An evolution in treatment options

UNDERSTANDING BIOSIMILARS IN THE US—

The development, approval, and potential impact of these biologics

The biosimilar approval pathway was established as a way to provide more treatment options, increase access to life-changing medicines, and potentially lower healthcare costs through price competition.[1]

teva | Biosimilars

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BIOLOGICS 101

What are biologics?

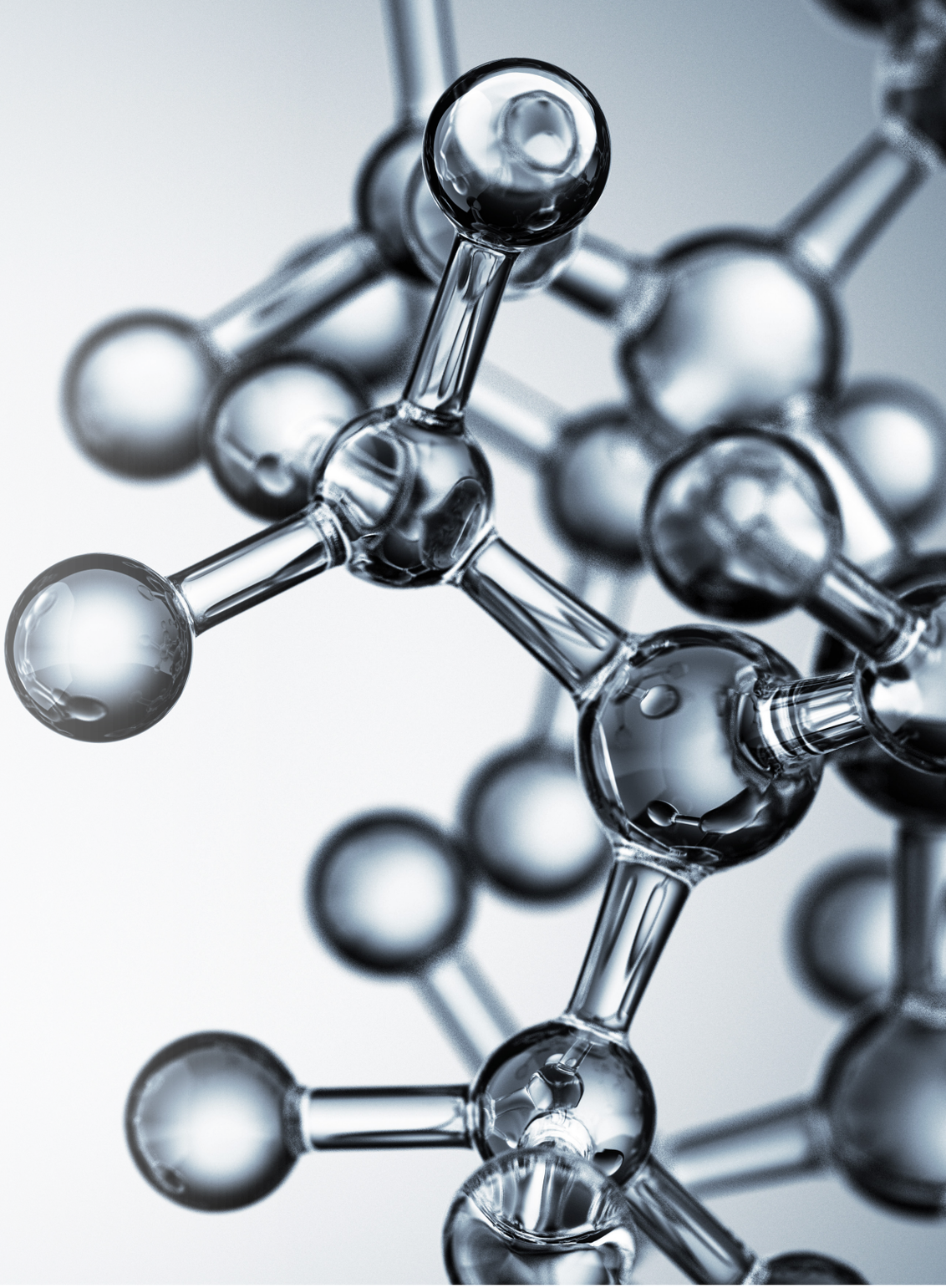
To understand biosimilars, it's important to first understand biologics. Without biologics there would be no biosimilars. Biosimilars are developed to be highly similar to a specific reference biologic.[2]

In the United States, biological products are the fastest growing class of therapeutic products and account for a substantial and increasing proportion of healthcare costs.[1]

Biologics are complex drugs of heterogeneous structure produced from living cells. For this reason, the manufacturing process for a biologic is very important and must be followed exactly.[3-5]

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) created an abbreviated approval pathway for biological products demonstrated to be biosimilar to or interchangeable with an existing FDA-approved reference product in order to provide[1,4]:

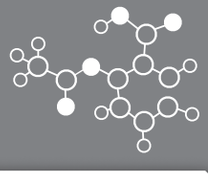
- Greater access to life-saving medications
- More treatment options
- A potentially lower cost through price competition



TO BETTER UNDERSTAND THE CHARACTERISTICS OF BIOLOGICS, LET'S COMPARE THEM TO CHEMICAL OR SMALL MOLECULE DRUGS

BIOLOGIC/ BIOLOGICAL DRUG[4-6]

- Produced by **living cell cultures**
- **High** molecular weight
- **Complex, heterogeneous structure** and manufacturing process
- Strongly **process-dependent**
- **Impossible to fully characterize** molecular composition and heterogeneity
- **Unstable**, sensitive to external conditions



CHEMICAL/SMALL MOLECULE DRUG[2,6]

- Produced by **chemical synthesis**
- **Low** molecular weight
- **Well-defined structure** and manufacturing process
- Mostly **process-independent**
- **Completely characterized** chemicals
- **Stable**

What is a biosimilar?

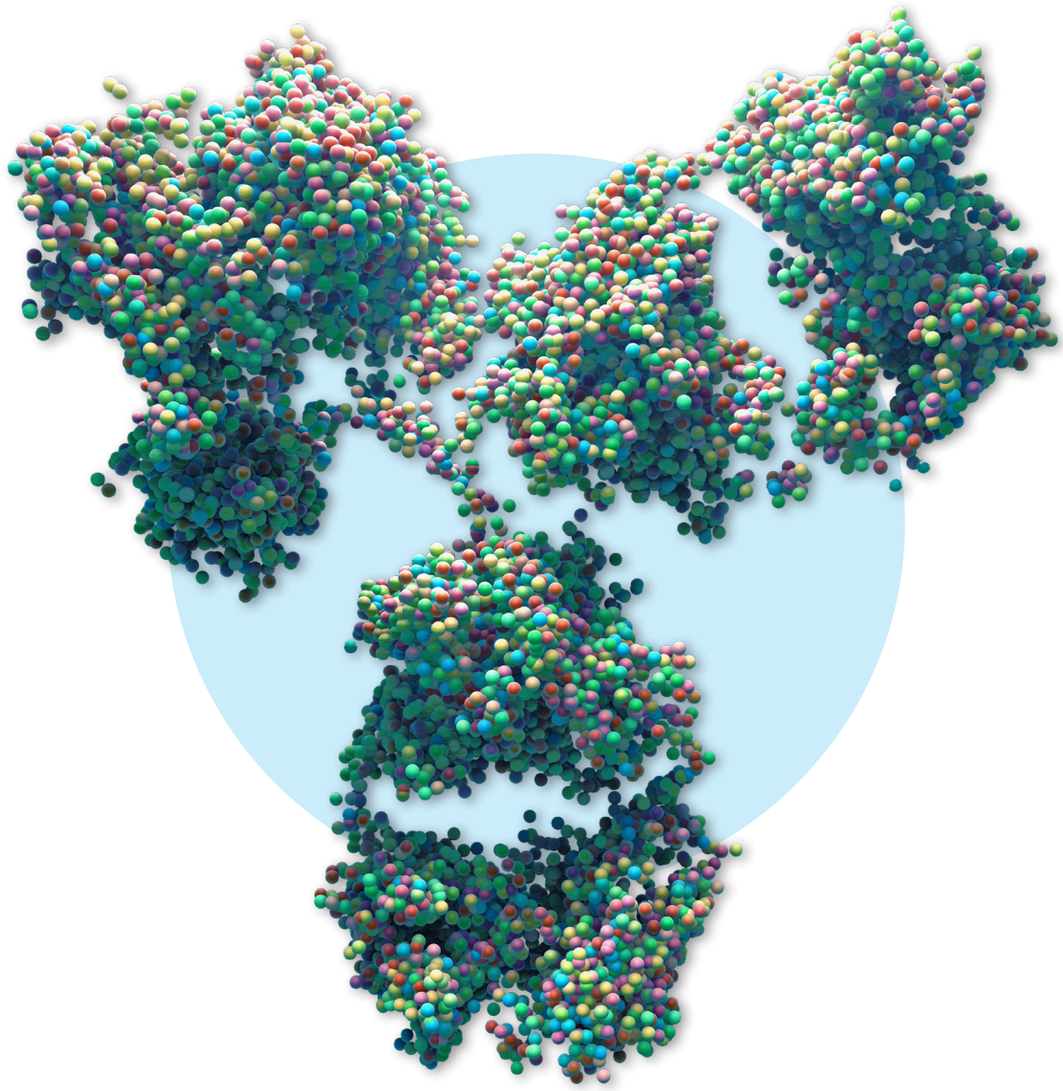
The FDA defines a biosimilar as **a biological product that is highly similar to the reference product, notwithstanding minor differences in clinically inactive components.** There are no clinically meaningful differences between the biosimilar product and the reference product in terms of safety, purity, and potency.[7]

To demonstrate biosimilarity, the manufacturer must provide sufficient data and information to the FDA to prove that there are no clinically meaningful differences between the reference product and the proposed biosimilar.[2]

Safety

Purity

Potency

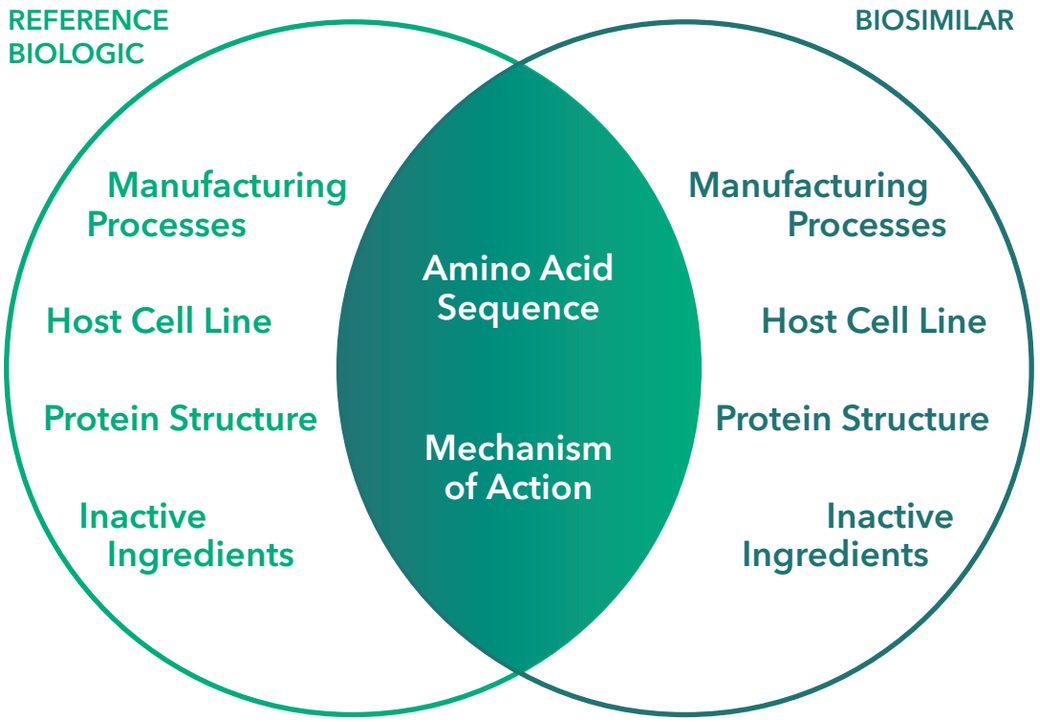


Biosimilars must be highly similar to a reference biologic.[2]

Biosimilars are biologics highly similar to an existing product

There is natural variability in the manufacturing of all biologics. Quality control measures are therefore put in place to help ensure a high similarity between biologic products.[8]

FEATURES SHARED BY A REFERENCE BIOLOGIC AND ITS BIOSIMILAR[2,9-11]



The amino acid sequence and the mechanism of action have no clinically meaningful differences.[2,9]

A distinct approval process

The goal of a biosimilar development program for gaining FDA approval is **demonstrating high similarity between the proposed biosimilar product and the reference product**—not to independently establish the safety and efficacy of the proposed product. Biosimilars must demonstrate no clinically meaningful differences from the reference biologic in terms of safety, purity, and potency.[12]

The FDA reviews the totality of evidence supporting biosimilarity when deciding whether to approve a biosimilar product. Including[2]:

Detailed analytics (structural and functional characterization)

Clinical pharmacology (PK/PD data)

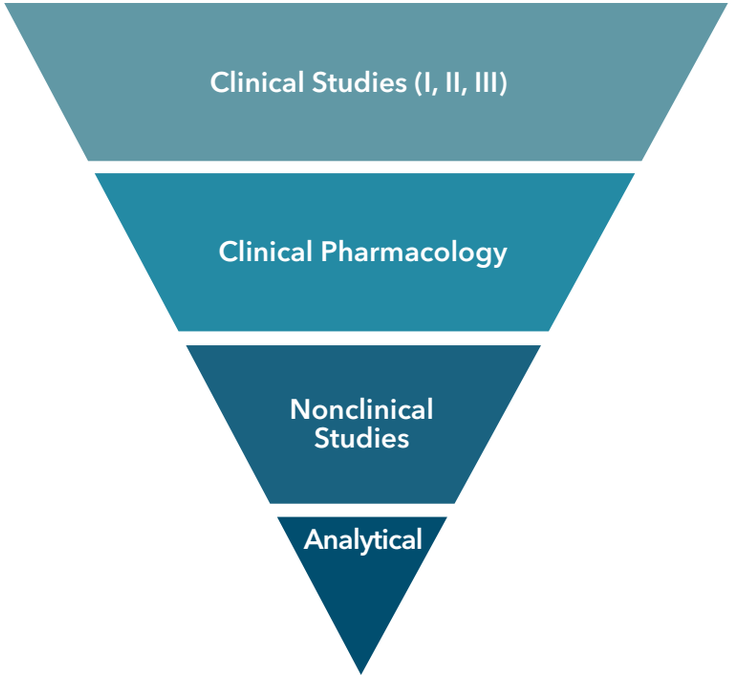
Nonclinical evaluation (animal studies)

Clinical immunogenicity data and other comparative clinical studies of biosimilarity

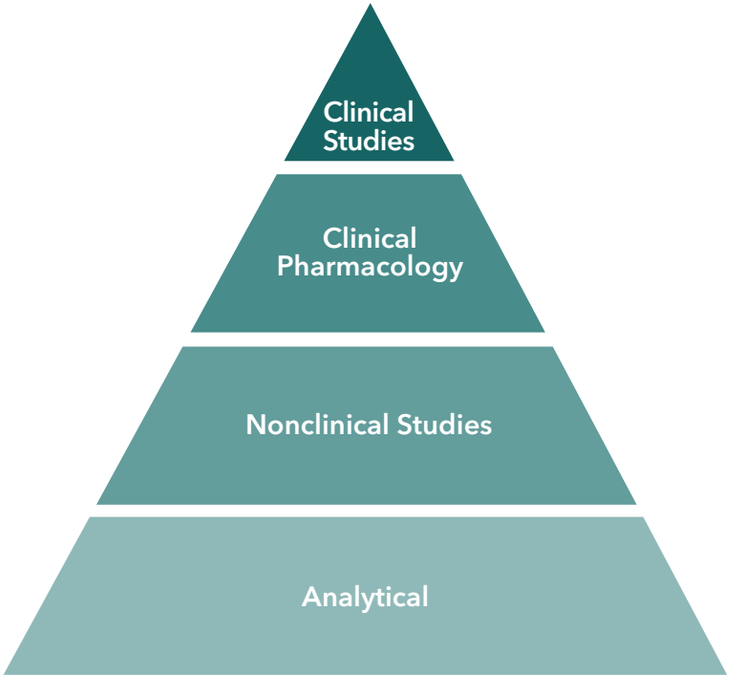
DIFFERENCE BETWEEN BIOLOGIC AND BIOSIMILAR APPROVAL PATHWAYS

The image on the left depicts the pathway of approval for a biologic. In contrast, the image on the right shows that biosimilar development must include data demonstrating biosimilarity to the reference product. The FDA reviews the totality of evidence supporting biosimilarity including detailed analytics (structural and functional characterization), non-clinical evaluation (animal studies), clinical pharmacology (PK/PD data), clinical immunogenicity data, and other comparative clinical studies in making this decision.[2] The goal of a biosimilar program is to demonstrate biosimilarity, not to independently establish the safety and efficacy of the proposed product.[12]

ORIGINATOR BIOLOGIC
351(a)[13]



BIOSIMILAR
351(k)[13]



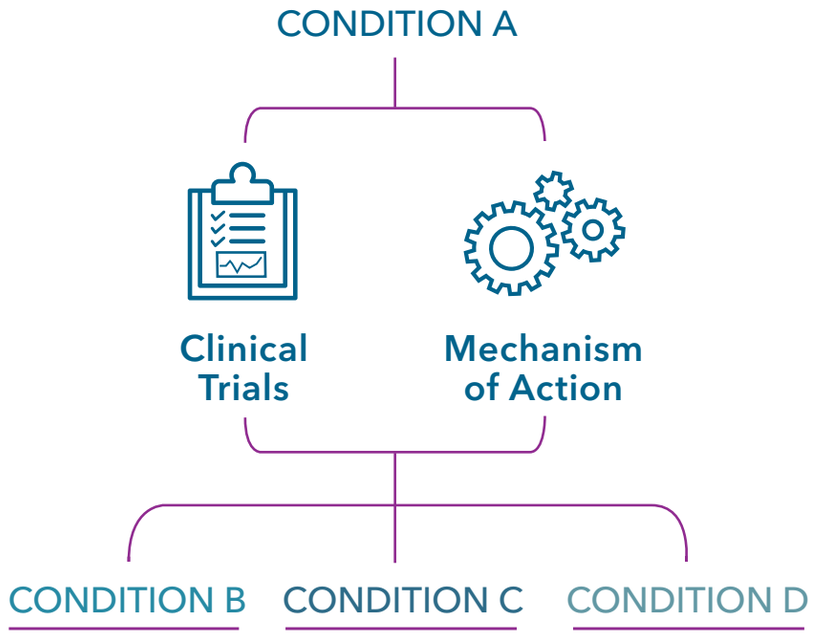
BIOSIMILAR TERMINOLOGY:
Important terms to consider about biosimilars—**extrapolation** and interchangeability

Extrapolation

Extrapolation is based on[2]:
- **All available data and information in the biosimilar application**
- **The FDA's previous findings of safety and efficacy for the reference product**
- **Knowledge and consideration of various scientific factors for each condition**

A biosimilar can be approved if there is sufficient scientific justification for extrapolating clinical data. Along with other factors, this may include[2]:

- **The mechanism of action** in each condition for which approval is being sought
- **The pharmacokinetic and pharmacodynamic properties** of the product in different patient populations
- **Differences in expected toxicities** in each condition of use and patient population



BIOSIMILAR TERMINOLOGY:
Important terms to consider about biosimilars—extrapolation and **interchangeability**

Interchangeability

Interchangeability is when a biosimilar may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.[14]

BIOLOGICAL PRODUCT INTERCHANGEABILITY

For a biosimilar product to be designated interchangeable, in addition to demonstrating biosimilarity, data must be submitted to show that it[14]:

1. **Demonstrates biosimilarity** to the reference product
2. **Can be expected to produce the same clinical result** as the reference product in any given patient

additional data

3. **Should be administered more than once to the same person** and the risk in terms of safety or diminished efficacy of alternating or switching between the biosimilar and its reference product is not greater than the risk of using the reference product without such alternation or switch

DEVELOPMENT OF BIOLOGICS

Manufacturing and quality control

Biologics are developed using living cells or organisms, such as bacteria, yeasts, viruses, or other animal cells.[4,15] Some degree of variation in batches of active ingredient is a normal part of the manufacturing process.[8] Biologics are typically more complex and are unlikely to be shown to be structurally identical to a reference product. Many potential differences in protein structure can arise.[2]

Manufacturing biologics is quite different than small-molecule drugs

Small-molecule drugs are manufactured using predictable chemical synthesis processes to yield a final structure that is always the same and is easily verified.[2,4] Quality measures that are sufficient for small-molecule drugs are inadequate for biologics, which have complex molecules that are sensitive to even small changes in the manufacturing process.[16]

It is important to understand that biosimilars are biologics and therefore are measured by the same FDA standards of Good Manufacturing Practices (GMP).[18]

BIOLOGIC MANUFACTURING CRITICAL STEPS INCLUDE[17]:

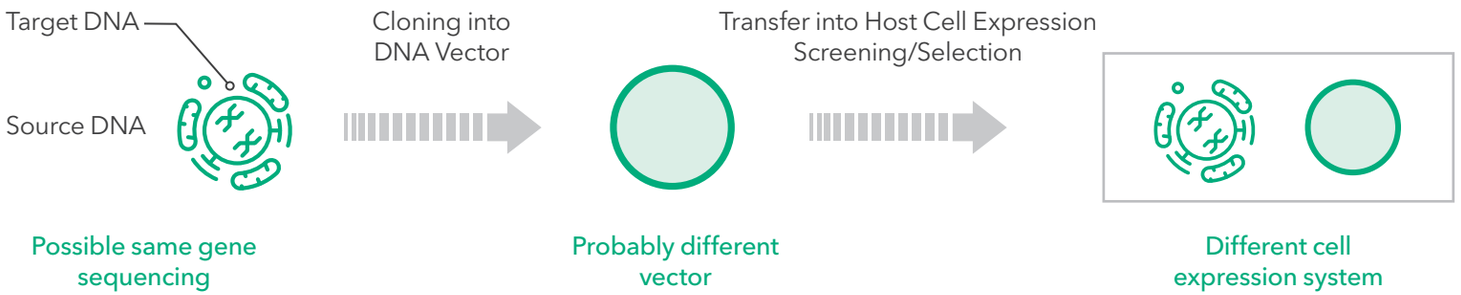
- **Expanding** the host cell population
- **Production of the biologic product** by host cells in bioreactors
- **Recovery**
- **Purification** of the product

These critical steps must be followed to ensure integrity between batches.

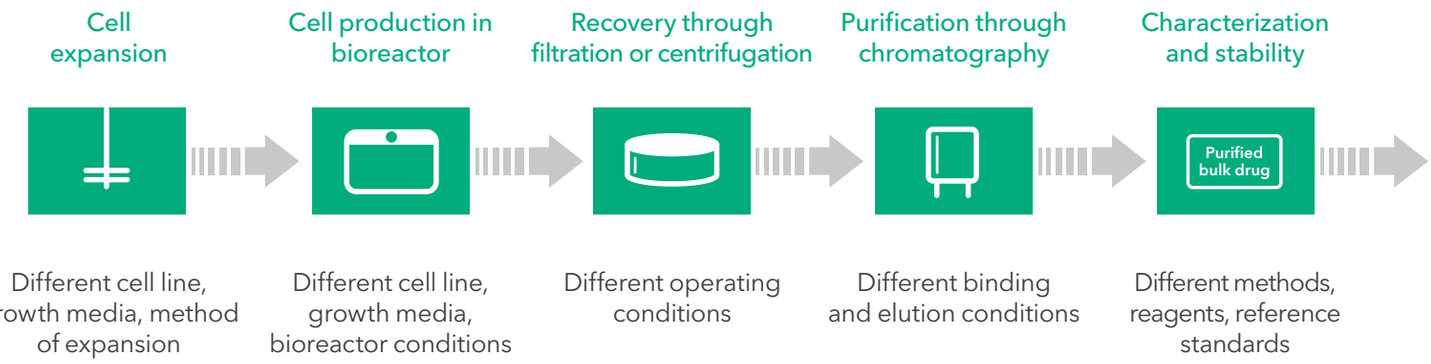
Biologic/biosimilar manufacturing process

The manufacturing process begins with isolation of DNA for the biological product. It is then attached to a vector (such as a virus), and transferred to a host cell, which will make the biologic product.[17]

CLONING AND PROTEIN EXPRESSION[17]



PROTEIN PRODUCTION, PURIFICATION, AND VALIDATION[17]



Critical quality attributes of biologics

During production of biologics, the manufacturer monitors several Critical Quality Attributes (CQAs), or characteristics to ensure that they fall within a range of normal variability of the drug product.[8]

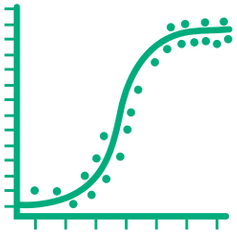
Some of the manufacturing issues that could impact CQAs include[19]:

STRUCTURE

Includes not only the linear amino acid sequence, but also protein folding and 3-dimensional structure. Incorrect protein structure can lead to efficacy that is reduced or more variable

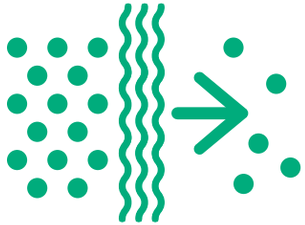
GLYCOSYLATION

The binding of carbohydrate molecules to a protein is common with proteins that are secreted by cells.[20] Variations in glycosylation can affect properties such as the drug half-life or how likely it is that the drug will cause an immune response



BIOLOGICAL ACTIVITY

Includes the ability to bind to its molecular target



MANUFACTURING PROCESS IMPURITIES

These include contamination with DNA or protein from the host cells that were used to grow the biological drug, as well as other chemical contaminants from the manufacturing process

The impact of drift on the manufacturing process

Over time, changes can take place in either the manufacturing process or the quality attributes of biologics. This can cause what is known as drift.[8]

What is drift?

Drift refers to unintended, unexplained, or unexpected change in either manufacturing process parameters or the final product over the product's lifetime. Drift may be gradual or sudden and occurs in any biologic drug and therefore would be expected to occur with its respective biosimilar.[8,16]

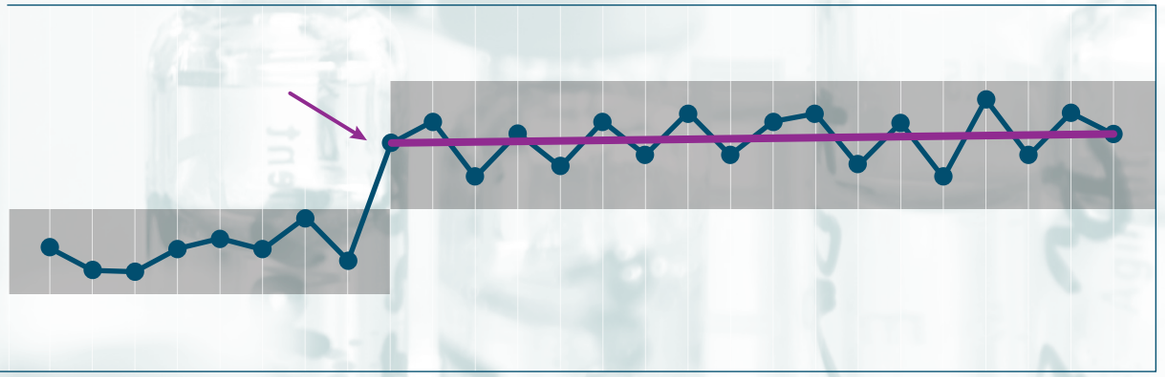
All manufacturing processes have inherent variability. Although some variability is normal between batches during the manufacturing process of biologics, any changes must be rigorously investigated and controlled through robust quality systems.

Drifts and shifts in biologics are highly regulated by International Guidance and batches of reference products after a manufacturing change must demonstrate they are "highly similar" to pre-change batches.[8] The FDA reviews confidence intervals on the biosimilars to be sure they are in range.[16]

GRADUAL UPWARD TREND IN PROTEIN CONCENTRATION

Arbitrary quality attributes

ABRUPT SHIFT TO NEW BASELINE



Arbitrary quality attributes

Simulated protein concentrations in different drug batches over time. The top image shows a gradual drift toward a higher protein concentration, while the bottom image shows an abrupt change.[16]

Gradual drift is also known as evolution

What is evolution?

The term evolution is used to refer to deliberate process changes implemented by the manufacturer.

For example, changes may be introduced to[16]:

- Meet regulatory requirements
- Increase production
- Improve efficiency

Other **changes over time** to the manufacturing process may be due to[16,19]:

- Modification to production materials
- Change in site
- Change in technology

Manufacturing complexities of biologics

Due to evolution and drift during the manufacturing process, biologics that have been on the market for a while are no longer necessarily identical to the original drugs.[21]

Some potential changes to the biologic or biosimilar manufacturing process that may affect the activity of the drug include differences in[21]:

Fermentation temperature

pH level

Filtration and purification

Inactive ingredients (stabilizers, solubilizers, buffers, pH, bulking agents)

Quality control is never complete—it continues throughout the lifetime of the product with regular assessment of batch-to-batch variability.[22] It is a dynamic and iterative process that involves quality systems that are internal to each manufacturer, with oversight of the product and manufacturing process by regulatory authorities.[16]

Manufacturing quality control

Although approved by different pathways, biosimilars and the reference biologic drug are held to the same high-quality manufacturing standards by the FDA, and both undergo post-approval monitoring to ensure that safety and efficacy remain equivalent throughout the life cycle of the product.[18] Manufacturers use various quality control systems to ensure consistency of the product across the life cycle. The quality oversight process monitors[16]:

Quality system*

Materials system

Facilities and equipment system

Production system

Laboratory control system

Packaging and labeling

*Ensures overall compliance with current good manufacturing practice and internal requirements.

FDA AND THE DEVELOPMENT OF BIOSIMILARS

Ensuring biosimilarity

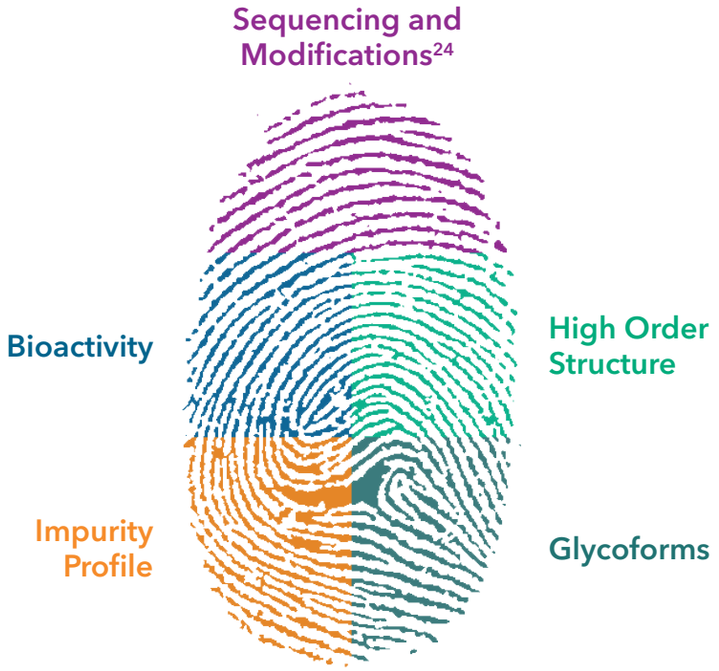
The FDA recommends a specific process for developing, characterizing, and comparing a biosimilar and its reference biologic. To make certain that the proposed biosimilar is highly similar to the approved reference product, a rigorous system is needed to characterize the two products and compare them with one another.[8,23]

This process is similar to quality control measures that monitor the consistency of an approved biologic after changes in the manufacturing process, and it also includes ongoing evaluation of product safety, or pharmacovigilance, after the biosimilar has been approved.[8]

By definition, a biosimilar needs to demonstrate that it is highly similar to the reference product and that there are no clinically meaningful differences between the biosmilar product and the reference product in terms of safety, purity, and potency of the product.[2]

BIOSIMILAR FINGERPRINTING

To evaluate similarity, the FDA recommends that biosimilar manufacturers use a "fingerprint-like" process that examines a large number of attributes of the product. This involves more than just comparing the two compounds on individual analytical tests to evaluate how the two products are similar and how they are different.[5]



BIOSIMILAR FINGERPRINTING IS[5]:

Above & beyond risk-based comparative characterization

Evaluation of overall pattern of similarity

An assessment of many product attributes together allows an extremely sensitive approach to identifying differences between the proposed biosimilar and the reference product.[5] As many as 100 different attributes may be compared between the biosimilar and the reference drug.[25]

Testing to reduce residual uncertainty

The amount and type of animal and clinical studies is determined after analytical testing to resolve uncertainties that remain about the safety and similarity of the proposed product.[2]

ANIMAL STUDIES[2]

- Pharmacokinetics
- Pharmacodynamics
- Toxicity[2]
  The FDA recommends comparative testing

HUMAN STUDIES[2]

- Pharmacokinetics
- Pharmacodynamics
- Immunogenicity[2]
  The FDA requires at least one clinical trial that compares immunogenicity of the biosimilar with its reference product
- Additional clinical studies of biosimilarity, as necessary[2]

Pharmacokinetics[26]

/ fär-mə-kō-kə-'ne-tiks *(noun, plural in form but singular in construction)*

measures factors such as absorption and elimination of the drug.

Pharmacodynamics[26]

/ fär-mə-kō-dī-'na-miks *(noun, plural in form but singular in construction)*

measures the effects of the drug on its biological target.

What is immunogenicity?

A concern with biologics is the potential to elicit an immune response in the patient receiving treatment that can have a negative effect on safety and efficacy.[27]

According to the FDA, **immunogenicity is defined as the propensity of the therapeutic protein product to generate immune responses to itself and to related proteins or to induce immunologically related adverse clinical events.**[27]

Immunogenicity occurs when a patient develops antibodies against the product. Antibodies can bind to and neutralize the biologic agent, which may reduce drug concentration and efficacy. Antibodies can also elicit immune responses that contribute to adverse effects.[27]

The biosimilar development process includes a careful comparison of immune responses, or immunogenicity, between the proposed biosimilar and the reference compound.[2]

Factors that influence immunogenicity[28]

Both the reference drug and the biosimilar are proteins that contain the same primary sequence of amino acids. However, they are produced from different cell lines and using different manufacturing processes, which contributes to some natural variability between the two.[25] This product variability can contribute to unwanted immunogenicity and requires careful evaluation.[29]

Pharmacovigilance: ongoing post-approval safety monitoring

Although the safety of biological products is rigorously assessed before approval, there is also an ongoing process of post-approval safety monitoring, or pharmacovigilance, to allow the FDA and the manufacturer to track adverse events.[14,16,23,30]

The FDA requires manufacturers to conduct post-marketing pharmacovigilance surveillance after any manufacturing change for all biologic agents, including both the reference biologic and its biosimilars.[14]

-abcd | -efgh | -ijkl

Naming convention to distinguish biosimilars

Pharmacovigilance requires that all products within the same category be distinguishable from each other. However, with the approval of a growing number of biosimilars derived from the same reference product, it may become increasingly complex to attribute adverse events to the correct agent and manufacturer.[30,31]

To help overcome this problem, the FDA has developed **a naming convention for biosimilar drugs that includes a unique random 4-letter suffix after the product's non-proprietary name.** Suffixes serve as a key element to identify specific products for adverse event reporting.[30]

THE BIOSIMILAR APPROVAL PROCESS

Biosimilars undergo rigorous evaluation

All FDA-approved drugs, including biologics and their respective biosimilars, undergo a rigorous evaluation.[2] Biosimilars and their biologic reference products each go through specific regulatory approval processes—but there are differences.

BIOLOGIC REFERENCE DRUG APPROVAL PROCESS

The reference drug approval process is different from a biosimilar because it is **approved in a "standalone" 351(a) application that must contain all data and information necessary to demonstrate its safety and effectiveness.** It will include clinical trials for the disease indications being sought by the manufacturer.[1,2]

Biosimilar drug approval process

In contrast, **the 351(k) biosimilar development program aims to demonstrate biosimilarity between the proposed biosimilar product and the reference product.** It does not independently demonstrate the safety and effectiveness of a proposed biosimilar.[12] The manufacturer of a proposed biosimilar product generates an array of data comparing the proposed product to the FDA-approved reference product to demonstrate biosimilarity.[2]

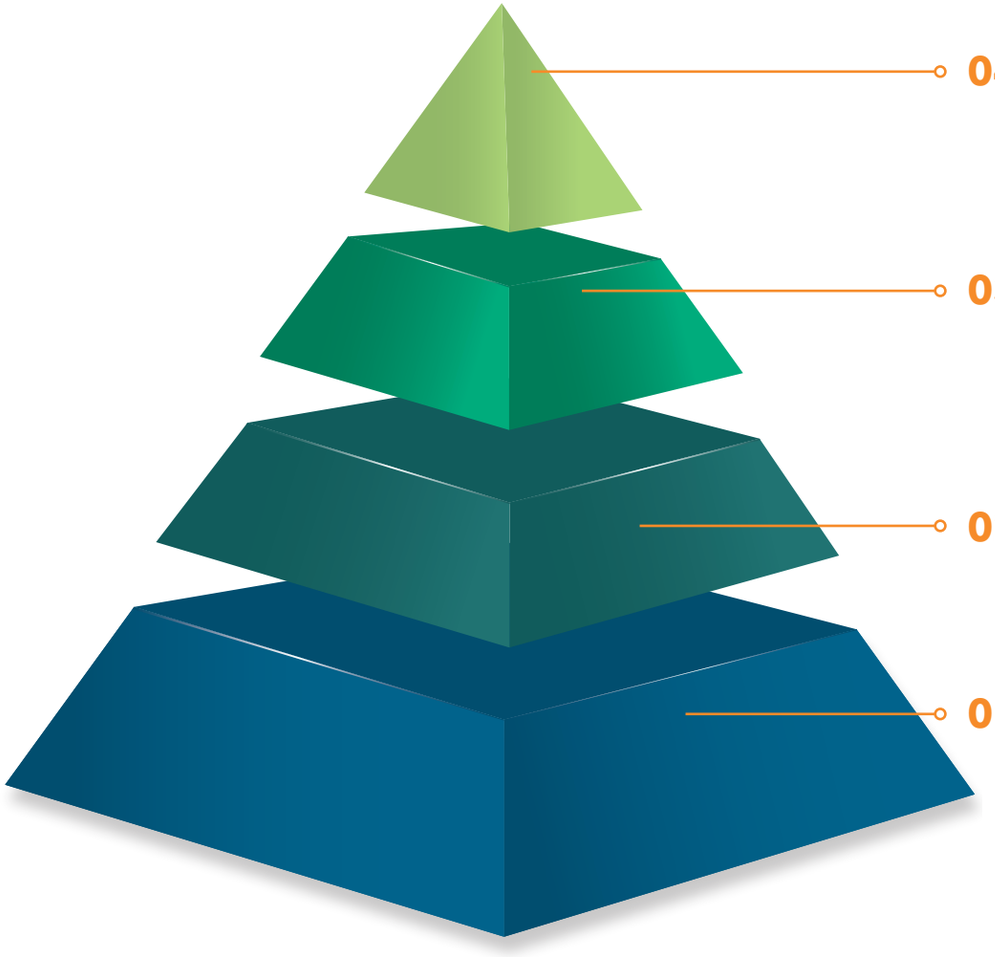
Clinical data is generated and evaluated in a stepwise fashion that begins with a foundation of detailed analytical (structural and functional) characterization and comparison of the products, and if necessary, moving on to animal studies and again if necessary, on to clinical studies.[12]

Consequently, rather than generating the same full profile of nonclinical and clinical data as a reference product, a manufacturer that shows its proposed biosimilar product is highly similar to and has no clinically meaningful differences from the FDA-approved reference product may rely in part on the FDA's previous determination of safety and effectiveness for the reference product for biosimilar approval.[2,12]

Biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and cost competition.[1]

Biosimilar product application

A biosimilar product application must include data demonstrating biosimilarity to the reference product.[12]



THIS USUALLY INCLUDES[12]:

04 | **Additional Clinical Studies**

03 | **Clinical Pharmacology Studies**

A clinical study or studies sufficient to demonstrate there are no clinically meaningful differences in safety, purity, and potency of the proposed biosimilar product

- Typically includes assessing immunogenicity, pharmacokinetics (PK), and, in some cases, pharmacodynamics (PD)

02 | **Nonclinical Studies**

Animal studies, including an assessment of toxicity

01 | **Analytical Characterization** (the foundation)

Analytical studies demonstrating that the biologic is highly similar to the reference product, notwithstanding minor differences in clinically inactive components

Approval in multiple indications based on extrapolation

A biosimilar product may be approved for a condition without direct studies of the biosimilar in that condition.[2]

If the totality of evidence in the biosimilar application supports a demonstration of biosimilarity for at least one of the reference product's conditions, then it is possible for the biosimilar manufacturer to use data and information to scientifically justify approval for other conditions that were not directly studied by the biosimilar manufacturer. This is known as extrapolation.[2]

Extrapolation allows for the approval of a biosimilar for use in a condition held by the reference product but not directly studied in clinical trials by the biosimilar manufacturer.[4]

EXTRAPOLATION IS BASED ON[2]:

- **All available data and information in the biosimilar application**
- **The FDA's previous findings of safety and efficacy for the reference product**
- **Knowledge and consideration of various scientific factors for each condition**

EXTRAPOLATION MUST BE SUPPORTED BY SCIENTIFIC JUSTIFICATION

For each condition of the reference product, the biosimilar manufacturer must provide scientific justification to support extrapolation. These scientific justification factors include knowledge of [2]:

Mechanism(s) of action

Pharmacokinetics

Pharmacodynamics

Efficacy and safety

Immunogenicity

The FDA works with biosimilar manufacturers during product development to determine what data is needed to support extrapolation. Moreover, the FDA decides on a case-by-case basis if extrapolation is granted for a given biosimilar.[1]

Evidence of the safety and efficacy of a biosimilar

The FDA recommends that the biosimilar product label include safety and efficacy data from the reference product. The data from the reference product will provide HCPs with the essential scientific information needed to treat patients.[12]

It is the FDA's view that biosimilar product labeling will not include a description of data directly from the development of the biosimilar. A clinical study supporting the licensure of the biosimilar product generally will not be designed to independently demonstrate the safety and efficacy of the product.[12]

Instead, adequate data is provided to support the demonstration that there are no clinically meaningful differences between the proposed biosimilar product and the reference product for the relevant condition in the biosimilar label. **Therefore, only the reference product data will be included in the label.[12]**

VARYING APPROVAL PROCESSES FOR BIOLOGICS, BIOSIMILARS, AND GENERICS

The process and required data are different for biologics, biosimilars, and generics.

BIOLOGIC[1]

- "Standalone" application

- Must contain all data and information necessary to demonstrate its safety and effectiveness for each condition

BIOSIMILAR[12]

- Relies on safety and effectiveness data from the approved reference biologic product

- Must demonstrate high similarity and no clinically meaningful difference in terms of safety, purity, and potency compared with the reference biologic product

GENERIC[3,32]

- Relies on data (preclinical/clinical) from an approved small molecule

- Must demonstrate bioequivalence in terms of their concentrations specifically over time compared with the reference small molecule

GLOSSARY

351a approval pathway – a standalone application for the FDA approval of a biologic drug, which must contain all data and information necessary to demonstrate its safety and effectiveness. It will include clinical trials for the disease indications being sought by the manufacturer[2]

351k approval pathway – process for the FDA approval of a biosimilar drug, with the goal of demonstrating biosimilarity between the proposed biosimilar product and the reference product, not independently establishing the safety and effectiveness of the proposed product[2]

Biologic – a complex drug of heterogeneous structure produced from living cells[3-5]

Biosimilar – a biological product that is highly similar to—and has no clinically meaningful differences in terms of safety, purity, and potency from—an existing FDA-approved reference product, notwithstanding minor differences in clinically inactive components[7]

Biosimilar fingerprinting – a "fingerprint-like" process used during manufacturing that examines a large number of attributes of the product[5]

Drift – unintended, unexplained, or unexpected change in either manufacturing process parameters or the final product over the product's lifetime[8,16]

Evolution – deliberate process changes implemented by a biologics manufacturer[16]

Extrapolation – the approval of a biosimilar based on the totality of evidence for a given condition held by the reference product but is not directly studied in comparative trials with a biosimilar[2]

Immunogenicity – the propensity of the therapeutic protein product to generate immune responses to itself and to related proteins or to induce immunologically related adverse clinical events[27]

Interchangeability – when a biosimilar may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product; has demonstrated the same clinical results as the reference product. For a biological product that is administered more than once to an individual, the risk of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.[14]

Pharmacodynamics – measures the effects of the drug on its biological target[26]

Pharmacokinetics – measures factors such as absorption and elimination of the drug[26]

Pharmacovigilance – an ongoing process of post-approval safety monitoring to allow the FDA and the manufacturer to track adverse events[14,16,23,30]

Reference product – an exisiting FDA-approved biologic drug that is used as the originator for the development of a biosimilar drug[12]

Totality of evidence – the spectrum of support reviewed by the FDA when evidence supporting biosimilarity is reviewed by the FDA when deciding whether to approve a biosimilar product. Includes detailed analytics (structural and functional characterization), non-clinical evaluation (animal studies), clinical pharmacology (PK/PD data), clinical immunogenicity data, and other clinical studies.[2] The goal of a biosimilar program is to demonstrate biosimilarity, not to independently establish the safety and effectiveness of the proposed product.[12]

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BIOSIMILARS AND THE CHANGING HEALTHCARE MARKETPLACE

This brochure is designed to provide an overview of biosimilars and to help you understand how they can play a key role in choosing an appropriate treatment option for your patients across a wide range of diseases and conditions.

- **Biosimilars are biologic drugs that are developed to be highly similar to an existing FDA-approved reference biologic, with no clinically meaningful differences in safety, purity, and potency[7]**
- **The FDA affirms that biosimilars are expected to produce the clinical results of the reference product[14]**
- **To evaluate similarity, the FDA recommends that biosimilar manufacturers use a "fingerprint-like" process that compares as many as 100 attributes between the proposed biosimilar and the reference drug[5,25]**
- **The process for gaining FDA-approval for a biosimliar drug is called the 351k biosimilar development program, with the goal of demonstrating biosimilarity between the proposed biosimilar product and the reference product, not independently establishing the safety and effectiveness of the proposed product[2,5]**
  - Not needing many expensive and lengthy clinical trials potentially leads to faster access to these products, additional therapeutic options, and cost competition
- **Extrapolation is approval of a biosimilar based on the totality of evidence for a given condition held by the reference product but is not directly studied in comparative trials with a biosimilar[2]**

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