# Biosimilars in Oncology

Internal Medicine Grand Rounds

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Disclosures: Nisha Unni, M.D. reports receiving consulting fees from Eisai and Novartis. Dr. Unni will not be discussing off-label uses in her presentation.

## Biographical Information

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## Purpose & Overview

To provide clinicians with both broad and oncology specific perspectives on biosimilars.

## Educational Objectives

At the conclusion of this lecture, the listener should be able to

1. Explain the similarities and differences between biosimilars, reference biologics, and small molecule generics
2. Compare available safety and efficacy data for available biosimilars and reference biologics and the potential impact of interchangeability, extrapolation of indications, and substitution on dose/response, adverse events, and clinical outcome
3. Summarize the key steps outlined by the FDA to demonstrate biosimilarity between a biosimilar and its reference biologic product.

# INTRODUCTION

Biologic drugs are one of the fastest growing classes of therapeutic compounds and play an important role in healthcare. These are rapidly outpacing small-molecule drugs, represent $232 billion in global revenue and make up more than 25% of the total global pharmaceutical market. The number of biologic drugs approved by the US Food and Drug Administration (FDA) continues to increase. In 2019, 48 new novel drugs were approved by the FDA, 15 of these were biologics. Approximately 40% of the biologics approved in 2018 were for the treatment of cancer. Biologic drugs are important therapeutic options for the treatment of patients with cancers, nonmalignant conditions as well as for supportive care management.

Biological products have a well-defined structure and are generally derived from living material--human, animal, or microorganism-- are large molecules, complex in structure, and thus are usually not fully characterized. They are regulated by the Food and Drug Administration (FDA).

Section 351 of the *Public Health Service (PHS) Act* defines a biological product as a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, applicable to the prevention, treatment, or cure of a disease or condition of human beings." FDA regulations and policies have established that biological products include blood-derived products, vaccines, in vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products. Biological products subject to the *PHS Act* also meet the definition of *drugs* under the *Federal Food, Drug and Cosmetic Act (FDC Act)*.

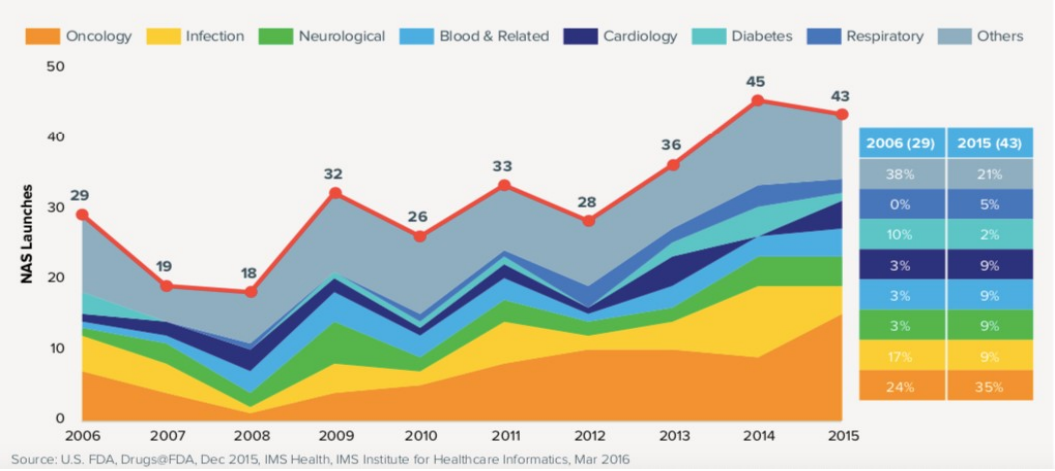
**Rising Cost of Global Healthcare**

Global Biological Drugs Market is estimated to reach $394 billion by 2024; growing at a CAGR (Compounded Annual Growth Rate) of 10.3% from 2016 to 2024. The North American healthcare biologics market dominated the global market with the highest growth rate seen in the Asia- Pacific region in 2018.

Growing elderly population, increasing prevalence of lifestyle and chronic diseases, and rising investments in various R&D programs are boosting the growth of the global biological drugs market. However, high costs of these drugs and possibility of adverse effects may hinder the growth of the market. In 2017, according to data from the IQVIA Institute, biologic drugs represented 2% of all U.S. prescriptions, but 37% of net drug spending.

The number of biologic drugs approved by the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) continues to increase, with 15 biologic drugs included in the 48 new molecular entities approved by the FDA in 2019. There were 15 therapeutic oncology new active substances (NASs) and one supportive care NAS launched in the US in 2018, 40% of which were for the treatment of cancer.

Figure 1. Oncology medicines comprised more than one-third of all launches in 2015



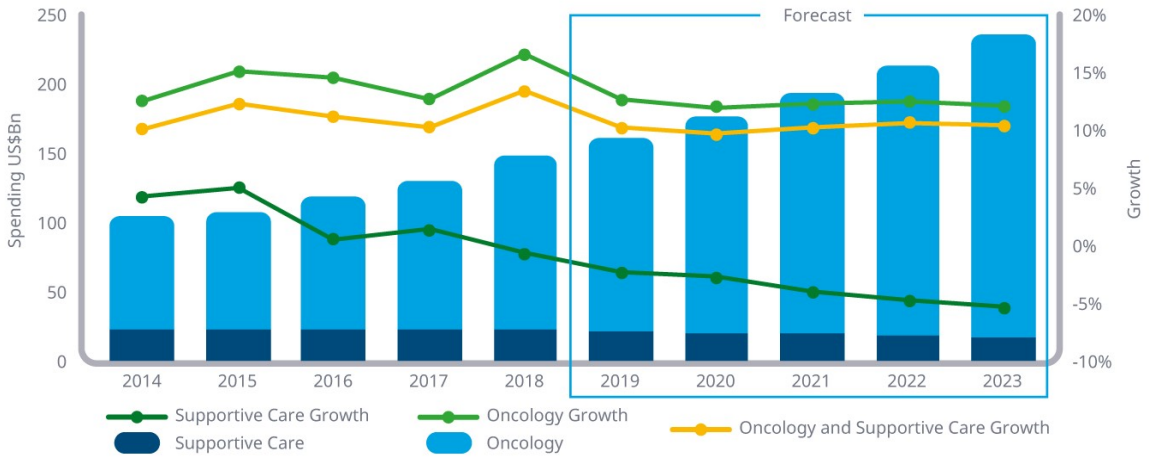

## Advances in Cancer Care

According to the American Cancer Society report, the cancer death rate in the United States fell 2.2% from 2016 to 2017 — the largest single-year decline in cancer mortality ever reported. Since 1991 the rate has dropped 29 percent, which translates to approximately 2.9 million fewer cancer deaths than would have occurred if the mortality rate had remained constant. This has been attributed to the decline in smoking rates, early detection of cancers and to advances in lung cancer and melanoma treatments.

Historically, FDA has used a histology-based approach, designating and approving oncology drugs for treatment of tumor types based on a single anatomic site. Recent developments in the genomics of oncogenesis have opened the possibility of a molecular marker defining a disease that spans multiple histology-based tumors in a tissue agnostic manner.

The average annual cost of new medicines continues to trend upward, in 2018 the cost per product ranged between $90,000 and over $300,000. The mean cost for new brands in 2018 was $175,578, down from $209,406 in 2017, but was above the $143,574 mean from 2012 to 2018.

Over the next five years, growth in oncology therapeutics spending of 11–14% is expected on a CAGR (Compounded Annual Growth Rate) basis. Overall oncology drug spending is expected to grow from 9–12% and reach $220–250 billion in 2023.




Source: IQVIA Institute, Apr 2019

Chart notes: Therapeutic oncologics include those classified by EphMRA (European Pharmaceutical Market Research Association) as cytotoxics in the L1 or L2 classes, as well as radiotherapeutics (V3C) and specific molecules classified elsewhere but used primarily in cancer (lenalidomide, aldesleukin, pomalidomide). Supportive care includes anti-nauseants and cancer detox agents (A4A and V3D), erythropoietins (B3C), GM-CSF white blood cell boosters (L3A), other interferon therapies used in cancer (L3B excluding multiple sclerosis drugs), and bisphosphonates used to prevent bone metastases (M5B4).

Report: Global Oncology Trends 2019 – Therapeutics, Clinical Development and Health System Implications. IQVIA Institute for Human Data Science, May 2019

Figure 2. Oncology spending projection through 2023, growing at 9–12%

The Association of Community Cancer Centers "2017 Trending Now in Cancer Care Survey" is a comprehensive survey designed to identify current and emerging trends across U.S cancer programs. This survey was conducted in partnership with Advisory Board's Oncology Roundtable. More than 290 respondents from 209 organizations, including community, hospital and academic practices participated in the survey, which provided insights into nationwide developments in the business aspects of cancer care. The majority of respondents (68%) selected cost of drugs and/or new treatment modalities as a top challenge and the biggest threat to their cancer program growth. When asked about overall health care cost savings, 62% of the respondents identified reducing the cost of drugs as a major factor in driving down the cost of cancer care.

A 2017 Nature Reviews Clinical Oncology article compared the costs of 1 month of therapy among the 10 highest-earning cancer drugs between the USA and Norway. Figure 3. illustrates the differences in both the price and affordability of these agents. Prices of these drugs in the USA are consistently higher than those in Norway, despite similar median monthly incomes.

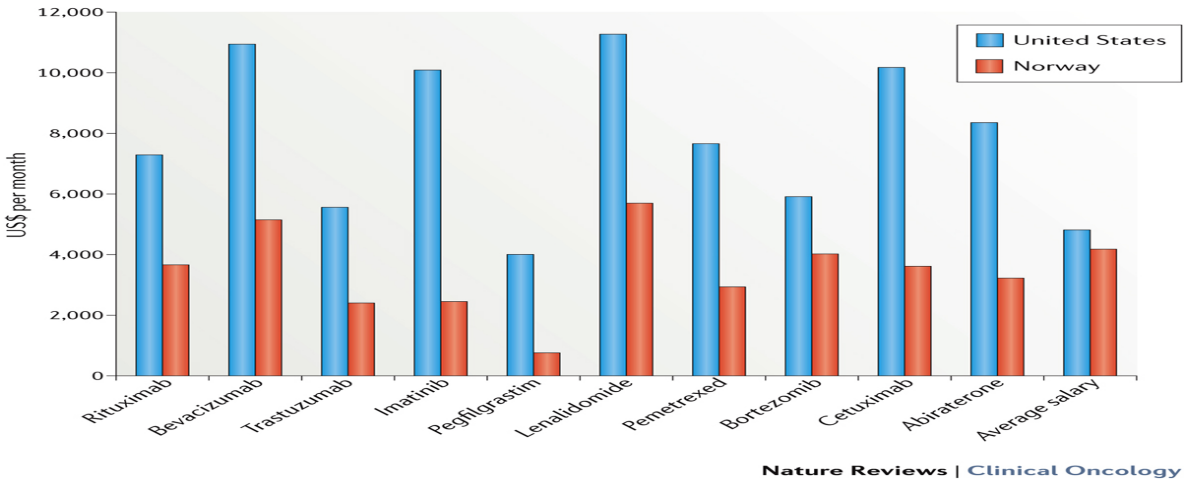



**Figure 3. Cost of one month of treatment with the top 10 bestselling anticancer drugs in the USA and Norway.**
Drug prices are calculated for an adult weighing 70 kg, with a body surface area of 1.7 m2.

## Trajectories of Injectable Cancer Drug Costs After Launch in the United States

Gordon et al studied the changes in mean monthly costs for a cohort of 24 patented, injectable anticancer drugs that were approved by the US Food and Drug Administration between 1996 and 2012. For each drug, cumulative and annual drug cost changes were calculated. Using a multivariable regression model, the association between market and cost changes over time were evaluated.

With a mean follow-up period of 8 years, the mean percent change in cost for all drugs was +25% (range, −14% to +96%). After adjusting for inflation, the mean cost change was +18% (range, −16% to +59%). The following drugs incurred high cost changes over time: arsenic trioxide, which was approved by the FDA in 2000 for the treatment of acute promyelocytic leukemia (95.5% cost increase from baseline in 12 years); nelarabine, which was approved in 2005 for the treatment of patients with T-cell acute lymphoblastic leukemia (83.2% increase from baseline in 12 years); rituximab, which was approved in 1997 for non-Hodgkin lymphoma (85.2% increase from baseline in 12 years); and trastuzumab, which was approved for metastatic human epidermal growth factor receptor 2–positive breast cancer in 1998 (78.4% increase from baseline in 12 years). The inflation-adjusted monthly costs for Rituximab and trastuzumab rose by 49% and 44%, respectively, since approval.

## Impact of Biosimilars on Healthcare Costs

The rationale for a biosimilar approval pathway is to promote competition among manufacturers to lower prices and potentially increase access to medications.
Based on the 2018 Rand Health Quarterly study, it is estimated that biosimilars will reduce direct spending on biologic drugs by $54 billion from 2017 to 2026, or about 3% of total estimated biologic spending over the same period, with a range of $24 to $150 billion. Actual savings will hinge on an evolving biosimilar regulatory and competitive landscape. Payment arrangements, regulatory policies and guidance, patient and prescriber acceptance of biosimilars, and other

issues will also influence the magnitude of potential savings. Savings will accrue to a range of stakeholders in the short term, although patients and taxpayers will benefit in the long term. The Biosimilars Council, a division of the Association for Accessible Medicines, estimated that as biosimilars become more widely available in the United States, they would expand therapeutic options, enhancing the likelihood that patients will be able to begin treatment with biologic medicines. An analysis by Avalere Health for the Biosimilars Council shows that 1.2 million U.S. patients could gain access to biologics by 2025 as the result of biosimilar availability. This data also suggests that women, lower income, and elderly individuals would disproportionately benefit from access to biosimilar medicines.

## Background

In Europe, the first biosimilar was approved in 2006, and since then, more than 50 biosimilars have been approved there. In the United States, the first biosimilar, Filgrastim-sndz (Zarxio), a myeloid growth factor similar to Filgrastim, was approved in 2015. As of December 2019, a total of 26 biosimilars have been approved by the FDA.

By end of 2020, 9 patents for the top 20 biologic drugs are set to expire. Between 2013 and 2024, 8 biologic drugs used in oncology will have patents expiring. With these pending patent expirations, there has been an increase in the number of biosimilars studied for the treatment of cancer, with more than 250 ongoing clinical trials.

## Clinical Applications of Biosimilars in Oncology

### Myeloid Growth Factors

Data from the 2012 National Inpatient Sample and Kids' Inpatient Database identified 91,560 and 16,859 cancer-related neutropenia hospitalizations/ year among adults and children, respectively. This translated to total cost of cancer-related neutropenia hospitalizations at $2.3 billion for adults and $439 million for children. Cancer-related neutropenia hospitalizations accounted for 5.2% of all cancer-related hospitalizations and 8.3% of all cancer-related hospitalization costs. For adults, the mean length of stay for cancer-related neutropenia hospitalizations was 9.6 days, with a mean hospital cost of $24,770 per stay. For children, the mean length of stay for cancer-related neutropenia hospitalizations was 8.5 days, with a mean hospital cost of $26,000 per stay.

A comprehensive systematic review and meta-analysis of 17 RCTs (3,493 patients) compared primary prophylactic G-CSF (Granulocyte- Colony Stimulating Factor/ Filgrastim) with placebo or untreated controls in adult solid tumor and malignant lymphoma patients. For infection-related mortality, RR reduction with G-CSF compared with controls was 45% (RR = 0.55; 95% CI, 0.33 to 0.90; P = .018); for early mortality (all-cause mortality during chemotherapy period), 40% (RR = 0.60; 95% CI, 0.43 to 0.83; P = .002); and 46% for febrile neutropenia (RR = 0.54; 95% CI, 0.43 to 0.67; P < .001). This study further solidified the impact of G-CSFs in primary prophylaxis and thereby reducing the risk of febrile neutropenia, early deaths and infection-related mortality in patients receiving certain chemotherapy regimens.

The most commonly used myeloid growth factors include filgrastim (Neupogen), peg-filgrastim (Neulasta). The On-body Injector for Peg-filgrastim (OBI/ On-Pro) is a device that is programmed automatically to administer Peg-Filgrastim, by injection, 24 hours after completion of chemotherapy. The device is usually placed on the stomach or the back of the arm.


**Filgrastim-sndz (Zarxio)**

Approval of Filgrastim-sndz was based on comparability of Biosimilar Filgrastim to Reference Filgrastim. Evidence from 22 analytical methods evaluating 19 different attributes including similarity in NMR Spectroscopy to both U.S and European versions, similar receptor binding affinity testing results, human Pharmacokinetic (PK) studies, human Pharmacodynamic (PD) studies, and confirmatory human safety and efficacy studies demonstrating biosimilarity to the reference biologic, Filgrastim/ Neupogen.

The phase III PIONEER study compared alternating biosimilar filgrastim, with the US-licensed reference product, Filgrastim/ Neupogen, for prevention of severe neutropenia in early breast cancer patients receiving myelosuppressive chemotherapy. A total of 218 patients receiving 5 µg/kg/day filgrastim over six chemotherapy cycles were randomized 1:1:1:1 into four arms. Two arms received only one product (non-alternating), biosimilar or reference, and two arms (alternating) received alternating treatments during each cycle (biosimilar then reference or vice versa). The primary end point was duration of severe neutropenia during cycle 1. There was no difference in the incidence of febrile neutropenia (FN); hospitalization due to FN; incidence of infections; depth and time of absolute neutrophil count (ANC) nadir and time to ANC recovery during cycle 1 and across all cycles. This study demonstrated that biosimilar and the reference filgrastim were similar with no clinically meaningful differences regarding efficacy and safety in prevention of severe neutropenia.

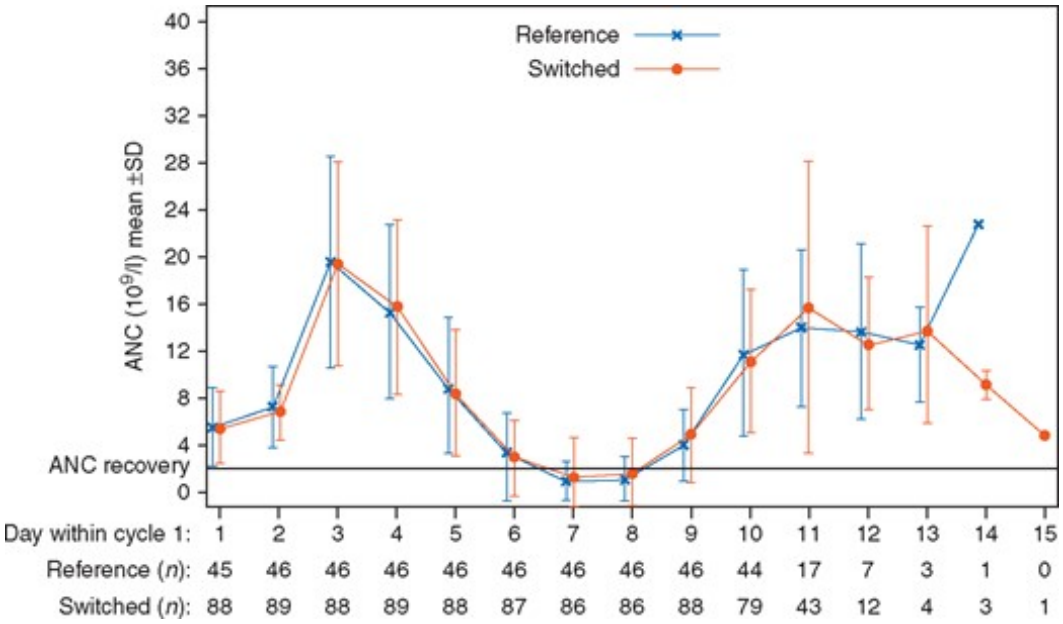



Figure 4. PIONEER Clinical Trial. Time course of ANC (mean ± SD) in cycle 1

**Key Concepts**

The Biologics Price Competition and Innovation (BPCI) Act of 2009 is part of the Patient Protection Affordable Care Act that was signed into U.S. law in 2010. The BPCI Act provides an abbreviated regulatory pathway for biosimilars via a 351(k) application, which is designed to reduce the amount of testing required in animals and humans compared with innovator biologics that are approved through a 351(a) Biologics License Application. Approval of a biosimilar requires evidence that it is highly similar to its biologic reference product, notwithstanding minor differences in clinically inactive components, and that it produces no clinically meaningful differences from its reference product in terms of safety, purity, and potency.

**"Reference Product/ Medicine"**

Defined as a single biological product licensed under section 351(a) of the Public Health Service (PHS) Act against which a biological product is evaluated in an application submitted under section 351(k). 351(a) is the traditional pathway for approval of biologics and innovator biologics under the PHS act. Under section 351(a), the submitted application must contain all the information regarding the safety and effectiveness of a biological product. It is also known as a "*stand alone*" application as its approval is not dependent upon any other biological product.

**"Biosimilar" or "Biosimilarity"**

Based on Section 351(i) (2) of the PHS Act.

Defined

(i) That the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and

(ii) There are **no clinically meaningful differences** between the biological product and the reference product in terms of the **safety, purity and potency** of the product.

A manufacturer developing a proposed biosimilar demonstrates that its product is highly similar to the reference product by extensively analyzing the structure and function of both the reference product and the proposed biosimilar. State-of-the-art technology is used to compare characteristics of the products, such as purity, chemical identity, and bioactivity. The manufacturer uses results from these comparative tests, along with other information, to demonstrate that the biosimilar is highly similar to the reference product.

Minor differences between the reference product and the proposed biosimilar product in clinically inactive components are acceptable. Any differences between the proposed biosimilar product and the reference product are carefully evaluated by FDA. Slight differences are expected during the manufacturing process for biological products, regardless of whether the product is a biosimilar or a reference product.

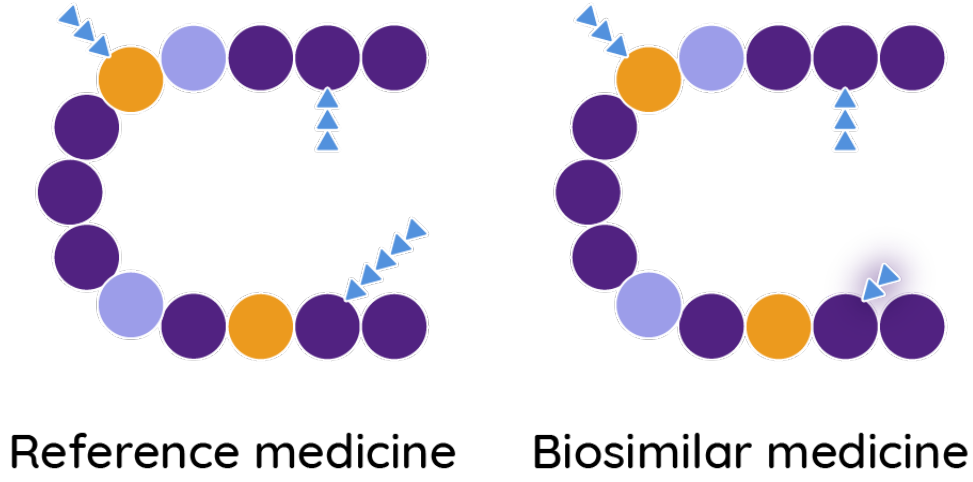



**Figure 5. Example of variability between a biosimilar and the reference biologic.**
**The blue triangles represent glycosylation of the amino acid chain, represented by the circles.**
**Variability, shown by the purple shadow, can be allowed, however, the amino acid sequence must stay the same. (EMA, 2017)**

**351(k) application**

351(k) application is a biologics license application process under the USFDA. The application is submitted by the manufacturers in order to get a product reviewed as a biosimilar. The PHS act requires that a 351(K) application should include information explaining that the biosimilarity is completely based on the data related to animal studies, clinical studies and analytical studies.

*General Requirements of 351(k) pathway*

The application must include the following information:

(i) Demonstration of the product-in-review to be biosimilar to a reference product.

(ii) Usage of same mechanism(s) of action for the intended condition(s) of use, limiting to the mechanisms of the reference product.

(iii) Previously approved condition(s) of use for labeling.

(iv) Route of administration, dosage form and strength as per the reference product.

(v) Details regarding the manufacturing of the product to ensure the safety and efficiency of the manufacturing plant and process.

## Developing a Biosimilar

Biologics, both reference and biosimilar medicines, are manufactured from living organisms. As such, it is normal to have lot-to-lot variability for all biological medicines. No lot of a biological medicine is an exact replica of prior lots, but all are within ranges that are known to be safe and efficacious. These ranges are the development target for the corresponding biosimilars. Likewise, a biosimilar is not a precise replica of its reference biologic, but the differences are acceptable if they are not clinically meaningful.

## Abbreviated FDA Pathway for Biosimilars

This involves a stepwise approach to generate data in support of use of biosimilars. A biosimilar product application must include data demonstrating biosimilarity to the reference product. This usually includes data from

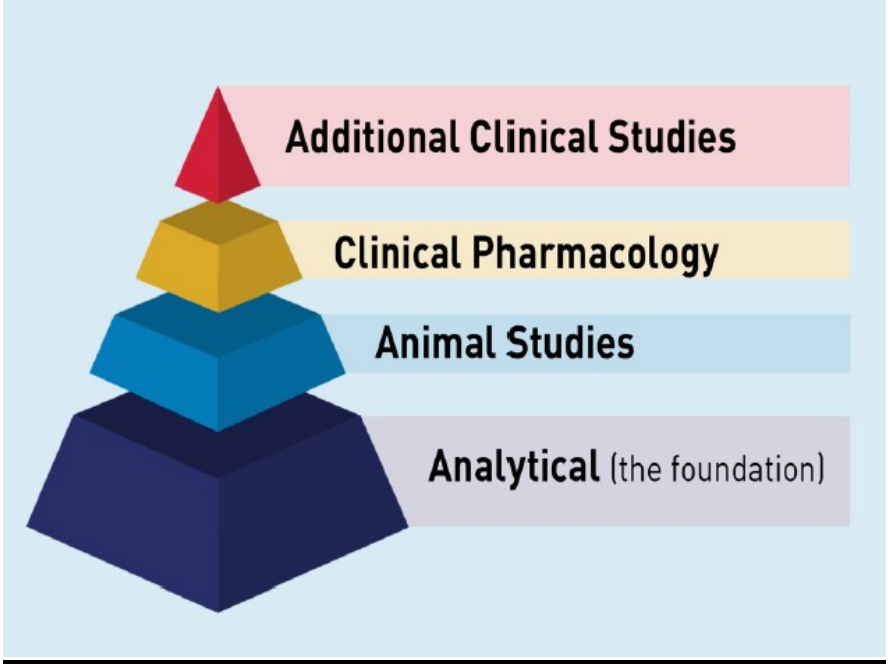



Figure 6. Abbreviated FDA Pathway for Biosimilars

**Analytical studies** demonstrating that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components. The goal of the analytical evaluation is to ensure that the biosimilar is within variability of the reference biologic across the multiple assays used, and that any minor difference is not clinically relevant.

Analytical studies are intended to demonstrate a molecular (physicochemical) and functional (bioassay) match to a previously-approved reference biologic. Structural and functional attributes include primary structure (ie, identical primary amino acid sequence), higher order structure (the three-dimensional shape), biological activity (as measured by bioassays that can include receptor binding or cell-based assays), protein content, sub-visible particles, impurities, thermal stability, post-translational modifications including glycosylation and higher molecular-weight variants or aggregates.

**Animal studies,** including an assessment of toxicity; this is useful when uncertainties remain about the safety of proposed product prior to initiating clinical studies.

**Clinical Pharmacological studies**; and

**Additional clinical study or studies** conducted to demonstrate safety, purity, and potency of the proposed biosimilar product in one or more of the indications for which the reference product is licensed. This typically includes assessing immunogenicity, pharmacokinetics (PK), and, in some cases, pharmacodynamics (PD) and may also include a comparative clinical study.

Biosimilars are tested in a stepwise fashion, with a targeted preclinical and/or clinical program following structural and functional characterization. The extent of the preclinical and/or clinical program depends on the residual uncertainty that may exist after the analytical and functional comparisons of the biosimilar and reference biologic. The targeted clinical development program is scientifically justified because the reference biologic has already been demonstrated to be safe and effective in the approved indications. The goal is not to prove it again with a biosimilar, but to confirm the absence of any clinically meaningful differences versus the reference biologic.

In the clinical stage of biosimilar development, human PK, and, if applicable, PD studies are central. Human PK studies are typically conducted in a healthy subject population because they are not receiving any other medications or have comorbid conditions that could confound the results. Immunogenicity studies, to assess development of neutralizing antibodies are also conducted in a sensitive population and must be long enough in duration to allow development of antibodies after extended exposure to the biologic medicinal product. Confirmatory studies may use a sensitive sub-population and endpoint which may be different from those used to establish *de novo* the efficacy and safety of an active substance.

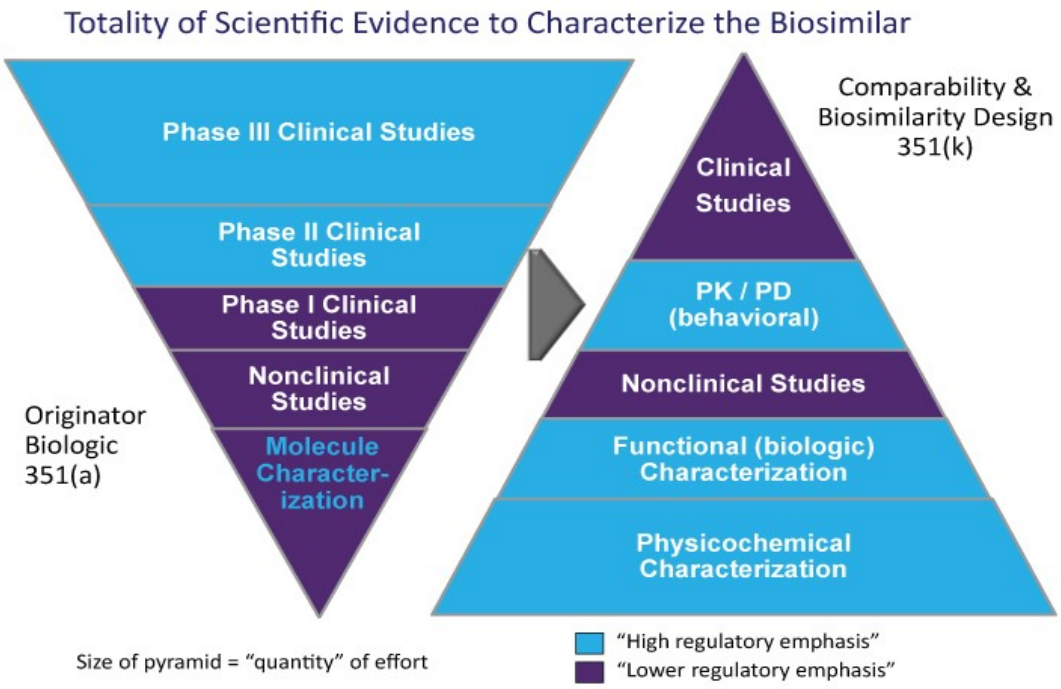



Figure 7. Comparison of Approval Pathways for Reference Product vs Biosimilar
Contrast between the standard 351(a) regulatory pathways to establish safety and efficacy of a new biologic product and the 351(k) pathways for a biosimilar approval.

**"Totality of the Evidence"**

The FDA's approach for evaluating biosimilarity is described as a "totality of the evidence," because multiple studies are evaluated to determine similarity between a biosimilar and its reference drug. This can be defined as the sum of data from analytical, preclinical, and clinical studies. The totality of the evidence standard is accepted worldwide, including by the FDA, EMA, and WHO. According to the FDA:
*"There is no one size fits all approach to biosimilar product development. The goal of a biosimilar development program is to use a "totality of the evidence" approach to demonstrate biosimilarity to the reference product, not to independently establish safety and effectiveness of the proposed biosimilar."*

**Extrapolation**

After a biosimilar has been approved by the FDA and is deemed to be similar to its reference drug, indications for the biosimilar may be extrapolated from the reference drug. Extrapolation is defined as "the approval of a biosimilar for use in an indication held by the reference product but not directly studied in a comparative clinical trial with the biosimilar." It is not necessary to repeat studies in all indications for which the reference biologic is approved because the concept of extrapolation can be applied. Extrapolation allows approval of a biosimilar for other indications for which the reference biologic is approved, even if the biosimilar was not studied specifically on those indication. The FDA bases extrapolation on sufficient scientific validation.

This is not a familiar concept for physicians who have traditionally relied on clinical trial information to judge safety and efficacy. With extrapolation, there may not be specific clinical trials performed in all subgroups and indications, which can come across as a paradigm shift. In order to properly engage, clinicians may want to know that the PK analysis shows equivalence, as it can differ by clinical context especially in malignant vs non-malignant conditions. Clinical efficacy should be demonstrated in appropriate patient populations with independent trials in malignant and non-malignant conditions (eg: Rituximab).

Nevertheless, extrapolation is an important concept for the use of biosimilars in oncology and eliminates the need for manufacturers to spend time and money on biosimilar research, thereby emphasizing the goal of expedited approval.

**"Interchangeable" or "Interchangeability"**

An interchangeable product is a biosimilar product that meets additional requirements outlined by the BPCI Act. As part of fulfilling these additional requirements, information is needed to show that an interchangeable product is expected to produce the same clinical result as the reference product in any given patient. To gain interchangeability status, manufacturers must undergo rigorous testing of their biosimilar, which requires time and an investment of money into the approval process to show "that the biosimilar is expected to produce the same clinical result as the reference product in any given patient."

Also, for products administered to a patient more than once, the risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product will have been evaluated. In addition, the risks for diminished efficacy and for adverse events when switching from a reference drug to a biosimilar must not be greater than the risk for using the reference drug without switching if the drug is administered more than once.

**An interchangeable product may be substituted for the reference product without the involvement of the prescriber.**

The FDA has not yet published official guidance on interchangeability, although a draft guidance is available. There is no data to support patients switching from a reference drug to a biosimilar and then back to the reference drug.

**To date, biosimilars are not interchangeable with their reference drug.**

**Biosimilars vs Generics**

The terms "biosimilar" and "generic drug" should not be used interchangeably, because of the extensive differences between them. Biologic drugs are typically large, complex molecules, difficult to synthesize. For that reason, biosimilars cannot be reproduced to the same degree as generic drugs, because of the inherent variability of biologic drugs. In contrast, small molecules are substantially lower in weight and can be synthesized using predictable chemical reactions. Biosimilars and generic drugs have different FDA approval

processes. Abbreviated New Drug Application 505(j) is used to approve generic drugs. Preclinical and clinical data are typically not required to show safety and efficacy for generic drugs if the generic version performs similar to the original drug.

Figure 8

**Differences Between Biosimilars and Generic Drugs**

| Variable | Biosimilar | Generic drug |
|---|---|---|
| Molecular weight | 4000 to >14,000 Da | <1000 Da |
| Chemical structure | Same amino acid sequence as the reference drug, but differences may occur | Chemically identical to the brand-name drug |
| FDA approval process | Biosimilar biologics license application<br>Demonstrates similar safety, purity, potency, and efficacy as its reference drug | Abbreviated NDA<br>Demonstrates bioequivalence to brand-name drug |
| Comparison with reference (brand-name) drug | A piece of DNA is added to a living cellular organism, which generates a protein<br>Has same amino acid sequence, but may have different posttranslational modifications, protein folding, or excipients | Same bioequivalence and purity as brand-name drug<br>It is predictable and bioequivalent to brand-name drug |

Da indicates Dalton; NDA, new drug application.
*Sources*: Nabhan C, et al. *JAMA Oncol.* 2018;4:241-247; Rak Tkaczuk KH, Jacobs IA. *Semin Oncol.* 2014;41(suppl 3):S3-S12; Harvey RD. *J Oncol Pract.* 2017;13(9_suppl):17s-23s.

## Nonproprietary Naming of Biological Products: Four-letter Suffix

The FDA requires that biologic drugs and biosimilars have the same nonproprietary or core name. This core name carries over if the biologic drug is a related biologic drug, a biosimilar, or an interchangeable drug. Four meaningless lowercase letters are then added after a hyphen to the end of the core name in case of a biosimilar or an interchangeable medication.

Originator biological product: replicamab (hypothetical example).

Biosimilar product: replicamab-dsfg

As of December 2019, there are 26 biosimilars approved by the FDA and multiple in clinical trials. More than half of these are for oncology indications.

## Trastuzumab in HER2/ neu amplified breast cancer

Monoclonal antibody used in HER2/ neu overexpressed or amplified breast cancer. It is approved in neoadjuvant, adjuvant and metastatic setting. Patent for branded trastuzumab expired in 2019. Biosimilar trastuzumab is studied and approved in all these setting. As of December 2019, there are currently 4 trastuzumab biosimilars approved.

- Trazimera (trastuzumab-qyyp)
- Ontruzant (trastuzumab-dttb)

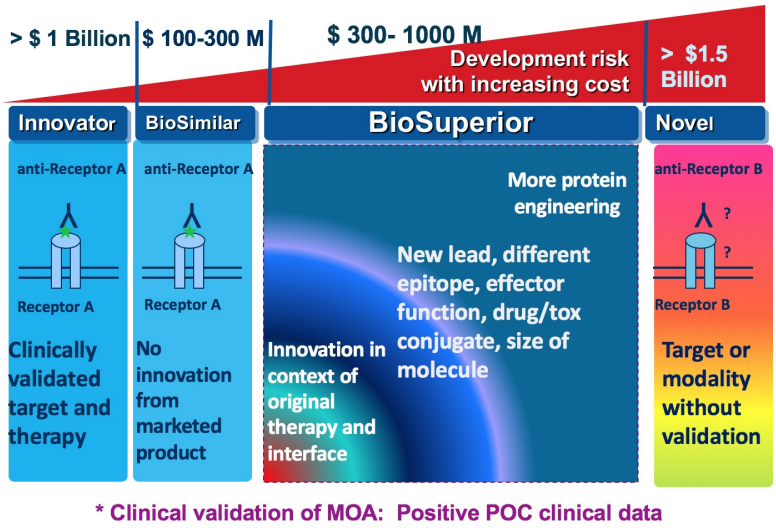
- Kanjinti (trastuzumab-anns)
- Ogivri (trastuzumab-dkst)

**Trastuzumab-dkst (Ogivri)**

The Phase III multicenter, randomized, double blind HERITAGE trial evaluated the efficacy and safety of Trastuzumab-dkst (Ogivri) vs trastuzumab, plus taxane as 1st-line therapy for patients with HER2+ metastatic breast cancer. Median PFS was 11.1 months in both groups. Median duration of response was 9.9 and 9.8 months. Median OS was 35.0 and 30.2 months for trastuzumab-dkst and trastuzumab, respectively. Long-term safety data similar in both groups.

"Bio-better" or "Bio-Superior"

These are biosimilars that have mechanisms of action (MOA) that are clinically proven or have a proof-of-efficacy that has been established and where addition values can be gained. There are several positive outcomes from creating a highly differentiated biosuperior drug. Unlike with a biosimilar, there is generally no need to wait for patents to expire because all biobetters are treated as new molecular entries from a regulatory perspective. Despite these benefits, developing biobetters does come with challenges. As compared to biosimilars, the regulatory process will be longer and more expensive, as the agent is treated as an entirely new entry. As a result, clinical development cost may not be too dissimilar to innovative drug development. Biobetters also face fierce challenges for demonstrating superiority in efficacy or safety against established biologics and market leaders, and unless the benefits are superior to biosimilars, the higher costs of biobetters may be questioned. It can be complex to establish biosuperority, and not every attempt at doing so will be successful.




Adapted from Medimmune

Figure 09. Comparison between reference product, Biosimilar, BioSuperior/ Biobetter, Novel drug

**Trastuzumab-anns/ Kanjinti (ABP 980)**

LILAC Study showed similar efficacy and safety of **Trastuzumab-anns/ Kanjinti** compared with Trastuzumab in early breast cancer.

| Cost | Trastuzumab/ Herceptin | Trastuzumab-anns/ Kanjinti |
|---|---|---|
| Cost Per Mg | $93.46 | $79.23 |
| Cost Per 150 mg Vial | $1401.84 | $1188.41 |
| Cost Per 420 mg Vial | - | $3327.53 |

Figure 10. Cost Comparison between Reference product Herceptin and Biosimilar Kanjinti

A typical dose of trastuzumab is 8mg/ kg loading dose followed by 6mg/kg every 3 weeks. This medication is continued till disease progression in metastatic disease and in early stage disease, continued for a total of 1 year (~17 cycles). So for an average woman weighing 60kg, a single dose will be approximately ~360mg, cost saving of $5,122.80 per session. This translates to a saving of $87,087.60 x 1 year per patient.

**Challenges to the Uptake of Biosimilars**

- Decreased awareness among clinicians
- Concern for decreased efficacy
- Concern for development of neutralizing antibodies. (immunogenicity)
- Approval process requires too large amount of data (increases costs)
- Needs greater healthcare provider confidence (too less data may lose clinician confidence)
- Lack of benefit to the patient (direct)
- Lack of recommendation by professional committees.
- Lack of incentives like co-pay assistance with biosimilars.

**Overcoming Challenges**

Many solutions have been proposed to address the issue of limited utilization of biosimilars. Legislation could be passed to increase the transparency in reporting of biologic patents, which would allow biosimilar manufacturers to more readily challenge their validity.

Additionally, regulatory agencies could scrutinize the anticompetitive practices of exclusionary contracts and enact stronger regulations against such practices. Lastly, the FDA could increase its efforts to educate physicians and the public about the bioequivalence of biosimilars and remove unnecessary naming policies that cause confusion among users, including the 4-letter suffixes given exclusively to biosimilars for the sole purpose of distinguishing them from their originators. Addressing these issues will inevitably result in increased biosimilar use.

## CONCLUSION

Biosimilars are biological products highly similar to the reference product notwithstanding minor differences in clinically inactive components. There are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product. Biosimilar development does not establish safety and efficacy, but rather shows biosimilarity to the reference drug. Increasing awareness and education are critical to utilization of biosimilars which in turn will improve access to high-quality medicines while decreasing healthcare costs.

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