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Biosimilar Medications: Key Considerations for Providers

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Introduction

Biologic therapies are large proteins that are developed using recombinant DNA technology in living systems and extracted via complex purification techniques.[1] Biologics include hormones, cytokines, clotting factors, and monoclonal antibodies. They are used to treat diabetes, hemophilia, cancer and autoimmune conditions. Although the overall number of prescriptions for biologics is relatively modest compared with that for small-molecule medications, their development and production are associated with significant costs.[1] Administration of a biologic agent to an individual patient ranges between $15,000 and $150,000 per year.[1] Biologics are also among the most expensive drugs, accounting for about 40% of total United States (US) pharmaceutical expenditures despite being used by less than 2% of Americans.[2] Medications that have similar properties to Food and Drug Administration (FDA)-approved biologics are termed biosimilars.[1] There are no clinically meaningful differences between the biosimilar product and the reference product in terms of safety, purity and potency of the product.[3] Biosimilars were introduced into the European markets in 2005 in an effort to improve patient access to life-saving medications. This newsletter will review current trends and regulations in the biosimilar United States (US) market.

FDA Guidance for Biosimilar Approval

The Biologics Price Competition and Innovation (BPCI) Act of 2009 was included as part of the Affordable Care Act (ACA) health-care-reform legislation enacted in 2010.[4] The BPCI Act created an abbreviated licensure pathway for biological products shown to be biosimilar with an FDA-licensed reference product. This regulation allowed the FDA to approve a biologic product based on less than a full complement of preclinical and clinical data if the sponsor could provide analytic studies showing its product was "highly similar" to an approved product.[4] The FDA guidance describes the process required to demonstrate biosimilarity, beginning with comprehensive structural and functional analyses, followed by animal studies to assess toxicity, and clinical studies on pharmacokinetics, pharmacodynamics, and immunogenicity.[1] A summary of currently approved biosimilars is presented in **Table 1.** Seven FDA-approved biosimilars have not yet been marketed due to patent litigation. More approvals are expected in the next few years because a patent cliff for biologics is imminent in the United States, with an estimated $100 billion worth of biologics set to lose patent exclusivity in 2020.[5]

Table 1. FDA-Approved Biosimilars

Reference Product	Biosimilar Products
AVASTIN (bevacizumab)	ZIRABEV (bevacizumab-bvzr) MVASI (bevacizumab-awwb)
ENBREL (etanercept)	ERELZI (etanercept-szzs)* ETICOVO (etanercept-ykro)*
EPOGEN (epoetin-alfa)	RETACRIT (epoetin-alfa-epbx)
HERCEPTIN (trastuzumab)	KANJINTI (trastuzumab-anns) TRAZIMERA (trastuzumab-qyyp) ONTRUZANT (trastuzumab-dttb) HERZUMA (trastuzumab-pkrb) OGIVRI (trastuzumab-dkst)
HUMIRA (adalimumab)	ABRILADA (adalimumab-afzb)* HADLIMA (adalimumab-bwwd)* HYRIMOZ (adalimumab-adaz)* CYLTEZO (adalimumab-adbm)* AMJEVITA (adalimumab-atto)*
NELUASTA (pegfilgrastim)	ZIEXTENZO (pegfilgrastim-bmez) FULPHILA (pegfilgrastim-jmdb) UDENYCA (pegfilgrastim-cbqv)
NEUPOGEN (filgrastim)	NIVESTYM (filgrastim-aafi) ZARXIO (filgrastim-sndz)
REMICADE (infliximab)	AVSOLA (infliximab-axxq) IXIFI (infliximab-qbtx) RENFLEXIS (infliximab-abda) INFLECTRA (Infliximab-dyyb)
RITUXAN (rituximab)	RUXIENCE (rituximab-pvvr) TRUXIMA (rituximab-abbs)

*Not yet Available In The United States Due To Patent Litigation

Biosimilar Interchangeability

A provision of the BPCI Act created a second level of approval that goes beyond biosimilarity, called interchangeability.[6] An interchangeable biological product is a product that has been shown to be biosimilar to the reference product, and can be expected to produce the same clinical result as the reference product in any given patient.[3] The FDA considers the totality of the evidence when evaluating proposed interchangeable products and recommends a stepwise approach for generating data to support a demonstration of interchangeability.[7] The Purple Book provides a listing of all originator, biosimilar, and interchangeable biosimilar products approved by the FDA.[8] As of March 2020, no biosimilar products have received the interchangeability designation from the FDA.

Interchangeable designation may permit substitution of biosimilars for the originator without intervention of the prescriber; however, US substitution policies are determined

by state laws, not by the FDA. State legislation varies, but typically requires FDA approval of a product as interchangeable. Interchangeability of biosimilars differs from generic substitution, whereby a reference drug is substituted by a generic version of the drug that is identical with respect to active ingredients and strength, concentration, dosage form, and route of administration.[9] In most states, pharmacists must notify prescribers and patients and retain records of interchangeable biosimilar substitutions.

In Oregon, biosimilar legislation is addressed in OAR 855-041-1105.[10] The biosimilar rule states: A pharmacy or pharmacist filling a prescription or order for a biological product may not substitute a biosimilar product for the prescribed biological product unless:
(a) The biosimilar product has been determined by the FDA to be interchangeable with the prescribed biological product;
(b) The prescribing practitioner has not designated on the prescription that substitution is prohibited;
(c) The patient for whom the biological product is prescribed is informed of the substitution prior to dispensing the biosimilar product;
(d) The pharmacy or pharmacist provides written, electronic or telephonic notification of the substitution to the prescribing practitioner or the prescribing practitioner's staff within three (3) business days of dispensing the biosimilar product; and
(e) The pharmacy or pharmacist retains a record of the substitution for a period of not less than three (3) years.[10]

Extrapolation of Approved Indications

Biosimilars are not required to have clinical data in each indication for which licensure is sought. Regulatory guidelines permit extrapolation of clinical data from one indication to support biosimilar approval for use in an indication that was not directly compared to the biologic in a clinical trial but for which the reference product is approved.[8] Extrapolation must be scientifically justified and based on the totality of the evidence from all stages of biosimilar development.[7] For example, Celltrion secured the FDA approval of its biosimilar infliximab for all indications of the original infliximab (Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis) by conducting comparative clinical studies in just rheumatoid arthritis and ankylosing spondylitis.[7]

Insulin Biosimilar Projections in the US

In the US, insulins are considered biological products but were historically approved through traditional FDA pathways under section 505 of the Food Drug and Cosmetic (FD&C) Act as a "follow on medication". Growth and reproductive hormones have also been approved as follow on medications and are not designated as generics. The BCPI Act stipulates that effective March 2020, an approved application for a biological product under the FD&C Act will be deemed to be a license for the biological product. Therefore, all newly developed products similar to a licensed biologic will be approved through the biosimilar pathway.

Incorporating Biosimilars into Practice

There are many challenges associated with introduction of new biosimilars, all of which could affect product uptake.[9] In some cases, multiple biosimilars are available; however, not all have the same indications as the reference product.[9] Additionally, differences in product presentation and the need for devices or auto-injectors, between a biosimilar and the reference product or among biosimilars could create confusion.[9] There are also challenges associated with reimbursement, patient preference, incorporation into electronic medical records (i.e. order sets), greater acceptance of biosimilars for supportive care versus more complex therapeutic indications, and limited pharmacy space.[9]

Conclusions

Biosimilars have the potential to increase accessibility to and expand the use of biologic therapies. Biosimilar approval is granted through FDA regulatory pathways that are distinct from small-molecule generics and novel therapeutics. Evolving regulatory guidelines for interchangeability may influence substitution practices and post-marketing pharmacovigilance, as well as the type and extent of information pharmacists can communicate to patients and other health care providers about biosimilar products.[7]

Oregon Health Plan Biosimilar PA Criteria

- For biologic PA criteria, all biosimilars are currently non-preferred products. Adalimumab and etanercept are preferred agents in this class.
- Oncology biosimilars are all preferred with no PA restrictions.
- Colony stimulating factor biosimilars are non-preferred.

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