# The Current Biosimilars Landscape and Methodological Considerations for Real-World Evidence Generation

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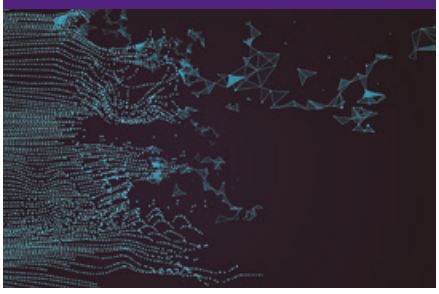
KEY POINTS . . .

Appropriate study design for real-world biosimilar studies depends on the study purpose and specific research question as well as an understanding of the local regulations, access, and clinical practice

Biosimilar identification can be challenging since it is not distributed through an outpatient pharmacy. Other challenges include inconsistent naming conventions, variations in local legislation regarding switching and substitution, and reimbursement and health care coverage decisions

Successful study design, execution, and analysis requires a strong understanding of clinical practice patterns; reimbursement and health care coverage; naming conventions; interchangeability and substitution; and availability, completeness, access, and privacy of any existing data sources



## Introduction

Biologic medicines are indicated for serious, chronic illnesses in rheumatology, dermatology, oncology, immunology, neurology, nephrology, and endocrinology [1]. These medicines have had a profound impact on health care. Novel therapies such as rituximab have demonstrated improved survival from non-Hodgkin's lymphoma [2]. Anti-tumor necrosis factor alphas revolutionized care for Crohn's disease and ulcerative colitis patients by sustaining the duration of remission and reducing the need for surgery [3] and have slowed disease progression in rheumatoid arthritis [4,5]. Novel research in genetic information and disease processes has greatly increased the number of targets that biologics affect [1]. That said, biologics are more costly to produce than small-molecule counterparts, in large part because the manufacturing process for biologics is less predictable than for small-molecule drugs, with greater batch-to-batch variation. Hence, biologics are expensive, creating a need for more accessible alternatives such as biosimilars.

Many countries, along with the World Health Organization, have based their guidance for biosimilars on the European Medicines Agency (EMA) guidelines or have fully adopted the EMA guidance as their own [5,6]. Whether the governing body is the EMA or the US Food and Drug Administration (FDA), the premise of a biosimilar development program is to demonstrate similarity, not patient benefit as that has already been established by the originator biologic. Biosimilars are licensed on the basis of a reduced and less costly data package by building on the originator's safety and efficacy experience.

As of March 2017, 23 biosimilars for 10 different originators are marketed in the European Union (Table 1) [7]. Four biosimilars have been approved for 4 different originators by the FDA under the 351(k) regulatory pathway [8,9], with the first approval in March 2015 and launch in September 2015 (Table 2) [10]. All 4 approved biosimilars received approval of extrapolation to many of the same indications for which the originator has licensure.

Since the approval of the first biosimilar in 2006, the European biosimilar experience has not revealed any unexpected safety concerns beyond which would have been anticipated from originator biologics [11-13]. In addition to safety, post-marketing studies have been used to examine treatment patterns and switching, as well as clinical effectiveness, particularly in indications for which no clinical studies were conducted as part of the biosimilar approval process. These studies include both biologically naïve patients as well as those who are switched from the originator to its biosimilar. Many studies did not include a contemporaneous comparator group and typically had relatively short follow-up (< 1 year), limiting the assessment of long-term benefits or risks. Most published studies were conducted in a single country or single hospital, with chart review studies of few patients in each indication. Larger, prospective studies are underway, including the comparative phase IV interventional NOR-SWITCH study in Norway to assess the effectiveness, safety, and immunogenicity of patients switching from Remicade to Remsima [14]. Studies such as NOR-SWITCH should contribute meaningful information to augment currently available data about the benefit-risk profile of specific biosimilars.

## Study Designs and Data Sources

Pharmacoepidemiology studies are used to describe treatment patterns, demonstrate safety and effectiveness, evaluate treatment heterogeneity, and identify delayed risks and benefits related to biosimilars. The appropriate study design and data sources will depend on the study purpose and research question and may differ according to stakeholder expectations and the extent to which channeling bias and other types of selection bias are likely to affect the results. This is a particularly important consideration >

for biosimilars because of the widespread price differentials between branded biologics and biosimilars, which, in some health systems, may lead to greater use of the biosimilars by people with lower socioeconomic status and less access to medical care. An understanding of the local regulations and clinical practice is also essential to successful study design and execution.

***Randomized Clinical Trials***

Randomized clinical trials (RCTs), also sometimes referred to simply as "interventional studies," are conventionally used to support market authorization and label expansion. Even when not required for regulatory purposes, RCTs, including pragmatic randomized clinical trials, are best suited to answer questions about comparative safety and effectiveness when the patients of interest are not treated with the originator or biosimilar of interest in routine clinical practice, or the use of the originator or biosimilar is ubiquitous. For example, everyone is using the medication of interest and there are no contemporaneous comparators, whether due to reimbursement decisions or physician adoption. An interventional design also may be the best option when there is a need for clinical data or assessments to be collected that are not routinely performed in regular clinical practice on all patients (e.g., immunogenicity). Finally, there is widespread familiarity with RCT and the perception that this study design produces the most rigorous level of evidence, so RCTs may be desirable when evidence is needed for the most skeptical of audiences. That said, the results of RCT may have limited generalizability since the biosimilar of interest, dosages, or local practices may vary substantially from protocol-driven observations.

***Prospective Observational Studies***

A prospective observational design (non-randomized), including data collection through patient registries, is generally the preferred study design when the patients of interest are being treated with the originator or biosimilar in routine clinical practice, all data being collected are captured during routine care visits, and data collection is aligned with routine clinic visits [15]. Prospective studies are used to quantify benefits and risks, either for a product alone or in comparison to the originator and/or other biosimilars. This design is frequently used for post-marketing safety studies, also known as post-authorization safety studies and has been widely accepted as sufficiently strong evidence in many countries. Careful design to minimize threats to validity (e.g., selection bias, information bias, and confounding) must be taken into consideration when designing the observational study. Prospective studies may be combined with existing data (see Enriched Studies below).

***Retrospective Studies***

Retrospective studies (studies that use existing data, not primary data collection), including chart reviews and existing database studies, may be sufficient and the least costly approach when the patients of interest are using the originator or biosimilar of interest and the product used by a patient can be identified from medical records or other existing databases, such as administrative health insurance claims. Retrospective approaches are used to provide descriptive information about the patient population receiving the biologic of interest, to quantify disease burden, evaluate treatment patterns, and compare across marketed products. Retrospective studies are frequently used for post-authorization safety commitments [16] and also for submission of data to payers.

Table 1. EMA-Approved Biosimilars (as of March 2017)

| INN | Biosimilar brand | Developing company | Approved |
|---|---|---|---|
| Somatropin* | Omnitrope® | Sandoz | Apr-06 |
| Epoetin α | Binocrit®/ Epoetin Alfa Hexal® | Sandoz (Hexal) | Aug-07 |
| | Abseamed® | Medice | Aug-07 |
| Epoetin ζ | Retacrit® | Hospira | Dec-07 |
| | Silapo® | Stada | Dec-07 |
| Filgrastim§ | Ratiograstim® | Ratiopharm | Sep-08 |
| | Tevagrastim® | Teva | Sep-08 |
| | Zarzio®/ Filgrastim Hexal® | Sandoz (Hexal) | Feb-09 |
| | Nivestim™ | Hospira | Jun-10 |
| | Grastofil® | Apotex | Oct-13 |
| | Accofil® | Accord | Sep-14 |
| Infliximab | Inflectra® | Hospira | Sep-13 |
| | Remsima™ | Celltrion | Sep-13 |
| | Flixabi® | Samsung Bioepis | May-16 |
| Follitropin α | Ovaleap® | Teva | Sep-13 |
| | Bemfola® | Finox Biotech | Mar-14 |
| Insulin glargine | Abasaglar® (formerzly Abasria) | Eli Lilly / Boehringer Ingelheim | Sep-14 |
| | Lusduna™ | Merck Sharp & Dohme | Jan-17 |
| Etanercept | Benepali® | Samsung Bioepis | Jan-16 |
| Enoxaparin sodium | Inhixa® | Techdow Pharmaceuticals | Sep-16 |
| | Thorinane® | Pharmathen | Sep-16 |
| Teriparatide | Terrosa™ | Gedeon Richter | Jan-17 |
| | Movymia™ | STADA | Jan-17 |

**Somatropin biosimilar Valtropin was approved in April 2006, but was withdrawn post-approval.*
*§ Biograstim biosimilars Filgrastim ratiopharm (approved September 2006) and Biograstim (approved September 2008) were withdrawn post-approval.*

Retrospective designs are favored where feasible when there is a need to look at large populations or to identify rare events. However, the necessary data may not be available or they may not have been collected in a systematic way or be linkable to an individual patient. It can be difficult to interpret missing data, and sensitivity analyses should be used to put boundaries on how much varying assumptions could influence the overall effect being measured. With different modalities of data collection across health care plans, regions, and countries, it is important to understand data coding and whether a data dictionary exists. Nonetheless, some post-

Table 2. FDA-Approved Biosimilars (as of March 2017)

| Non-proprietary name | Biosimilar brand | Developing company | Approved |
|---|---|---|---|
| Filgrastim-sndz [8] | Zarxio® | Sandoz | Mar-15 |
| Infliximab-dyyb [8] | Inflectra® | Celltrion | Apr-16 |
| Etanercept-szzs [8] | Erelzi™ | Sandoz | Aug-16 |
| Adalimumab-atto [8] | Amjevita™ | Amgen | Sept-16 |

marketing regulatory safety commitments may simply require drug utilization studies, which have much fewer data requirements than do studies of effectiveness and safety, making this the design of choice since it is the most economical.

***Enriched Studies***

Existing data also can be combined with prospective data capture, adding tremendous value for what may be relatively small incremental cost. Prospectively collected data can be combined periodically with existing data, going forward in time, allowing for creation of multiple data sets and looks in time to provide a comprehensive view of the patient's disease, care, and outcomes. The enriched study approach employs specific data collection where needed, such as including patient-reported outcomes and special clinician-reported assessments, and relying on existing data when they are sufficient.

An enriched study design can be used both for prospective non-interventional studies as well as pragmatic clinical trials, where treatment assignment to an originator or biosimilar is made by randomization and all follow-up is naturalistic.

## Considerations for Exposure Identification

Documenting individual exposure to biosimilars is challenging to obtain using observational methods alone, because of their mode of administration, naming conventions, local legislation around switching and substitution, as well as reimbursement and health care coverage decisions.

Knowing how the biologic medicine is administered (e.g., self-administered injection or intravenous infusion) will help determine where to find the relevant data on treatment exposure, and in the United States, whether the biologic medicine is covered under the medical or pharmacy benefit. Switching and substitution also must be taken into consideration. The terms switching (physician makes the decision to exchange one medicine for another with the same therapeutic intent in patients undergoing treatment) and substitution (the pharmacy can dispense one medicine instead of another equivalent and interchangeable medicine without consulting the prescriber) have been used synonymously, but actually are distinctly different [17]. For originator biologics and biosimilars, this concept puts an extra burden on researchers for accurate exposure identification and to understand who is legally authorized to receive a biosimilar, whether the decision to substitute or switch a patient is made by the pharmacy or prescriber and whether documentation of the switch or substitution will be available at the time the study is being conducted.

Reimbursement and health care coverage can also affect the opportunity for treatment with a biologic or biosimilar. Many countries in Western Europe, such as the United Kingdom, have national health insurance schemes that are likely to influence who receives the originator biologic or the biosimilar, especially new users. In contrast, in countries where patients bear much if not the full treatment cost, there could be fundamental differences in those who choose the biosimilar versus the originator. Depending on reimbursement decisions and local substitution laws, switching may occur multiple times over the course of a study and switchers may change in many ways (e.g., between the originator, biosimilar, or other biosimilars for the same originator with or without physician awareness). Being able to distinguish the particular biosimilar from its originator is imperative to attribute the benefits accurately and risks correctly.

Exposure identification is also dependent on understanding naming and coding of biologics and biosimilars in a given market. Currently, there is no global harmonization of naming conventions. The World Health Organization has proposed including a four-letter suffix assigned at random as a biologic qualifier for naming purposes [18]. The EMA uses identical international non-proprietary names for originators and biosimilars and recommends that the trade name or brand name be used when prescribing to be able to distinguish between the products [19]. The FDA has used different naming practices for nonproprietary names from the first approved biosimilar to the second, third, and fourth approved biosimilars. The first biosimilar in the United States was named "filgrastim-sndz" with the 4-letter suffix representing the manufacturer's name, whereas the biosimilars approved subsequently carry a random 4-digit suffix (infliximab-dyyb, etanercept-szzs, and adalimumab-atto) [8]. The FDA has yet to grant interchangeability status to a biosimilar. Whether an interchangeable biosimilar will have a unique 4-letter suffix or the same suffix as the originator is still to be determined [20]. For the time being, researchers should assume that naming conventions for biosimilars will vary by jurisdiction.

## Conclusions

The best approaches to pharmacoepidemiology studies of biologics and biosimilars will consider the study purpose, target countries, and health systems of interest to account for the myriad of local regulations and practices regarding access, interchangeability, switching practices, naming conventions, and when and where relevant data may be obtained.

Understanding what to look out for and how these issues may impact results are essential for achieving strong evidence and reliable interpretation.

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*Additional information:*

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