs rose to a current rate of $1 billion every other day, totaling $193 billion in 2011 and $1.07 trillion over the last 10 years (2002–2011) [5]. The report also revealed that savings from the use of generic drug products in 2011 increased 22% over the prior year, marking the largest year-over-year increase since 1998, and 10% higher than the 10-year average.

Savings from newer generic medicines that have entered the market since 2002 continue to increase exponentially, totaling $481 billion over the past 10 years. In 2011, approximately 80% of the 4 billion prescriptions written in the United States were dispensed using generic medicines, while accounting for only 27% of the total drug spending. The study also predicts that future savings to be achieved through generic prescription medicines will climb at an ever-increasing annual rate. Consumers chose the generic alternative 94% of the time in 2011 and this is a clear indication of the quality, safety, and efficacy of the FDA-approved generic products.

THERAPEUTIC EQUIVALENCE, DRUG PRODUCT QUALITY, AND DRUG PRODUCT PERFORMANCE

Drug product performance, in vivo, may be defined as the release of the drug substance from the drug product leading to bioavailability of the drug substance [6]. Bioavailability is defined as the rate and extent to which the active ingredient or

active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action [3]. Thus, drug product performance applies to both locally acting drug products, such as topical corticosteroids, and drugs intended for systemic absorption. The performance of each drug product must be consistent and predictable to assure both clinical efficacy and safety.

Defects in product quality can lead to poor drug product performance and affect safety and/or efficacy. Each component of the drug product and the method of manufacture contribute to quality. Quality is maintained by implementing systems and procedures that are followed during the development and manufacture of the drug product. Bioavailability, bioequivalence, and drug release/dissolution are important measures of drug product performance. Equivalent drug product performance is necessary to assure therapeutic equivalence. Thus, manufacturers of new and generic drug products must take into consideration drug product quality and drug product performance, so that each manufactured batch is equivalent and performs similarly in vivo. Likewise, both the generic drug product and its brand name alternative must also perform similarly, which is the basis of therapeutic equivalence.

GENERIC DRUG PRODUCT DEVELOPMENT

Generic drug product development uses a different approach and strategy compared with that used to develop a brand name drug product containing a new chemical entity. Generic drug product manufacturers must formulate a drug product that will have the same therapeutic efficacy, safety, and performance characteristics as its brand name counterpart. To gain market approval, a generic drug product cannot be "superior" or "better" than the brand name drug product. The key factor is that the generic drug product should meet all the necessary criteria to be therapeutically equivalent to the brand name (reference) drug product.

The manufacturer of a generic drug product has certain constraints in formulation development that differ from the formulation development of a brand name drug product. Generic drug manufacturers also face a variety of legal challenges from the brand name (innovator) pharmaceutical industry. For example, a generic drug manufacturer may not be able to use the same or similar inactive ingredients or excipients as in the brand formulation due to existing patents by the innovator. These issues will be discussed more thoroughly in subsequent chapters.

Initially, the generic manufacturer must find a source of the API and develop a finished dosage form (Figure 1.1). The method of manufacture of the API and its physical chemical characteristics, such as polymorphic (crystalline) form, should not infringe with patents filed by the innovator. In addition, an impurity profile for the generic API may be different from the brand due to a different synthetic routes of manufacture. The finished dosage form (e.g., an immediate-release or modified-release tablet) must also not infringe on formulation patents. To avoid patent infringement, the dosage form manufactured by the generic drug product manufacturer may use a different drug release mechanism compared with the brand; therefore, the

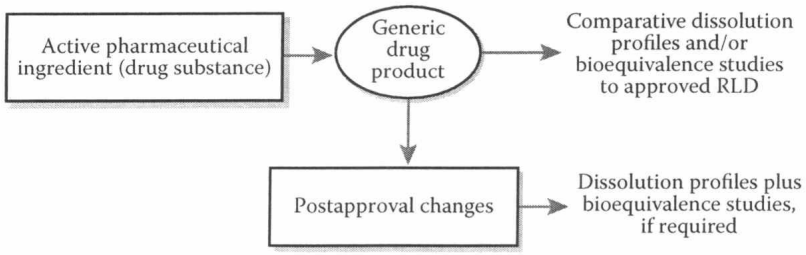

FIGURE 1.1 Drug product performance and generic drug product development. Reference listed drug (RLD) product performance may be determined in vivo by bioequivalence studies or in vitro by comparative drug/release dissolution studies. (From Shargel, L. et al. *Applied Biopharmaceutics & Pharmacokinetics*, 6th edition. McGraw-Hill, New York, 2012, Chapter 15.)

relationship between drug release and bioavailability may not be predictable in vitro. After drug approval, any scale-up, post-approval changes, including a site change, may also require comparative bioavailability studies to confirm bioequivalence.

SELECTION OF A GENERIC DRUG PRODUCT FOR MANUFACTURE

The main driving force for the selection of generic drug products for manufacture is the estimated sales volume for the branded product and the potential market share that the firm expects to have once the generic drug product is manufactured and approved for marketing (Table 1.1). Patent and legal considerations are also very important and are discussed more fully in Chapter 15. The generic drug manufacturer must consider the expiration date of the patent for the active ingredient and any other patent claims and exclusivities that the innovator firm has filed. In addition, the generic drug manufacturer needs to consider the lead time that is needed to make the product and submission of an Abbreviated New Drug Application (ANDA) to the FDA for approval. Timing is important, because the generic manufacturer would like to have their product submitted and approved just before patent expiration of the innovator's drug product. There is a large financial incentive to being the first generic drug product filed and approved by the FDA. The Hatch–Waxman Act, as

TABLE 1.1
Considerations in the Selection of a Generic Drug Product for Manufacture

Sales and potential market share
Patent expiration and exclusivity issues
Availability of API
Timing
Available technology
Formulation and dosage form
Experience
Development costs

explained below, provides a 180-day exclusivity, under certain conditions, for the generic manufacturer who is first to file.

The availability of technology and the cost of acquiring technology to manufacture the product will also impact the choice of generic drug product. For example, the proposed generic drug product might require special manufacturing equipment, a sterile environment, specialized packaging, or other expensive items. The firm must then consider whether this equipment, technology, and/or expertise are available in-house or must be acquired. Formulation considerations include the availability of raw materials, chemical purity, polymorphic form, and particle size of the API and any patents that the innovator company has filed, including patents for the synthesis of the API and composition of the dosage form. Experience with certain drug products will also affect the choice of generic drug product development. For example, some generic drug manufacturers may make a wide variety of dosage forms as well as solid and liquid oral dosage forms, including immediate-release and modified-release products as well as topical drug products (ointments and creams). Other generic firms may make specialty drug products such as transdermal, inhalation, or sterile drug products. Niche drug products, such as transdermal drug products, ophthalmic products, and others, may be difficult to make and also riskier but may have a greater financial reward due to less competition from other generic drug firms.

The decision to proceed with the development of a generic drug product should therefore be based on well-researched data that primarily indicate market value together with a sound knowledge of patent expiry dates, predicted market share, and growth rate for the product, among others. Government spending trends on medicines, which, in some countries, may be in the region of 40% or even more of the total market, should not be overlooked. The predicted profitability of the new generic product will require strategic planning for the subsequent launch timing, which must take into account the expected generic price and knowledge of anticipated competitors, such as who they are and when they are expected.

LEGISLATIVE AND REGULATORY ISSUES

The FDA was established in 1906 by the Federal Food, Drug, and Cosmetic Act (the Wiley Act) to prevent the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein, among others [7]. In 1938, the Act was amended to require drug manufacturers to file a New Drug Application (NDA) for each newly introduced drug product and to provide data to establish the safety of the drug product. In 1962, the Kefauver–Harris Amendments to the Act required all drug manufacturers to establish that their products were effective for their claimed indication(s), in addition to adhering to the safety requirements. Consequently, the FDA contracted with the National Academy of Sciences/National Research Council in 1968 to evaluate those drugs first introduced between 1938 and 1962 for effectiveness. This review program was called the Drug Efficacy Study Implementation (DESI) review, and drugs for which effectiveness was determined through the DESI review could be marketed with approval of an NDA. For drugs approved through the DESI review