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General Commentary

Past, Present, and Future of Bioequivalence: Improving Assessment and Extrapolation of Therapeutic Equivalence for Oral Drug Products

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ABSTRACT

The growth in the utilization of systems thinking principles has created a paradigm shift in the regulatory sciences and drug product development. Instead of relying extensively on end product testing and one-size-fits-all regulatory criteria, this new paradigm has focused on building quality into the product by design and fostering the development of product-specific, clinically relevant specifications. In this context, this commentary describes the evolution of bioequivalence regulations up to the current day and discusses the potential of applying a Bayesian-like approach, considering all relevant prior knowledge, to guide regulatory bioequivalence decisions in a patient-centric environment.

Introduction

Historically, the development of the regulatory sciences has been stimulated by public health catastrophes, as illustrated by the chain of events in the United States. Before 1938, one could introduce a drug product in the United States market without any toxicity testing or demonstration of effectiveness. The deaths of 107 children in September and October of 1937, who were poisoned by an elixir of sulfonamide which contained ethylene glycol intended to solubilize the drug, symbolized the catastrophic flaw in the *caveat emptor* approach.[1] Almost immediately, in 1938, amendments to the Food and Drugs Act of 1906 requiring toxicity testing and safety studies before the introduction of any medicine into the marketplace were enacted.[1,2]

The thalidomide tragedy, which originated in Europe in the early 1960s, marked a further turning point in regulatory supervision of the pharmaceutical market, as it prompted regulatory agencies across the globe to develop systematic toxicity testing protocols.[2] In the United States, for example, the Federal Food, Drug, and Cosmetic Act was amended in 1962 by the so-called Kefauver-Harris Amendments, which required not only more stringent toxicological testing but also evidence of efficacy for the product's intended use to support a new drug marketing application (NDA), that is, premarket clinical trials.[3,4] Because of a grandfather clause, no further studies were required for drugs that were already on the market before the 1938 law; however, efficacy data for drugs that entered the U.S. market after 1938 became mandatory.[3,4] Some manufacturers contested the legality of the Kefauver-Harris Amendments, but the U.S. Supreme Court upheld the retroactive efficacy requirement.[5] Owing to the lack of resources to evaluate the efficacy of the several thousand drug products that had been approved between 1938 and 1962, the U.S. Food and Drug Administration (FDA) recognized that a transitional period would be necessary and elaborated an abbreviated procedure to handle generic drugs. According to this procedure, if the regulatory agency already had evidence supporting the safety and efficacy of a certain drug substance in the dossier of the respective

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innovator drug product, generic manufacturers would not have to submit clinical trials. Instead, generics were required to be proven equivalent to the respective brand name products to maintain their marketing authorizations.[4-7] For the first time, the focus shifted from the drug substance to the formulation. Nevertheless, at that time, bioequivalence (BE) standards were in a state of flux and had not yet been established.[4,5,8]

The post-1962 scenario is even more complex. New clinical trials had to be conducted even for generics and, thus, the cost of developing generics of post-1962 drugs increased dramatically.[7] This period was marked by intense legal battles among the regulatory authority, the innovative pharmaceutical companies, and the generic manufacturers. Worth mentioning is the *Roche Products Inc.* v. *Bolar Pharmaceutical Co.* case, in which the innovative company questioned whether the generic manufacturers could conduct testing on patented products solely for obtaining approval of competitor products, and the *United States* v. *Articles of Drug, appeal of the Lannett Company, Inc.* case, in which the generic manufacturer contended that because the drug substances had already been proven to be safe and effective by the innovative companies, clinical trials should be superfluous for the amended new drug application. Federal courts reached contrary decisions on these matters, increasing the uncertainty around what was required to bring a generic product to market.[5,7] Consequently, as many as 150 brand name drug products lacked generic versions, despite being off-patent, in the following years.[7,9]

Paralleling the judicial disputes, academic concerns about the *in vivo* equivalence of generics arose after some clinical results were published showing that different formulations containing digoxin led to different pharmacokinetic (PK) profiles.[10-12] For instance, Lindenbaum et al.[11] investigated the systemic exposure of digoxin released from 4 different formulations in healthy volunteers. The authors found pronounced differences in the bioavailability (BA) of different commercially available digoxin tablets. These differences in BA results, in combination with the well-known narrow therapeutic index of digoxin, caught the attention of the regulators at the FDA. Subsequently, Wagner et al.,[13] under contract with the FDA,[4,8] confirmed Lindenbaum's findings of lack of equivalence between the plasma levels of digoxin released from multisource tablets. In fact, Wagner et al.[13] reported nonequivalence in the systemic exposure of digoxin even with tablets that met the pharmacopoeial standards for both potency and disintegration time. Similar observations were also reported for other drug products, including those containing tetracycline,[14,15] chloramphenicol,[16] phenylbutazone,[17,18] and oxytetracycline.[19] An editorial written by Levy and Gibaldi[20] in 1974 reinforced the urgency of developing an adequate means of assuring the BA of oral drug products. Recognizing the existence of BA problems in marketed products, the FDA Office of Technology Assessment convened a panel of 10 senior medical consultants who concluded that the then current compendial reference standards and regulatory practices did not assure uniform BA.[21]

Finally, in 1984, almost 20 years after the Kefauver-Harris Amendments, the U.S. Congress passed the Drug Price Competition and Patent Term Restoration Act (commonly known as the Hatch-Waxman Act), which was intended to make low-cost generics more widely available while simultaneously maintaining adequate incentives for innovation, by, for example, extending brand name market exclusivity. The Act authorized the FDA to approve generic drug products through BE studies, fostering the development of multisource drug products and generic-based public health policies worldwide.[6,9]

In Europe, concepts for generic drugs and BE evolved at the national level, with each country forming its own rules. The first efforts to standardize European regulations regarding drug approval in general were made before the formation of the EU, with the passage of EC Directive 65/65/EEC in 1965.[22] After the formation of the EU in 1993, there were significant changes, eventually leading to a centralized procedure for new drug applications at the European Medicines Agency (EMA) but continuing to allow approval of generic versions at a national level. Today, generic drug approvals within the EU can be obtained in one of the 3 ways: a central approval which applies to the whole European market, stepwise approval at the national level (which can lead to approval throughout the EU once 3 countries have approved the drug product, provided a certain mix of countries has been involved), or approval only at the national level, which can be instigated for example when the sponsor decides that the product will only be marketed in that given country.[23]

Generics have played a role in many European countries for many years, as in the United States. The first generic drug company in Germany, Ratiopharm, was founded in 1973, and in that year, generic products, such as acetylsalicylic acid and paracetamol tablets, were introduced into the market. Other companies soon followed (e.g., Stada in 1975), and by 1997, generics already accounted for around 40% of prescriptions.[24] This percentage has continued to climb to over 80% over the ensuing 20 years.

Again taking Germany as an example, the regulation of generics in Europe provides a variety of ways in which generic drug products can be introduced into the market. In Germany, there are still so-called "*Standard Rezeptur*" products on the books—and some of these are on the market. *Standard Rezeptur* products must be manufactured according to a predefined composition and, if this is the case, no BE testing is required to achieve a marketing authorization.[25] Furthermore, when a drug product has established itself over a number of years in the market and scientific material additional to the approval package is available, a generic manufacturer is permitted to rely on this database. For example, glucocorticoids and endocrine hormones were introduced into the market in the 1950s and 1960s, and since then, many scientific papers and clinical studies have been published regarding their use. Against this background, it was deemed to be no longer necessary to perform clinical studies for the approval of generic versions. However, this type of waiver is only granted when the drug, excipients, and dosage form are all identical with products already on the market.[25] Another interesting modality for generic drug approval in Germany is the literature-based approval, known as the "*bibliographische Zulassung*" procedure. In this case, regulatory relief in the form of a waiver of preclinical and clinical data is entertained. Requirements are that the drug must have already been on the market for 10 years and that the sponsor must produce thorough literature evidence of efficacy combined with an acceptable side-effect profile. Both positive and negative literature must be cited and discussed, with peer-reviewed publication being accorded more weight than internal documents or non–peer-reviewed articles.[26] It should be noted, however, that the usual procedure for approval of generic products in Germany (and elsewhere in Europe) is to demonstrate BE using PK studies in healthy human volunteers.

Outside the United States and Europe, there are many different approaches to approval of generic drugs, ranging from very stringent requirements and a low % of prescriptions filled with generics in Japan (around 18% in 2007) to the situation in Iran, where, because of a government decree shortly after the revolution, only generic versions were permitted to be marketed. Still today, approximately 96% of drugs available on the market are manufactured by local generic companies.[27,28] Interestingly though, 86% of Iranians hold the perception that bioequivalent generics are not therapeutically equivalent to the respective reference drug products,[29] a statistic which has driven both the government and generic manufacturers to sponsor prospective, blinded efficacy, and