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Review Article

Follow-on products for treatment of multiple sclerosis in Latin America: An update

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ABSTRACT

Both proprietary and non-proprietary medicines are expected to undergo rigorous pre-approval testing and both should meet stringent health authority regulatory requirements related to quality to obtain approval. Non-proprietary (also known as copy or generic) medicines, which base their authorization and use on the proprietary documentation and label, are often viewed as a means to help lower cost and thus increase patient access. If these medicines fail to meet quality standards, such as good manufacturing practice and bioequivalence (in humans), they are then defined as substandard copies and can pose serious risks to patients in terms of safety and efficacy.

Availability of this type of compounds is more prevalent in regions where health authorities do not enforce registration regulations as stringent as those of the Food and Drug Administration, European Medicines Agency, or World Health Organization, including preestablished quality standard requirements. This article focuses on non-proprietary medicines for multiple sclerosis, that are not identical to proprietary versions and could thus fail to meet efficacy or have different impact on the safety of patients with multiple sclerosis.

1. Introduction

Multiple sclerosis (MS) in Latin America (LATAM) has generated considerable expenditure, in relation to diagnosis acquisition, pharmacological treatment and long term care, both at social and economic levels. This represents a challenging problem for a region where developing health systems are not prepared to approve MS care costs as part of their budgetary responsibilities. Although MS prevalence in LATAM is low, the economic impact of the disease is significant given its early onset, progressive course and lifelong need for treatment. Limited access to FDA- or EMA-approved disease modifying therapies (DMT) in most countries in the region has meant that few patients can access modern therapeutic protocols [1].

Third-party carrier insurance coverage is uncommon in most LATAM countries. National health care is the rule, provided through Ministry of Health-supervised public hospitals, and national Social Security Institutes (SSI). SSI economies are dependent on trade union management, as well as on industry and government subsidies, providing health services to limited segments of the community, in general union members and their families. Furthermore, coverage of prescription drugs, rehabilitation services, and special equipment, as well as access to disability benefits vary markedly among countries [1].

Economic pressures from consumers and manufactures are the major driving force for development of follow-on products (Box 1 provides definitions of key terms). Innovative agents tend to be very expensive for patients and third –party payers [2]. Costs of a follow-on will depend heavily on the possibility of expedited testing to demonstrate comparability of the innovator product, passing full-scale clinical testing and permitted abbreviated regulatory application. Availability of cheaper alternatives after patent expiry of original products may contribute to increased access to treatments and reduction of disease management costs.

Expectations are that generic versions of small molecule drugs will cost the consumer at least 50%–80% less than the original product [3]. For follow-on biological compounds however, more complicated manufacturing processes are involved, therefore prices are expected to be only 30% less than the corresponding innovator product [3].

As some MS treatments are soon coming off-patent, local regulatory authorities will be facing significant challenges to safeguard patients when defining appropriate requirements for follow-on products that show high degree of similarity to standard treatments [4]. However, in several LATAM countries, patent protection for innovative products is often not enforced, which means that follow-on DMTs can be marketed at any time, sometimes even before the original innovator compound. Some LATAM countries do uphold data protection laws, usually for a period of 5 years, which means innovative drug data cannot be used in

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Box 1
Key definitions.

Biological: Copy of a brand-name drug that is the same in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.

Biosimilar: Biological medicinal product that is a new product claimed to be similar to an approved reference biologic, marketed by an independent entity, subject to all applicable intellectual and marketing protection rights for the innovator product.

Counterfeit medicines: No data. Unknown origin and composition.

Follow-on: A medicinal product that is intended to serve as a pharmaceutical and therapeutic equivalent to an already available agent.

Generic: Copy of a brand-name drug that is the same in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.

Innovator drug or proprietary medicines: The approved brand medicinal product also known as the reference product or proprietary medicine, which demonstrate evidence-based clinical efficacy, safety and quality.

Non proprietary medicines: Relies on proprietary medicine documentation and label. Bioequivalence demonstrated. Quality established.

Substandard medicines: Does not meet specifications necessary to ensure quality, efficacy and safety.

Substandard copies: Relies on proprietary medicine documentation and label. No bioequivalence demonstrated and/or quality not established.

submissions to regulatory authorities for marketing and development of follow-on DMTs. These facts notwithstanding, follow-on products should provide efficacy, safety and tolerability, protecting patients at levels comparable to those demonstrated by the innovator product [3,5–6]. Interest in follow-on DMT is driven by biotechnology, economics, ethics, and politics, but significant controversies surround their use. These include the steps required for their development, and regulatory requirements that need to be in place to convincingly establish that a follow-on compound is equivalent to the corresponding innovative product [3,5–8].

Safe, high-quality medicines are essential to ensure optimal clinical impact for patients. Use of ineffective, poor-quality, or harmful medicines can cause therapeutic failure, disease exacerbations and important side effects [9–10]. This undermines confidence in health systems, health professionals, pharmaceutical manufacturers, and distributors. Proprietary medicines follow new drug application review requirements, undergoing preapproval testing in animal studies and clinical trials, meeting stringent health authority regulatory requirements for quality, and submitted to long term safety monitoring (Fig. 1) [10–14]. Non proprietary medicines (also known as copies or generics) must fulfill requirements on quality, and be subject to good manufacturing practices before approval. Substandard medicines are genuine medicines produced by manufacturers authorized by national regulatory authorities that do not meet specifications necessary to ensure quality, efficacy and safety (Fig. 1) [10–14]. Availability of this type of compounds is more prevalent in regions where health authorities do not enforce registration regulations as stringent as those of the Food and Drug Administration (FDA), European Medicines Agency (EMA), or World Health Organization (WHO), including preestablished quality standard requirements.

Regulatory agencies need to establish clear guidelines to set up comparability or similarity of 3 different types of molecules used in the treatment of MS as follow-ons: 1) small molecules of chemical synthesis, 2) biological drugs, and 3) non-biological complex drugs (NBCDs).

2. Small molecule follow-on products of chemical synthesis

In Europe and the US, regulatory organisms are encouraged to provide rapid market access to lower-priced copies of original medicinal products after patent expiry, to reduce healthcare costs. Patient outcome will depend on the quality of active pharmaceutical ingredients (APIs) and excipients, and should be strictly controlled. Some excipients may alter API bioavailability or modify product shelf life. Cases in which excipient nature and source differ from those of the proprietary drug have adversely affected medicine efficacy and patients safety [15]. In one study, the API of proprietary fingolimod was assessed across a series of quality parameters and compared to APIs of 11 non-proprietary products [16]. Parameters analyzed included microparticle size, distribution, heavy metal content and inorganic impurities. APIs of these 11 copies failed to meet international or proprietary specifications for one or more of the parameters tested. Inadequate control of excipients or APIs used in follow-on product synthesis have resulted in cases of toxicity, disability, failure to slow or prevent disease progression, and loss of public resources [10,17–18]. In addition, approved substandard medicines have also generated problems leading to product recalls and withdrawals [19].

Regulatory pathways are based on demonstration of pharmaceutical equivalence (identical active substance, dosage form, and route of administration), as well as of bioequivalence (comparable pharmacokinetics) established in a small healthy volunteer study (Box 2). Abbreviated regulatory pathways established by EMA and FDA after patent expiry do not require formal clinical efficacy or safety studies, nor are FDA equivalence requirements between generic and innovator drugs absolute. Because performance variability can be expected for any drug in humans, FDA generally accepts data demonstrating a generic product performs within 20% variance of the original. For agents with narrow therapeutic index and for which monitoring to guide dosage adjustments is available (e.g. blood levels), the FDA will accept pharmacological and bioequivalence data within 80% to 125% of original product values for area under plasma concentration-time curve (AUC) and peak plasma concentration (C_{max}) [20]. In this regard, the EMA recommends tightening acceptance intervals for AUC to 90%–111% [21]. Populations in bioequivalence studies usually consist of healthy volunteers, which may not reflect medicine efficacy in patients, generating further concerns. Patients with schizophrenia for example can tolerate doses of dopamine-blocking antipsychotics that cause severe adverse events in healthy volunteers [22]. Therefore, the FDA recommends patients with stable disease, rather than healthy controls be enrolled in bioequivalence studies [20].

The Biopharmaceutical Classification System (BCS) is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. The purpose of this system was to help determine which compounds may be exempt from in vivo bioavailability (BA) and/or bioequivalence (BE) studies [23]. Table 1 summarizes the characteristics of the chemical compounds according to BCS.

In accordance with FDA, EMA, and WHO guidelines [23–25] and based on BCS, class I and class III compounds can request a waiver of in vivo BA and/or BE studies, while in vivo studies are mandatory for BCS class II and IV compounds. However, BCS-based biowaivers are not