Case Study

Level 2: Regulatory and Scientific Concepts

Introduction

Biological products (biologics) have been used as therapies in the United States for several decades. They also represent a growing proportion of treatment options and costs in the US health care market. Biologics treat a number of chronic illnesses like cancer, rheumatoid arthritis, and diabetes. In this case study, you will learn about biosimilar products (also called biosimilars) and interchangeable biosimilar products (interchangeable biosimilars), how FDA assesses a biosimilar in comparison to its reference product, prescribing considerations, and resources available to you as you learn about biosimilars.

Topics

- Variation in biologics
- Terms related to biologics
- Approval pathways
- Comparative studies to assess safety and efficacy
- Purple Book and naming
- Biosimilar labeling
- Addressing patient questions

As you read…

What are the differences in approval pathways for biosimilars and biologics?

What is the significance of the nonproprietary naming convention for biologics?

How can biologics be safe and effective with inherent variations?

How does FDA assess a biosimilar in comparison to the reference product?

When can a biosimilar be prescribed instead of a reference product and why?

How does biosimilar labeling differ from the reference product?

What is the Purple Book?

What resources are available to address patient questions?

Biosimilars in Patient Care

A prescriber considers a biosimilar for a patient

As Dr. Zeta looked over the list of patients coming into the office, she noted that a new biosimilar, darfloximab-swnt, was available that could be used to treat one of her patients.

Dr. Zeta had prescribed the reference product, for several years, to other patients so she was familiar with its safety and efficacy profile. Recalling an FDA webinar she attended on biologics, Dr. Zeta visited the website again to see what information was available on biosimilars in the United States. She also visited her health association's website to research darfloximab-swnt as a treatment option. In addition to some articles on darfloximab-swnt, Dr. Zeta noted a reference to FDA's website on biosimilars as a source for more information on biologics, including definitions, their approval pathways, and safety and effectiveness.

Variation in Biologics

Dr. Zeta knew that even with the exact same genetic code and amino acid sequence, proteins produced from living cells often contain small additions, like sugar molecules, and can undergo other natural processes that result in small changes to the protein structure. This means the resulting biologic is a mix of slight variations of the same molecule within each sample or lot of the biological product.

Terms

Reference Product
The original FDA-approved biologic against which the biosimilar is evaluated.

Biosimilar Product
A biologic that is highly similar to and has no clinically meaningful differences when compared to the reference product.

Interchangeable Biosimilar Product
A biosimilar product that meets additional requirements and may be substituted at the pharmacy for the reference product without the intervention of the prescriber.

Looking at a resource on FDA's website, Dr. Zeta made a note that as with other biologics, slight variation is also expected for biosimilars, and that manufacturing of the biosimilar is designed to closely match the pattern of variations observed with the reference product (Figure 1).

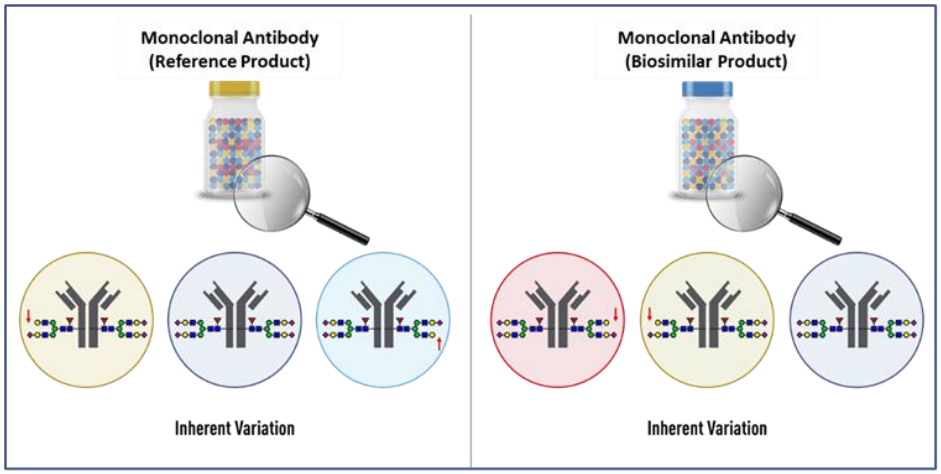

Figure 1: Inherent variation is observed in both reference products and biosimilar products, shown here as monoclonal antibodies, during the manufacturing process (as indicated by red arrows representing small differences in glycosylation). Identical biological variants are depicted as circles with the same color.

Approval Pathways

Exploring the website more, Dr. Zeta noted FDA's description of two approval pathways for biological products: (1) the 351(a) pathway, which is the approval pathway for the reference product; and (2) the 351(k) pathway, which is the abbreviated approval pathway for biosimilar and interchangeable biosimilars, that are compared to the reference products (Figure 2). Dr Zeta thought out loud, "So, to receive approval for a biosimilar, manufacturers need to show that biosimilar products are highly similar to and have no clinically meaningful differences from the reference product."

Looking at a figure on the page comparing the 351(a) and 351(k) pathways, Dr. Zeta observed to herself, "For the reference product, the main focus is on the clinical trial data to show safety and efficacy. For biosimilar approval, it looks like the analytical assessment serves as the foundation to show the biosimilar is highly similar to the reference product. That assessment, when coupled with other information, can show that there are no clinically meaningful differences between the reference product and the biosimilar.

Dr. Zeta's observation was correct. Because the reference product was approved and marketed under the 351(a) pathway, a number of studies were required to establish its safety and efficacy. In contrast, the 351 (k) biosimilar regulatory pathway relies in part on FDA's determination of safety and effectiveness for the reference product since biosimilar products are shown to be highly similar to and have no clinically meaningful differences from their reference products. For the biosimilarity evaluation, a significant focus is on the analytical side, which compares the clinically active components of the biosimilar to those of the reference product. Analytical capabilities have progressed over the years and current technologies allow for extensive molecular characterization. The tools compare not just the structure of the molecule, but its attributes and biological activity. Not only does the biosimilar molecule have a similar structure as the reference product, but it also is expected to function the same way.

Comparative Studies

Analytical Studies
Assess quality attributes using multiple tests and state-of-the-art technology; examine the structure and bioactivity of the molecule.

Animal Studies (if needed)
Provide safety information prior to human exposure (i.e., first-in-human studies).

Clinical Pharmacology Studies
Examine pharmacokinetic (i.e., exposure) and pharmacodynamic (i.e., response) to a biologic.

Clinical Studies
Include immunogenicity assessments, if needed, to understand the incidence and severity of immune response to a biologic.

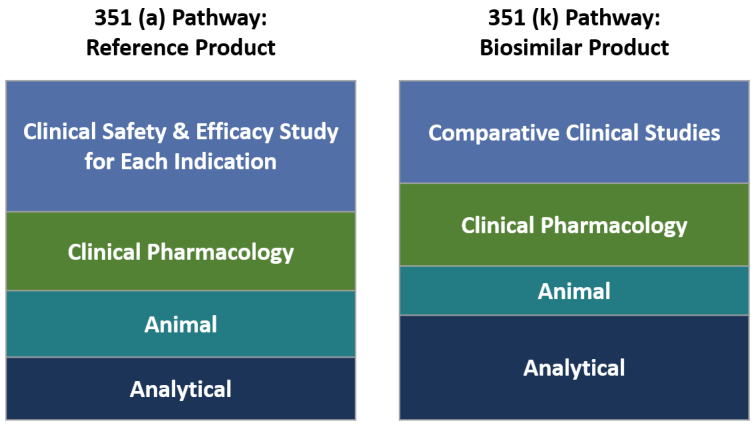

Figure 2: Comparison of reference product and biosimilar product regulatory approval pathways

Dr. Zeta remarked to herself, "Basically, FDA evaluates the results of these analytical studies, as well as results from animal studies, pharmacokinetic and pharmacodynamic studies, and the immunogenicity assessment of the biosimilar compared to the reference product. If FDA finds that the totality of the evidence shows biosimilarity to the reference product, then I can expect the same benefits and risks as for the reference product as well. The biosimilar also has the same dosing and route of administration as the reference product."

This generally means that biosimilar manufacturers do not need to repeat the costly and lengthy clinical trials supporting approval of the reference product, potentially leading to faster access to these products, additional therapeutic options, and potentially reduced costs for patients.

Dr. Zeta noted an additional term: interchangeable biosimilar. This is important to know because it refers to a biosimilar that FDA has concluded meets additional requirements and that may be substituted without the intervention of the prescriber, depending on state law.

Because darfloximab-swnt is a biosimilar but not an interchangeable, Dr. Zeta would need to write a prescription specifically for the biosimilar if her patient agreed with the treatment plan.

Purple Book and Naming

With an understanding of the approval pathways for biosimilars and the definitions for reference, biosimilar, and interchangeable products, Dr. Zeta clicked the link for another FDA resource called the Purple Book (Figure 3), a searchable database of FDA- licensed biological products.

From the Purple Book, Dr. Zeta clicked on the advanced search function and began typing "darfloximab," the core name shared by both the reference and biosimilar product. As she typed, the results auto-populated with the corresponding products, each sharing the familiar core name but with a unique 4-letter suffix (e.g., darfloximab-swnt) that many biologics have to help distinguish products from one another when ordering, prescribing, dispensing, and recordkeeping, and facilitate pharmacovigilance efforts. The search result provided relevant information, such as the product type (e.g., reference product),

dosage forms and strengths, and approved routes of administration.

Figure 3: Please visit https://purplebooksearch.fda.gov

Biosimilar Labeling

Dr. Zeta clicked on the link to Drugs@FDA where she explored the labeling information for darfloximab-swnt. It shared much in common with the reference product labeling. After reviewing the labeling information, Dr. Zeta confirmed the biosimilar is approved for treatment of her patient's condition. Looking through the other resources available on Drugs@FDA, she located FDA's clinical review documents on the biosimilar, which included data from the direct comparison of the biosimilar and reference product. The documents also showed the data and information that demonstrated biosimilarity to the reference product as assessed by multiple tests. It also contained FDA's conclusion that highlighted the evidence supporting that the biosimilar has no clinically meaningful differences from its reference product for the uses for which approval was requested.

Shared Decision Making and Addressing Patient Questions

Once the patient, Jane, came into Dr. Zeta's office, she suggested a treatment plan for Jane that included options for the reference product (darfloximab-rpos) and biosimilar product (darfloximab-swnt).

"Thank you, Dr. Zeta. I'm interested in the potential health benefits of that biologic, but I've only heard of the reference product. I'm not familiar with biosimilars. I'm willing to try it if you recommend it, but I have a few questions." Dr. Zeta addressed Jane's questions:

1. The biosimilar medicine is expected to be as safe and effective as the reference product.
2. The biosimilar medicine is administered the same way as the reference product (e.g., same dose, same route of administration).
3. Different insurance carriers may offer coverage for different reference products and biosimilar medicines, so it is important to speak with your carrier about your coverage.

Dr. Zeta provided details on the biosimilar, drawing directly from the data she had reviewed that morning. Dr. Zeta also moved her screen around so Jane could see it and brought up FDA's biosimilar page. She pointed Jane to the patient materials so that Jane could explore at home. Dr. Zeta also checked to see if the biosimilar was covered under Jane's insurance plan. While she couldn't provide the exact cost details, she did mention that the biosimilar was in the preferred tier of her insurance plan's formulary, and that this may mean a savings on her out-of-pocket expenses compared to the reference product, but that Jane should reach out to her insurer directly to confirm.

"Okay, Dr. Zeta. Thanks for taking the time to answer my questions and share that resource with me. I am ok with whatever option you suggest."

"Great," said Dr. Zeta. "I'm always here for questions. The pharmacist will also be able to answer questions you might have about the medication."

Biosimilar Resources

FDA Pages

- Biosimilar materials
- Provider materials
- Patient materials
- Purple Book
- Drugs@FDA (Drug Information)
- Search page for FDA guidances
- Advisory committee materials for Biosimilars
- Biosimilar approval process information

Additional Resources for Health Care Students

- Slide Decks:
  - Foundational Concepts
  - Regulatory and Scientific Concepts
- Case Study:
  - What Is a Biosimilar?
  - Biosimilars in Patient Care
  - Interchangeable Biosimilars
- Info Sheets:
  - Biological Products, Biosimilar Products, and Interchangeable Biosimilar Products
  - Generics and Biosimilars
  - Manufacturing and Variation
  - Biosimilar Regulatory Approval Pathway
  - Variation in Biological Products
  - Comparative Clinical Studies
  - Prescribing Biosimilar and Interchangeable Biosimilar Products
- Explanatory Videos:
  - Biosimilars: Manufacturing and Inherent Variation
  - Biosimilars: Approval Process
  - Biosimilars: Critical Quality Attributes
  - Biosimilars: Interchangeability
- Discussion Questions:
  - Foundational Concepts
  - Regulatory and Scientific Concepts
- Exercises (provided in the Resource Guide for Teaching Faculty)