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Publisher *Taylor & Francis*

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Journal of Biopharmaceutical Statistics

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597263>

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Online publication date: 12 January 2010

To cite this Article Fox, Andrew(2010) 'Biosimilar Medicines—New Challenges for a New Class of Medicine', Journal of Biopharmaceutical Statistics, 20: 1, 3 – 9

To link to this Article: DOI: 10.1080/10543400903549892

URL: <http://dx.doi.org/10.1080/10543400903549892>

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BIOSIMILAR MEDICINES—NEW CHALLENGES FOR A NEW CLASS OF MEDICINE

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Biosimilars are a new class of medicine. The European Medicines Agency has pioneered the legal, regulatory, and scientific framework for approval of these products. One of the foundational principles of the European framework is that biosimilars are expected to be similar, not identical, to the innovator biologics they seek to copy. This contrasts with the legal, regulatory, and scientific framework for copies of chemical medicines, generics, which are based on the expectation that the innovator and generic drug substance are identical. This article reviews the European biosimilar regulatory pathway and reviews some of the clinical data being made public following the approval, rejection, and withdrawal of biosimilar marketing applications.

Key Words: Bioequivalence; Biologic; Biosimilar; EMEA; Equivalence; FDA; Guideline.

1. INTRODUCTION

The use of generic medicines is commonplace in medical practice. Abbreviated legal and regulatory pathways for approval of generics were developed around the world in the 1980s, and since then, the regulatory standards for approval have become well established. These standards are based on the expectation that the active substance in generic medicines is identical to the innovator medicine they seek to copy and allow the waiver of formal clinical studies to evaluate efficacy and safety. In the place of such clinical studies, the generic applicant must, among other things, demonstrate that the active substance is identical and that the rate and extent of absorption of the active substance meet a standard of bioequivalence. Bioequivalence is defined in the United States in the Code of Federal Regulations, Title 21, Part 320.1, as:

the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (CFR, as amended).

Received April 2009; Accepted June 2009

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In the European Union (EU) in the EMEA draft guideline on the investigation of bioequivalence issued in July 2008 states:

Two medicinal products containing the same active substance are considered bioequivalent if their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy (EMEA, 2008).

It is important to note, however, that such standards for approval of generic medicines and establishment of bioequivalence were developed for chemical medicines, which in the 1980s were the mainstay of medicinal intervention. These standards therefore were not developed with biologic or biotechnology-derived medicinal products (biologics) in mind. With patents for such biologics now expiring or about to expire around the world, regulatory agencies are now addressing the question of whether we can adopt an abbreviated legal and regulatory pathway to approve an attempted copy of a biologic.

2. WHAT ARE CHEMICALS AND BIOLOGICS?

Chemical medicines are typically organic molecules produced by a defined chemical pathway whose molecular structure can be reliably assessed and defined by simple analytical methods in the laboratory. Biologic medicines are typically large, complex, heterogeneous, protein-based molecules produced by a living-cell-based system that cannot be fully characterized by analytical methods in the laboratory (Woodcock et al., 2007).

These differences in production, size, and complexity between chemical medicines and biologics do not prevent a company, from a scientific standpoint, from attempting to copy an innovator biologic. However they do present a challenge when it comes to determining whether or not the attempted copy can be considered identical to the innovator, thus posing the question of whether or not the established legal and regulatory standards for approval of generic medicines, whose very basis is one of sameness or identity, could be applied to attempted copies of innovator biologics.

3. THE EUROPEAN UNION APPROACH

The European Commission and European Medicines Agency (EMA) have already addressed this very question: Can an attempted copy of an innovator biologic be held to the same standards as generic medicines and approved by the same legal and regulatory framework?

The European Commission reached the conclusion that, unlike standard generics, which are identical copies of innovator chemical medicines, copies of biologics can only be similar to—but not identical to—innovator biologics. They therefore cannot be considered and regulated as generics (European Commission, 2006). Accordingly in 2004, the EU pharmaceutical legislation was revised to establish a new legal pathway for approval of “similar biological medicinal products”, more commonly known as biosimilars (European Commission, 2001).

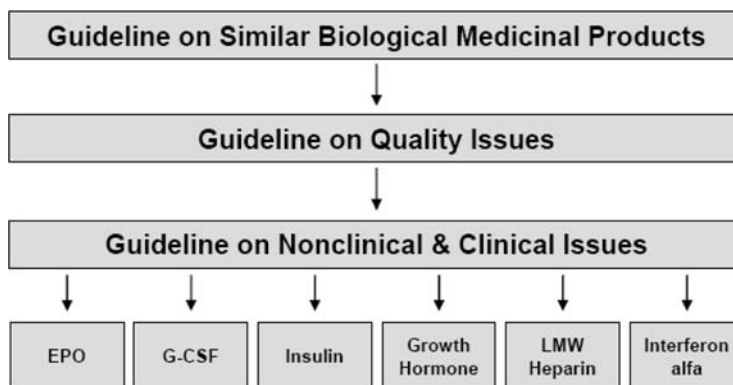


Figure 1 Overview of biosimilar guidelines developed by EMEA.

This new legal pathway was closely followed by a regulatory framework for the evaluation, authorization, and monitoring of biosimilars developed by the EMEA. Starting in 2006, the EMEA has issued scientific guidelines on the quality, nonclinical, and clinical standards for approval of biosimilars (EMEA, 2006e,f) (Figure 1).

The EMEA guidelines were developed through a public consultation process and have been reviewed and reported by many authors. The important distinction from the approval of generic medicines is that the biosimilar is not expected to be identical to the innovator biologic (EMEA, 2006f). Accordingly, they cannot be approved based on establishing bioequivalence to the innovator biologic (EMEA, 2005). The scientific principle underpinning this approach is that if the active substance is not identical to that of the innovator, then we do not know that its biological activity, when administered to a patient, will be the same as that of the innovator biologic. Assessing merely the pharmacokinetic characteristics of the biosimilar in a bioequivalence study will not provide data on whether the similar but not identical nature of the active substance has resulted in changes to the safety or efficacy.

Therefore, in order to be approved as a biosimilar under the EU framework, the biosimilar manufacturer must conduct further nonclinical and clinical studies that seek to demonstrate that the biosimilar and the innovator biologic have similar safety and efficacy profiles (EMEA nonclinical/clinical guideline). In addition to providing general guidance on how this standard is met, the EMEA has also issued a series of product class-specific guidelines for biosimilar erythropoietin, granulocyte colony-stimulating factor (G-CSF), insulin, human growth hormone, interferon alpha, and low-molecular-weight heparin (EMEA, 2006a,b,c,d, 2007, 2009).

The product class-specific guidelines provide the detail on the nature of nonclinical and clinical studies that a biosimilar manufacturer is expected to conduct and provide to regulators in order to secure approval under the biosimilar pathway. One important point to note is that these studies are not simply expected to demonstrate the safety and efficacy of the biosimilar itself. They are expected to be comparative in nature and detect or more specifically exclude a difference in response between the biosimilar and the innovator. In other words, they are

designed to demonstrate an absence of clinically meaningful differences to the innovator biologic.

It is therefore important to note that the quality, safety, and efficacy of a biosimilar must be similar to those of the innovator biologic it seeks to copy. If any of these characteristics are worse than, better than, or demonstrably different from the innovator, then the product would be either rejected or required to follow the full, stand-alone pathway as a new product application.

4. PRODUCT CLASS-SPECIFIC GUIDELINES

Having established that demonstrating bioequivalence alone is not adequate for approval of a biosimilar, the crucial question that follows is—how much more data is necessary to approve a biosimilar? Clearly one expects that, in order to qualify as an abbreviated legal and regulatory pathway, the amount of nonclinical and clinical data must be less than that provided by the innovator to secure its clinical indications, but how much less is acceptable?

The EMEA has taken a thoughtful and systematic approach to this question and reached the conclusion that there is no standard data set that can be applied to all classes of innovator biologic in order to secure approval of a biosimilar. Each class of biologic varies in its benefit/risk profile, whether surrogate markers for efficacy are available and/or validated, the nature and frequency of adverse events, and the nature and breadth of clinical indications. Accordingly, the EMEA has developed product class-specific guidelines that define the nature of comparative studies to be conducted but stop short of providing precise equivalence margins. This being the case, the guidelines do not prescribe a fixed standard for approval and there is still considerable room to maneuver when it comes to negotiating precise standards for approval of any one biosimilar.

Naturally, these guidelines vary by class but they apply the principles shown in Table 1.

With the EU system now having been in place for more than 3 years and with some biosimilars being approved and others rejected by the EMEA, we can see that meeting this standard of clinical similarity to the innovator biologic requires clinical studies that include on the order of 200 to 500 subjects, depending on the product class in question. This, when considering that innovator biologics will normally be studied in several thousand subjects in order to secure their range of clinical indications, is a considerable reduction in the clinical testing required before approval.

5. EQUIVALENCE MARGINS—HOW SIMILAR IS SIMILAR?

Having outlined the nature of clinical studies required to support approval of a biosimilar in the EU, a logical next question is, what standard has been met by biosimilars in the EU? As mentioned earlier, the EMEA stopped short of defining equivalence margins in its guidance documents, instead preferring to require that such margins were prespecified and justified on clinical grounds by the applicant. With six biosimilar molecules now approved in the EU (13 separate marketing authorizations), one biosimilar rejected, and three biosimilar insulin applications

Table 1 Summary of EMEA product-class-specific guidelines

Parameter	Method to demonstrate similar clinical characteristics in comparative study (studies)
Pharmacokinetics	Acceptance range should be based on clinical judgment. Standard bioequivalence criteria (i.e., 90% confidence interval within 80–125% for select PK parameters) developed for orally administered products may not be appropriate.
Pharmacodynamics	Pharmacodynamic markers should be selected on their relevance to therapeutic efficacy. Examples: reticulocyte count for erythropoietin, absolute neutrophil count for G-CSF, euglycemic clamp for insulin.
Efficacy	Demonstrate similar efficacy in at least one indication of the reference product. Indication chosen should be a sensitive indication where differences in efficacy, should they exist, could be detected. Demonstration of the clinical similarity in one indication may allow the extrapolation of the results to the other indications of the innovator biologic.
Safety	Demonstrate similar safety in at least one indication of the reference product.
Immunogenicity	Antibody testing should be part of all clinical studies.
Post-approval	Data from pre-authorization clinical studies normally are insufficient to identify all potential differences. Clinical safety of biosimilars must be monitored on an ongoing basis post-approval, including continued benefit-risk assessment.

Source: EMEA Nonclinical/Clinical guideline and product-class-specific guidelines.

withdrawn from the review process, it is possible to delve deeper into the public data and determine how the EMEA has made the transition from the application and equivalence margin to PK measures in a bioequivalence study supporting generic approval to assessing similarity in clinical outcomes for biosimilar approval.

The first point of note is that biosimilars have been expected to meet a standard of statistical equivalence (i.e., not non-inferiority) on the basis that clinical studies are expected to demonstrate that a biosimilar is not worse and not better than the innovator, i.e., similar. Interestingly, one application for biosimilar somatropin initially applied a superiority standard to its pivotal clinical study (Omnitrope European Public Assessment Report [EPAR], 2006) and another a non-inferiority standard (Valtropin EPAR, 2006), but both were reanalyzed to an equivalence standard before approval. Where data are available, all other biosimilars, whether approved, rejected, or withdrawn, have applied an equivalence standard.

Having established that equivalence is the statistical standard expected by the EMEA, the question then becomes, what clinical margins have been applied to the outcome measures tested in the clinical studies? Naturally, this varies by product class and has been justified by each biosimilar applicant on clinical grounds based on what difference in outcome might be considered clinically meaningful.

For example, the application for a biosimilar interferon alfa-2a applied a margin of $\pm 15\%$ (two-sided, 95% confidence interval) for the 3-month responder rate in patients with hepatitis C (Alpheon Refusal Assessment Report, 2006); a biosimilar G-CSF applied a margin of ± 1 day of severe neutropenia (two-sided, 95% confidence interval) in patients with chemotherapy-induced neutropenia

(Tevagrastim EPAR, 2008). It seems unlikely that such margins will be formalized in the form of guidance and so will be negotiated on a case-by-case basis for each biosimilar application.

As the number of biologic classes subject to biosimilar applications grows in the future, a challenge will be how to establish and communicate these equivalence margins so that there is a common understanding amongst regulators, healthcare professionals and patients alike of what “similar” means from the clinical perspective.

6. BIOSIMILAR PATHWAYS WORLDWIDE

The EU has a well-established and well-documented legal and regulatory pathway for the review and approval of biosimilars. Other countries and organizations around the world, including Australia, Canada, Japan, and Switzerland and the World Health Organization, are also following the same scientific principles for an abbreviated approval pathway for biosimilars. In contrast, the United States is at the very beginning of the process, with a legal pathway being discussed by Congress for a number of years. The Food and Drug Administration (FDA) views on biosimilars can be examined from a publication (Woodcock et al., 2007) and from communications from the FDA to Congress (Torti, 2008). While not formal regulatory guidance, these documents seem to indicate FDA is contemplating similar scientific principles to those established by the EMEA.

7. CONCLUSIONS

The development of legal and regulatory pathways for biosimilars has prompted much debate among lawmakers, regulators, industry, academia, health care professionals, and patients. The EU has taken a thoughtful, thorough, and evidence-based approach to this legal/regulatory challenge, has established a pathway that acknowledges the scientific challenges posed by biosimilars, and has created a tailor-made legal and regulatory pathway, separate and distinct from the generic pathway. This pathway is now held up as the gold standard around the world.

With biosimilars that meet this standard being approved in the EU and those that fail to meet this standard being either rejected or withdrawn, there is an emerging set of data to review in order to understand the answer to the question, “How similar is similar?”

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