Study Companion: Answers to Clinicians' Questions About Biosimilar Use in Inflammatory Conditions

OVERVIEW

We have the answers, do you know the questions? If so, you'll enjoy this Jeopardy-style game focused on biosimilars. Biosimilar antirheumatologic disease-modifying therapies have been approved by the FDA and are becoming increasingly available in the United States. Yet, concerns among some clinicians and patients remain. In this activity, Jonathan Kay, MD, discusses the approval process and other issues related to biosimilar development and use so that you can be confident when discussing them with and prescribing them for your patients.

CONTENT AREA

- Biosimilars
- Reference product
- Rheumatology
- 351(k)
- Extrapolation
- Substitution
- Interchangeable
- Purple Book

FACULTY

Jonathan Kay, MD
Timothy S. and Elaine L. Peterson Chair in Rheumatology
Professor of Medicine and Population and Quantitative Health Sciences
UMass Chan Medical School and UMass Memorial Medical Center
Worchester, Massachusetts

TARGET AUDIENCE

This activity was developed for rheumatologists, gastroenterologists, dermatologists, primary care physicians, along with nurse practitioners, physician assistants and pharmacists who manage patients who are candidates for a biosimilar therapy.

The faculty for this activity has disclosed that there will be discussion about the use of products for non-FDA approved applications.

This activity is supported by an educational grant from Pfizer Inc.

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Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Compare biosimilars with their reference products
- Describe the FDA's stepwise, totality-of-the-evidence pathway for biosimilar development, including pharmacovigilance
- Identify the regulatory and statutory requirements regarding biosimilar interchangeability and substitution
- Develop strategies to discuss biosimilar risks and benefits with patients who are currently treated or considering treatment with a biologic

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Jonathan Kay, MD
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Chris Fischer, MSc (Medical Writer)
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The estimated time to complete the activity is 1.0 hour.

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CATEGORY 1: DEFINING TERMS

Clue: A biologic product with no clinically meaningful differences from its reference product

What is…

- **A biosimilar**

The FDA defines a biosimilar as a biological product that:[1,2]

- Is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and
- Has no clinically meaningful differences from an existing FDA-approved reference product in terms of the safety, purity, and potency of the product.

Biosimilars are approved through a specific regulatory pathway that involves analytical and clinical assessments to assess function, safety, pharmacokinetics, and immunogenicity relative to their reference products.

Biosimilars are not intended to improve on the performance of the reference product, and thus are not second-generation biologics. Single-enantiomer drugs are small molecules that have more than 1 isomer.

Clue: The FDA-approved biologic product against which a biosimilar is evaluated

What is a…

- **Reference product**

A reference product is the single biological product already licensed by the FDA, against which a biosimilar is evaluated.[1,3] The reference product has been approved based on an extensive development program that includes phase 3 clinical trials to establish its safety and efficacy. A proposed biosimilar is evaluated in comparison to the reference product to ensure that it is highly similar and has no clinically meaningful differences. The reference product may also be referred to as the originator or innovator product.[4]

Biologics are a class of medications produced in living cells using recombinant DNA technology.[4] Although transformative, biologics are costly, and biosimilars may be a cost-saving alternative to branded reference products.

Clue: The addition of this to the nonproprietary name of the reference product is required to identify biosimilar products

What is…

- **A 4-letter suffix**

The reference product and biosimilar share a proper name (ie, the core or nonproprietary name that the reference product was assigned when it was approved) and related biologic products are differentiated by the addition of a distinguishing 4-letter suffix.[5-7] The suffix is a unique identifier. The primary purpose of this naming convention is to promote patient safety by ensuring a mechanism to accurately dispense and monitor biologic products.[5] The FDA intended to implement a naming convention that would differentiate biologic products without suggesting that the reference or biosimilar were in some way different.

As an example, the suffix -rzaa is appended to the proper name risankizumab for the reference product, risankizumab-rzaa; each future risankizumab biosimilar would have a unique 4-letter suffix. An exception to this convention is that some biologics were approved before this naming convention was established, meaning that some reference products were not assigned their own suffix.[6] For example, the reference product for adalimumab does not have a suffix and one will not be retroactively added, but adalimumab biosimilars that have been

approved each have a 4-letter suffix appended to their nonproprietary name (eg, adalimumab-adaz).

Clue: The largest difference between a biosimilar and its reference product that is clinically acceptable

What is the…

- **Equivalence margin**

The equivalence margin is defined as the largest difference between a biosimilar candidate and its reference product that is clinically acceptable.[8] The endpoints for the studies designed to establish equivalence of a biosimilar candidate and its reference product are chosen to demonstrate that the proposed biosimilar is neither inferior nor superior to the reference product in terms of each endpoint.[1]

In clinical trials of biosimilars approved to treat inflammatory diseases, equivalence margins have been established for clinical endpoints such as the percentage of ACR20 or PASI75 responders.[9]

Equivalence Margins in Clinical Trials of Rheumatology Biosimilars

Compound	Biosimilar	Study Size (N)	Endpoint	Equivalence Margin
Etanercept	Etanercept-ykro (SB4)	596	ACR20 responders	-15 to +15
	Etanercept-szzs	531	PASI75 responders	-18 to +18
Infliximab	Infliximab-dyyb	606	ACR20 responders	-15 to +15
	Infliximab-abda (SB2)	584	ACR20 responders	-15 to +15
Adalimumab	Adalimumab-atto (ABP 501)	526	ACR20 responders (risk ratio)	0.738 to 1.355
	Adalimumab-bwwd (SB5)	544	ACR20 responders	-15 to +15
	Adalimumab-adbm	645	ACR20 responders (at week 12)	-12 to +15

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Mielke J, et al. Br J Clin Pharmacol. 2018;84(7):1415-1431.

Equivalence margins also may be established for nonclinical endpoints such as PK parameters. For example, area under the concentration-time curve (AUC) and maximum concentration (C_{max}) for US-sourced adalimumab, European-sourced adalimumab, and an adalimumab biosimilar candidate (SB5, or adalimumab-bwwd) were compared in a pharmacokinetic study in healthy volunteers.[10]

Comparison of Primary PK Parameters Between an Adalimumab Biosimilar and Adalimumab Reference Products

Comparison	PK parameter	Ratio	90% CI
Adalimumab-bwwd vs EU-ADL	AUC_{inf}	0.990	0.885; 1.108
	AUC_{last}	1.027	0.915; 1.153
	C_{max}	0.957	0.870; 1.054
Adalimumab-bwwd vs US-ADL	AUC_{inf}	1.001	0.890; 1.126
	AUC_{last}	1.025	0.911; 1.153
	C_{max}	0.972	0.881; 1.073
EU-ADL vs US-ADL	AUC_{inf}	1.011	0.904; 1.131
	AUC_{last}	0.998	0.887; 1.122
	C_{max}	1.016	0.920; 1.121

EU-ADL, European-sourced adalimumab reference product; US-ADL, US-sourced adalimumab reference product; AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration-time curve from time zero to the last quantifiable concentration; C_{max}, maximum concentration.

Skin D, et al. Ann Rheum Dis. 2015;74:458-465.

In this study, pairwise ratios of mean AUC and C_{max} were determined, and the equivalence margin for the 90% confidence intervals of these ratios was within the predefined equivalence margin of 0.8 and 1.25, establishing pharmacokinetic equivalence of adalimumab-bwwd to reference adalimumab. In a later clinical trial with patients with moderate-to-severe rheumatoid arthritis, the ACR20 response rate was 72.4% for adalimumab-bwwd, compared to 72.2% for reference adalimumab.[11] The 95% confidence intervals for this difference of 0.2%, (-7.83% to 8.13%) fell within the predefined equivalence margin of -15% to +15%, confirming clinical equivalence of the biosimilar to its reference product.

Clue: They may be substituted for a prescribed biologic without intervention from the prescribing physician

What is a…

- **Biosimilars that have been approved by the FDA as "interchangeable"**

Biosimilars that have been approved by the FDA as interchangeable and interchangeable biosimilar can be substituted by a pharmacist for the reference product without the authorization of the prescribing healthcare provider. Interchangeable biosimilars must first be

approved by the FDA as being biosimilar and then undergo a second level of evaluation with a switching study in which there are 3 switches, or at least 3 switches, between the reference product and the biosimilar, ending up on the biosimilar, is compared to a continuous treatment arm in which subjects are treated with the reference product throughout the study. The primary endpoints are pharmacokinetic endpoints which are most sensitive to detecting potential differences between a biosimilar that is adequately interchangeable and one that might not be so.

Once a biosimilar has been approved as being interchangeable, the prescriber can prevent substitution by writing "dispense as written" or "brand medically necessary." However there's no real reason to do so because a biosimilar has been shown to be equivalent in efficacy and comparable in safety and immunogenicity to its reference product and, as long as it is a lower-cost biologic agent, can safely be substituted for the reference product.

The interchangeable biosimilars have that indication written in their product label and also recorded in the Purple Book. The regulations regarding use of interchangeable biosimilars in substitution are at the state level, and all 50 states have approved legislation that governs the use of interchangeable biosimilars. In all cases, the pharmacy must communicate with the prescriber about any allowable substitution that has been made and the patient must be notified that a substitution or switch has been made. In some states, the patient must provide consent before the switch is made and the pharmacist and prescriber must retain records of substituted biologic medications. The state must also maintain a public or web-based list of permissible interchangeable products. In some states, the legislation requires the pharmacist to explain the cost or price of the reference biologic and that of the interchangeable biosimilar to the patient. In some states, pharmacists are granted immunity if they make a substitution in compliance with state law.

The important thing to remember about interchangeability is that if interchangeability facilitates access to patients for lower-cost biosimilars that are equivalent in efficacy and comparable in safety and immunogenicity, the interchangeable biosimilar provides the patient with effective therapy at a lower cost, thereby offering effective treatment to more patients.

CATEGORY 2: DIFFERENCES IN DOLLARS OR DESIGN

Clue: This increased after the introduction of a second biosimilar to the Norwegian market in 2016

What is…

- **The number of patients treated with infliximab**

Ferrario et al studied total expenditures and number of doses of infliximab from 2008 (when only the branded reference product was available) to 2014 when 1 infliximab biosimilar was introduced, and then until 2016 when a second biosimilar entered the Norwegian market.[14] In 2015, total spending for infliximab increased, but the number of patients treated also increased. By 2016, the price per dose of infliximab reference product remained relatively unchanged; however, infliximab biosimilars were discounted to 40%-60% of the cost of the infliximab reference product. This resulted in sales of infliximab biosimilars surpassing those of infliximab reference product and a decrease in total spending for infliximab despite an increase in the number of patients being treated with infliximab.[14,15]

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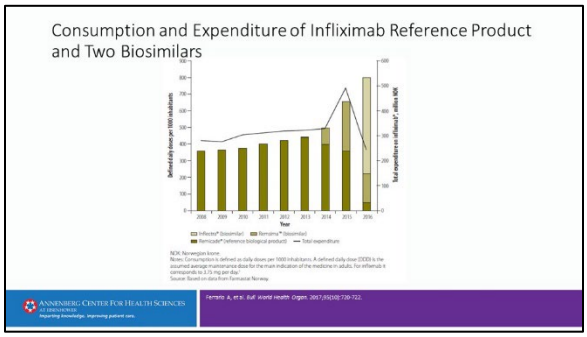

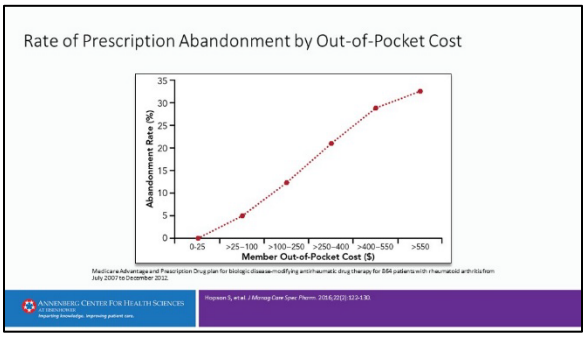

Biologics are expensive—in the US, biologics account for 25% of prescription drug costs but less than 1% of all prescriptions.[16] Studies in Norway and Italy, where biosimilars have been introduced into the market, support the concept that price competition from biosimilars should drive down the cost of biosimilars and result in lower healthcare expenditures.[14,15,17] A biosimilar short-acting filgrastim (filgrastim-sndz) had a 24% market share within 4 months of its approval in the US, and had an average wholesale price that was 15% lower than that of filgrastim reference product.[18] If accepted, uptake of biosimilars in the US market could result in an estimated savings of up to $66 billion over the next decade by 1 estimate.[19]

Another potential benefit of price competition among biologics is increased access. Hopson et al identified an association between out-of-pocket costs for antirheumatic drugs and the rate of prescription abandonment.[20] Required copayments for biologics may be up to 20%-35% for some patients.[19] Experience in Norway suggests that introduction of lower-priced biosimilars can increase access to biologics.[14,15]

Clue: The variability in quality attributes of a biologic that arises over its lifecycle

What is…

- **Biologic drift**

Biologics are large, complex macromolecules produced in living cells rather than by the in vitro chemical reactions used to synthesize small molecules.[21] While this process begins with a known gene sequence, manufacture of biologics is an inherently variable process.[21-24] As a result, no 2 batches of a biologic that are manufactured in the same way would be expected to be structurally identical. There may be differences in quality attributes—the molecular or product characteristics, such as posttranslational modifications—that contribute to the identity, potency, and stability of the biologic.[1,22] Biologic drift is the variability in quality attributes that arise over the lifecycle of a biologic.[21]

The FDA has considered drift as process drift, or the variation in quality attributes that arise as a result of postapproval changes in the manufacturing process for any biologic.[22]

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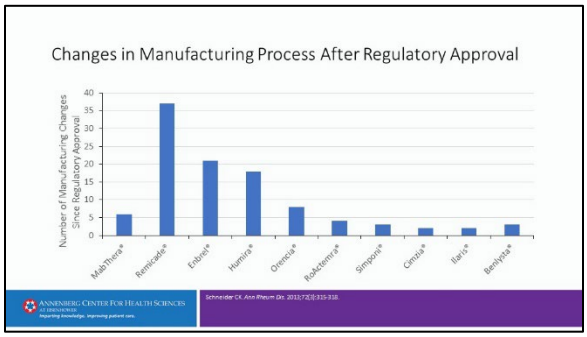
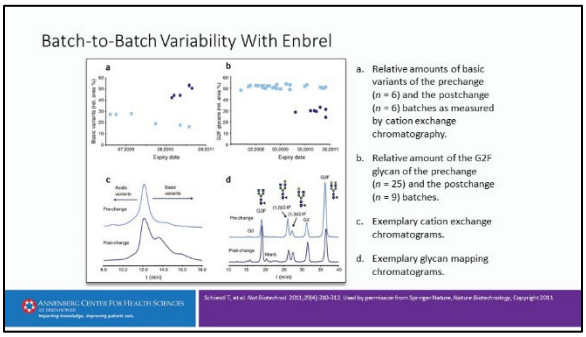




Changes in manufacturing processes are common, and the FDA has established a comparability exercise to ensure that changes in manufacturing process do not affect the quality, safety, or efficacy of a biologic.[22] After making a change in the production of a biosimilar, manufacturers are required to assess relevant quality attributes to establish that the resulting biologic is not necessarily identical, but highly similar to, the prechange product to the extent that any differences would not have an adverse impact on safety or efficacy of the product.[22]

How the quality attributes (eg, glycosylation and N- and C-terminal structure) of the etanercept reference product evolved over time as a result of biologic and process drift was investigated in a study of etanercept batches from 2007 to 2010.[21] In this study, Schiestl et al found that the glycosylation profile of etanercept was highly uniform until 2009, when some batches of etanercept appeared that had a different glycosylation profile that the authors speculate was due to a manufacturing change. This study demonstrates that biologics may evolve over time, and that the biologic in use today is not identical to the biologic that was approved, because of biologic drift and/or process drift.[25]

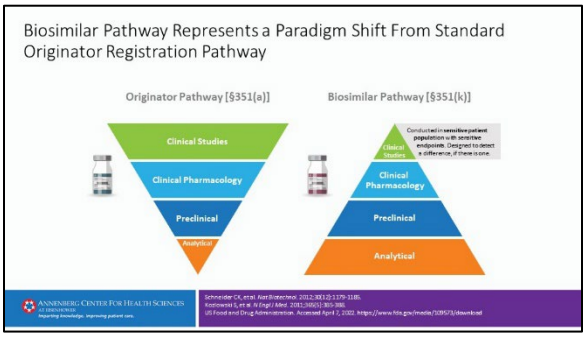
Clue: Studies that are considered the foundation for development of a biosimilar

What are…

- **Analytical studies**

Section 351(k) of the Public Health Service Act delineates the abbreviated licensure pathway for biosimilars. This pathway does not require the full complement of preclinical and clinical data that are required for new biologic drugs licensed under the "stand-alone" approval pathway, section 351(a).

For biosimilars, the FDA considers analytical characterization to be the foundation of the approval pathway.[1,26]



Minor variations in the molecular composition of a biologic are expected, and the analytical phase of development includes structural and functional studies to demonstrate that the variations between the biosimilar and reference product are minor, affect only clinically inactive

components, and would not be expected to result in a clinically meaningful difference.[1,27] Subsequent animal toxicity studies and clinical studies depend on the findings from the analytic studies, and are designed to address any residual uncertainty of biosimilarity to the reference product.[1,27] The clinical studies of the biosimilar are designed to address any remaining uncertainty that the biosimilar is highly similar to the reference product with respect to its safety, purity, and potency, and to establish that there is no clinically meaningful difference between the biosimilar and the reference product.

The analytic phase may include:

- Structural and functional characterization of the biosimilar;
- Identification of clinically active components and impurities;
- A study of the reference product's heterogeneity, impurities, and critical characteristics;
- An evaluation of the manufacturing process;
- An evaluation of the biosimilar's stability.

Clue: The development of a biosimilar may directly use some (but not all) of this from the reference product

What is…

- **Information included in the package insert**

The package insert for a biosimilar must incorporate data and information from its reference product label.[6,28] The premise of this decision by the FDA lies in the definition of biosimilarity—ie, that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety, purity, and potency.[28] Consequently, the established safety and efficacy described in the package insert for the reference product contains the essential scientific information needed to prescribe the biosimilar.[28]

The clinical studies used to demonstrate biosimilarity are not typically described in the label for the biosimilar.[28] Instead, the biosimilar product label incorporates clinical safety and efficacy data from the reference product label. The FDA decided not to include data from the biosimilar clinical studies because these studies are not designed to independently support safety or efficacy; including them could lead to an inaccurate comparison of the risk-benefit profile for biosimilar biologics. The exception to this is that clinical data for the biosimilar may be included, if needed to inform its safe and effective use.

The label for a biosimilar also includes a statement in the HIGHLIGHTS section which indicates the compound is biosimilar to the reference product, with a footnote that defines biosimilarity.[28] The biosimilar is identified by its proprietary name and nonproprietary name with its unique suffix when discussing information specific to the biosimilar. This includes references in the INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING, BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and DRUG INTERACTIONS sections, for example. The INDICATIONS AND USAGE section is specific for the licensed indications for the biosimilar, which may not include all the indications for which the reference product has been approved.

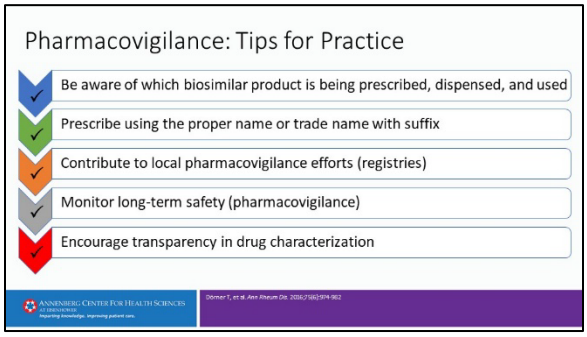
The American College of Rheumatology supports labeling that clearly indicates which biosimilars are interchangeable with their reference products, for which indications biosimilar products are approved, and whether the data supporting the approved indications are derived from studies of the biosimilar or the reference product.[4]

Clue: Pharmacovigilance is needed to identify rare adverse events or safety issues for these

What are….

- **All drugs, including biologics and biosimilars**

Pharmacovigilance is the detection, assessment, understanding, and prevention of adverse effects of any other drug-related problems.[29] Pharmacovigilance is needed for all biologics, both biosimilars and their reference products, because clinical trials are inadequate to identify uncommon adverse events.[30] Postapproval pharmacovigilance remains important for identifying unexpected, rare adverse events, that are not identified in clinical trials, for both biosimilars and their reference products, regardless of how long the product has been on the market.[31] The naming convention for biologics and biosimilars is designed to facilitate pharmacovigilance efforts. Biosimilars cannot be approved for an indication the reference product is not approved for, but may be approved for indications, without a clinical trial, by extrapolation.



CATEGORY 3: DEVELOPMENT

Clue: Here you can find a list of FDA-approved biologics, biosimilars, and interchangeable biosimilars

What is the…

- **Purple Book**

The Purple Book is an online, searchable database of biological products, including biosimilar and interchangeable biologic products, that are FDA-approved.[32] Searching the Purple Book (available at https://purplebooksearch.fda.gov/) for a biologic returns a list of biosimilar, interchangeable, and reference products, with links to their product labels.

Clue: An exact copy of a drug

What is…

- **A generic drug**

A generic drug is a small molecule that is an exact copy of a branded drug.[3,33] The structure of these small molecules can be completely defined and entirely reproduced.[1] To be approved as a generic drug, the manufacturer must meet the standard of demonstrating bioequivalence to the branded drug, and the active ingredients of a generic are the same as for the branded drug.[3] A biosimilar is not a generic nor is it identical to the reference product. Biosimilars meet the standard of being highly similar to their reference products, with any differences having no clinically meaningful effect on safety and efficacy. Both generics and biosimilars undergo abbreviated, but different, approval processes to demonstrate bioequivalence or biosimilarity, respectively; this process does not require an independent demonstration of safety and efficacy.

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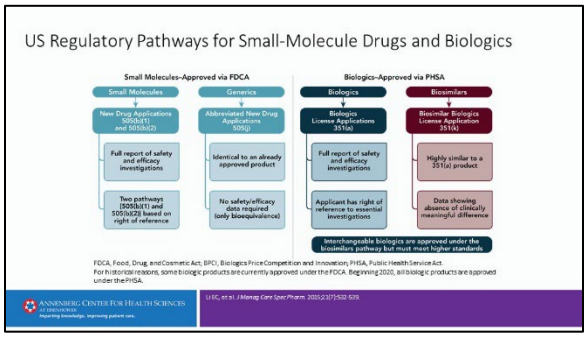


Separate batches of a biologic, whether a biosimilar or a reference product, are not necessarily identical since their manufacture is an inherently variable process that may result in minor differences in quality attributes.

Clue: A biosimilar must be this when compared to its reference product

What is…

- **Highly similar**

A biosimilar must be highly similar to its reference product, notwithstanding minor differences in clinically inactive components, and there must be no clinically meaningful differences between the biosimilar and its reference product in terms of its safety, purity, and potency.[1] Biosimilars are not expected to be identical to the reference product with respect to their molecular structure. A biosimilar need not have been proven to be interchangeable with its reference product—this higher standard requires the conduct of additional clinical studies to demonstrate no significant difference in pharmacokinetic parameters, efficacy, or safety in patients who are treated with repeated switches between the biosimilar and its reference product, compared to those treated with the reference product alone and without switching.[12] The clinical phase of the biosimilar approval process is designed to verify that there are no clinically meaningful differences in safety or efficacy between the biosimilar and its reference product.[26]

Clue: The approach taken by regulators when reviewing data to support designation of biosimilarity

What is…

- **Totality of the evidence**

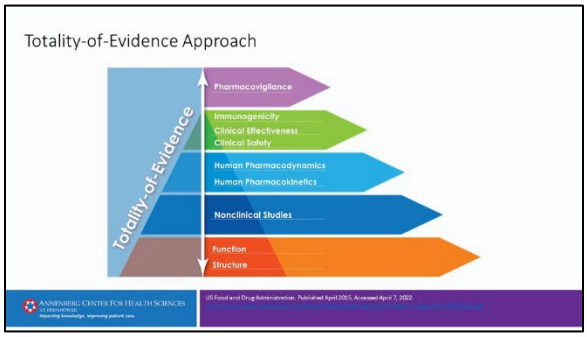
The totality-of-the-evidence approach is that approach taken by the FDA to evaluate biosimilar candidates. Biosimilar candidates undergo a sequential group of assays, first analytical and functional assays, and then pharmacokinetic and pharmacodynamic studies in humans, if there's a biomarker that allows assessment of pharmacodynamics. Then finally, at least 1 clinical trial in which efficacy of the biosimilar candidate is compared to that of the reference product. If efficacy is equivalent, and safety and immunogenicity are comparable, then the biosimilar candidate undergoes the approval process and, when the totality of the evidence, looking at all of the different studies that have been conducted comparing the biosimilar candidate to its reference product, indicates biosimilarity, the FDA can then grant that designation to the molecule.

The FDA decides what studies are needed on a case-by-case basis to reduce residual uncertainty. If, after analytic studies and the pharmacodynamic study, such as that which would be conducted for an insulin biosimilar candidate measuring glucose levels or a filgrastim biosimilar candidate measuring neutrophils, the agency may decide that a clinical trial is not necessary in addition to the pharmacodynamic study that was conducted. However, the purpose of clinical studies during biosimilar development, as I said, are to reduce residual uncertainty using this totality-of-the-evidence approach, incorporating all of the

different lines of evidence into the assessment of biosimilarity.

Because this approval process demonstrates that the biosimilar is essentially like another batch of the reference product and the reference product has been studies, approved and used in all of the conditions for which it has been approved, the biosimilar can be then used in each of the conditions without separate clinical studies because the experience with the reference product can be extrapolated to the biosimilar.

In summary, the FDA uses a totality-of-the-evidence approach, incorporating all of the different studies that are performed comparing a biosimilar candidate to its reference product to determine biosimilarity and make certain that biosimilar medications are available to patients and are safe and effective.

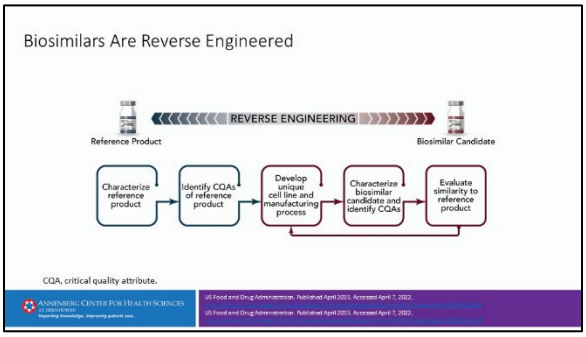


Clue: The approach to development of biosimilars that is based on structural analysis of the reference product

What is…

- **Reverse engineering**

The development of a biosimilar starts with protein synthesis from a gene that encodes the amino acid sequence that is known for its reference product. However, the expression vector and the remaining production and purification steps for the reference product are proprietary and known only to the reference product's manufacturer. Each biosimilar manufacturer has to develop their own cell line to express the biosimilar, and fermentation conditions, purification protocols, and packaging. These steps are not trivial, since they can affect posttranslational modifications and higher order structure of the biosimilar.[1,34] To develop a biosimilar, manufacturers analyze its reference product extensively and reverse engineer a manufacturing process which can produce a biosimilar that is highly similar to its reference product. As part of this process, critical quality attributes (ie, the molecular and product characteristics, such as posttranslational modifications and functional activity, that define the identity, potency, and safety of a biologic) must be identified so that they can be replicated by the manufacturing process.[21,22] Throughout development, the critical quality attributes of the biosimilar candidate are compared to those of its reference product to inform modification of the manufacturing process so that the biosimilar meets the standard of being highly similar to its reference product without clinically meaningful differences.



Study Companion: Answers to Clinicians' Questions About Biosimilar Use in Inflammatory Conditions

CATEGORY 4: DELIVERY TO THE CLINIC

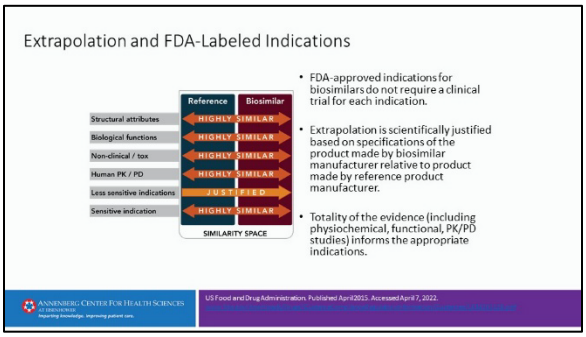
Clue: The regulatory approach that may be used to approve a biosimilar for indications for which its reference product is approved without conducting additional clinical trials

What is…

- **Extrapolation of indications**

Extrapolation of indications is the regulatory approach to approve a biosimilar for indications other than those in which it was studied during clinical development, but for which the reference product has already been approved for. Extrapolation of indications does not assume that a biosimilar is safe and effective across indications: the manufacturer must provide a scientific justification for extrapolation to indications not tested during the clinical program.[1,35] Clinical testing for a biosimilar is designed to demonstrate the absence of clinically meaningful differences, not to demonstrate efficacy. Thus, the FDA guidance directs manufacturers to choose an indication that would be adequately sensitive to detect a difference.[1,36] The scientific justification for extrapolation to other indications should address whether:[1]

- The mechanism of action is similar for each condition;
- Pharmacokinetics and pharmacodynamics are comparable in the different patient populations; and
- Toxicity and immunogenicity of the product are similar in the different patient populations.



If biosimilarity can be established using analytic and functional studies, and no clinically meaningful differences are identified in clinical testing in a patient population selected for its sensitivity to identify a difference in efficacy or safety, the totality of the evidence may support extrapolation to other indications. This process is analogous to that used for approval of changes in manufacture of biologics.[35]

Extrapolation has been used to approve biosimilars for the same indications that the corresponding reference product is indicated except under 2 circumstances:[37]

- The reference product was granted a new indication after the biosimilar was approved; or
- A reference product had been granted market exclusivity for an indication.

Clue: The property of a biologic to induce an immune response that may neutralize the protein and reduce therapeutic efficacy

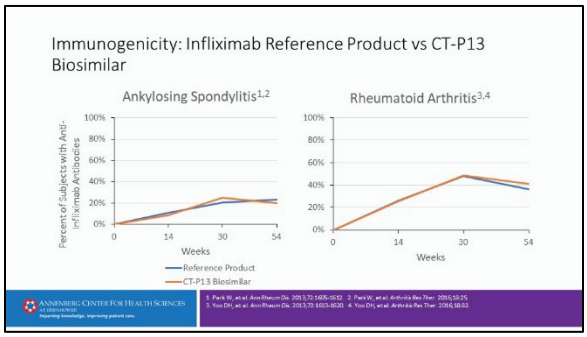
What is…

- **Immunogenicity**

Immunogenicity is the property of a protein to induce an immune response that may neutralize the protein and reduce its therapeutic efficacy. Immune responses to a biologic can affect both its safety and efficacy.[1] Comparative clinical studies to assess the immunogenicity of a biosimilar are expected to be included in the

process to demonstrate biosimilarity; immunogenicity is assessed in comparative pharmacokinetic and pharmacodynamic clinical studies. The goal of the clinical immunogenicity assessment is to identify any differences between a biosimilar and its reference product in the incidence and severity of immune reactions. The extent of these studies—which include both premarketing clinical trials and postmarketing surveillance—depends on the expected incidence and severity of immune reactions, and the degree of analytic similarity of the biosimilar to its reference product.

Differences between a biosimilar and its reference product in post-translational modifications or other clinically inactive aspects could contribute to differences in immunogenicity.[38]



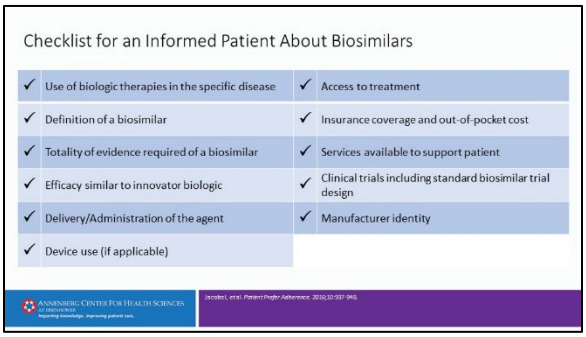
Clue: The negative responses to a biosimilar that are not related to its pharmacologic properties

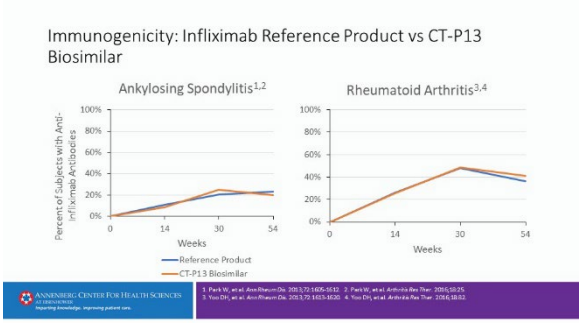
What is…

- **The nocebo effect**

The "nocebo" effect refers to the perceived increase in adverse events or negative responses to a medication that are not due to its biological properties.[39] Both patients and healthcare providers may have concerns about the efficacy and safety of biosimilars, which have been a barrier to their acceptance in both Europe and the United States. These concerns are rooted in misconceptions about biosimilars (eg, that they are second- or third-line treatments, can only be used in treatment-naïve patients, or are less effective or more immunogenic than their reference products).[40] Patients with these concerns have expressed unwillingness to switch to a biosimilar, even if their out-of-pocket costs might be lower.[41,42] As a result, patients have reported a higher incidence of adverse events with some biosimilars than with their reference products; in some biosimilar trials, this has resulted in an increase in drug discontinuation in the absence of objective evidence of disease worsening.

Countering the nocebo effect requires shared decision making and positive communication about biosimilars.





Clue: A structured process to engage the patient in evaluating treatment options and selecting treatment

What is…

- **Shared decision making**

Patients are new to biosimilars and, as a result, are somewhat nervous or concerned about changing from a medication on which they've been experiencing good results and when a biosimilar is introduced as a potential treatment, obviously there's some trepidation about switching. Patients may be concerned about safety and effectiveness of a biosimilar and, as a physician, you can reassure them that biosimilars have been studied extensively in comparison to their reference products and reviewed and approved by the FDA or other regulatory bodies and demonstrated to be equivalent in efficacy and comparable in safety and immunogenicity. Thus, a patient should not worry about switching from a reference product to its approved biosimilar any more than they should be worried about switching from one lot of the medication that they have been taking to a new lot of that medication.

The nocebo effect refers to symptoms and/or physiologic changes that follow the administration of an inert, chemically-inactive substance that a patient believes to be an active drug. It is essentially the opposite of the placebo effect. Placebo means I will please, and nocebo, in Latin, means I will harm. The nocebo effect may also account for side effects experienced by patients taking an active drug and the nocebo effect contributes to the potential adverse effects that patients may experience when switching from a reference product to its biosimilar. Thus, it is very important to communicate carefully and in a nonthreatening way, with the patient, about switching to the biosimilar.

Providers should use informed, shared decision making and use motivational interviewing and open collaborative discussion to get patients to think about and articulate their reasons for and against this change. They should discuss the patient's expectation of adverse events and provide encouragement and reassurance and avoid imparting negative expectations about a drug. Finally, providers should offer education to improve awareness, be confident and capable of transferring this confidence in helping patients to make a decision without unintended negative suggestions.

An excellent study, the BIOSWITCH study, conducted in Nijmegen in the Netherlands, enrolled subjects who were on reference etanercept and who were switched to a biosimilar etanercept, but subjects were given education by pharmacists and nurses working in the rheumatology clinic that the biosimilar was less expensive and also had fewer injection site reactions than the reference product. With this information, the retention on the biosimilar was comparable to that on the reference product in an historical cohort of patients treated with reference etanercept. Thus, shared decision making, careful discussion with patients about their expectations and counseling them and reassuring them that the decision to switch to a biosimilar is both safe and potentially advantageous to them from an economic point of view is very important.

Clue: A patient who is not responding to treatment with a biologic, or who experienced an allergic reaction to it

What is…

- **A patient who should not be switched to its biosimilar**

Biosimilars have undergone extensive comparison to their reference products and approved biosimilars are equivalent in efficacy and comparable in safety to their reference products and, in terms of the molecular structure, are highly similar without clinically-meaningful differences. Thus, patients who have not responded to reference products should not

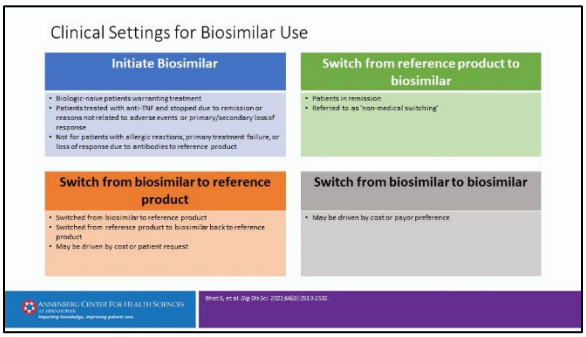
be switched to their biosimilars because one would not expect them to respond to another batch of the reference product and the biosimilar can be thought of as another batch of the reference product.

Nonresponders to the reference product, patients who have experienced an allergic reaction to the reference product and patients who have developed neutralizing antidrug antibodies to the reference product should not be switched to its biosimilar.

There are many clinical scenarios where a biosimilar could be considered. Patients who are doing well on a reference product can be switched effectively and safely to the biosimilar to achieve cost savings. Now, these cost savings are to the patient's payer and perhaps are shared with the provider in terms of easier access and less requirement for prior authorization. However, the patient should also benefit financially from using a lower cost medication, perhaps with a reduced or waived copayment.

In addition to biosimilars substituting for the reference product, a biosimilar may also be used in a patient who is not responding adequately to one medication and then the decision is made to switch them to a different biopharmaceutical and the biosimilar of that new biopharmaceutical is chosen because of lower cost. This is a situation in which the switch is made for medical reasons, but the biosimilar is chosen instead of the reference product of the other medication.

In summary, it is important to remember that a patient who has not responded to or had an allergic reaction or loss of efficacy to the reference product should not be switched to its biosimilar and patients with appropriate shared decision -making should feel very comfortable that substitution of a biosimilar for the reference product will provide them with safe and effective care.



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