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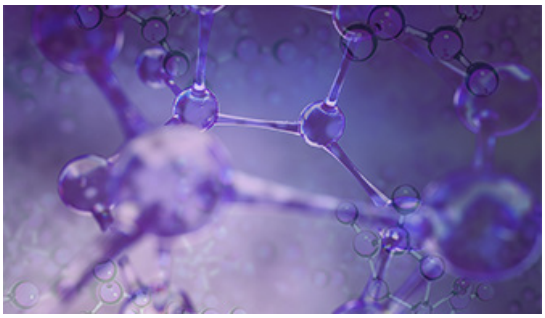
StudyCompanion

StudyCompanion—Narrowing the Gaps: Understanding Biosimilars

A CME Activity

Overview

This activity is modeled after an exam study guide.



The guide presents case-based questions that challenge you to consider the structural, functional, and clinical differences between biosimilar products and their reference drugs, as well as their potential clinical applications. Multiple choice questions allow you to test your knowledge and ability to apply current evidence to clinical scenarios.

Content Areas:

- Manufacturing process
- Approval basis
- Pharmacoeconomic impact
- Clinical implications

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CME Information

Target Audience

This activity was developed for rheumatologists, oncologists, dermatologists, gastroenterologists, nephrologists, pharmacists, and other clinicians who currently use or may consider using biosimilars in clinical practice.

Learning Objectives

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

- Recognize manufacturing differences between biosimilars and their reference biological product as well as generic small molecule drugs
- Describe how the FDA uses a "totality of evidence" strategy to evaluate biosimilar compounds
- Consider how the availability of biosimilars will impact clinical practice

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The estimated time to complete the activity is 2.0 hours.

This activity was originally released on July 7, 2017 and is eligible for credit through July 6, 2018.

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Question 1

Biologic agents in multiple fields have revolutionized the therapeutic treatment options in a number of areas of medicine including: autoimmune disease; autoinflammatory diseases; and cancer. The cost of these drugs is high, which contributes to high patient out-of-pocket costs, restrictive policies by payers, and decreased access.

In an effort to reduce the cost of biologics through competition, the US Food and Drug Administration (FDA) has recently developed regulations for the development and approval of biosimilar products, which are defined as:

A. Chemical, small molecule medicinal products that are structurally and therapeutically equivalent to an originator product whose patent and/or data protection period has expired
B. Biologics that are highly similar in structure and function to a reference product as demonstrated through analytics, with no clinically meaningful differences
C. Large molecules that contain the same active pharmaceutical ingredient as an originator medicine or reference product
D. Biobetter, genetically-engineered proteins that are derived from human genes

The correct answer is B.

Rationale

The United States Food and Drug Administration defines biosimilar products as large, complex molecules derived from biologic processes that are similar but not identical to the original agent.[1] They are "highly similar" to their reference products in physicochemical characteristics in that they contain a version of the active substance of an already authorized, original biological medicinal product (reference medicinal product). Section 351(i) of the US Public Health Service Act defines a biosimilar as a "product that is highly similar to the reference product, notwithstanding minor differences in clinically inactive components," and "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."[1]

In contrast, generic medications are chemical, small molecule medicinal products that are structurally identical and bioequivalent to an originator product.[2] The demonstration of bioequivalence of the generic medicine with a reference product is usually appropriate and sufficient to infer therapeutic equivalence between the generic medicine and the reference product. Biologics (therapeutic proteins), in general, are difficult to characterize due to the final product of any biologic being a molecular population of proteins; thus their regulatory framework of development, evaluation, and licensing, differs from the approach used to infer therapeutic equivalence between generic medicines and their reference products, and naturally requires additional data.[3]

A biobetter is an originator drug that has undergone modification to enhance it, that actually is structurally different from the original license firm biopharmaceutical.[4] Regulatory authorities differ slightly in the definitions of biosimilars (Table), but they all share the same common elements of recognizing that these are highly similar with no clinically meaningful differences to the reference.

Table: Classification of biosimilarity[3]

European Medicines Agency	US Food and Drug Administration	World Health Organization
"…a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product). Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established."	"…the biological product is 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."	"A biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product."

Question 2

Your hospital recently reported a 9% annual increase in drug expenditure for the supportive care agent, pegfilgrastim. In order to reduce costs, the Pharmacy and Therapeutics (P&T) committee discusses the potential for including filgrastim-sndz, which is a biosimilar to filgrastim, on its formulary.

During review, committee members ask you how the manufacturing process for generic small molecule drugs and biosimilar agents differ. Your answer is:

A. That biosimilars are essentially generic biologics, which means that they are replicated via predictable chemical manufacturing processes such that the final active ingredient is identical between products
B. That biosimilars are different from small molecule generics because rather than being identical to the reference, they have been modified slightly to be functionally similar (and not identical) to the reference
C. That biosimilars are biologics that are made through living systems and accordingly, the manufacturing process has been reverse-engineered such that the physicochemical and functional characteristics of the biosimilar product are highly similar to the reference product
D. That biosimilars are copying the entire manufacturing process of the reference manufacturer, thus creating identical 3-dimensional copies of the reference

The correct answer is C.

Rationale

Recombinant DNA technology in living systems, such as bacteria, yeast, and mammalian cells, is used to develop biologic proteins or peptides. Though some information regarding the product is disclosed in the patent, specific processes use to produce reference products is proprietary. Therefore, to develop a biosimilar, manufacturers must reverse engineer the biological molecule based on structural and functional analysis of the reference product.

Biological products are inherently heterogeneous; however, the variability is within well-defined quality attributes. The complexity of biological molecules precludes duplication by chemical synthetic procedures.[5] The reverse engineering process includes multiple steps (Figure) to identify and isolate gene sequences, then transfer the targeted DNA into an expression vector system before expressing, producing, purifying the protein, and validating the final product.[6] An FDA-sanctioned process called Quality-by-Design (QbD) is utilized to ensure that the variability within biophysical and functional attributes of the biosimilar product falls within the same specifications of the variability of the reference product. For example, the variability within the degree and location of their glycosylation sites, their isoform profiles, and the degree of protein aggregation of the reference has been well documented, and the biosimilar will conform to these same specifications.[7]

It is recognized that the nature of some quality attributes (eg, cytotoxicity assays, glycosylation patterns) can change over time as a consequence of modification in production process. These changes are referred to a manufacturing "drift" and are subject to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) regulations (recognized by FDA and EMA) intended to mitigate clinically meaningful differences as a consequence of process changes.[8] In the development of a biosimilar, it is essential to maintain the variability seen in the reference product since these characteristics influence their pharmacokinetic and pharmacodynamics profile, including biological activity, clinical efficacy and safety in patients.[7] Manufacturing factors that influence molecule properties during the fermentation process include time, pH, temperature, culture media, oxygen levels/lactic acid accumulation, while removal of host cell DNA and proteins, protein concentration, and final formulation buffer during purification, also influence molecular structure.[6]

In contrast, small-molecule products have simpler structures. They are synthesized using predictable chemical manufacturing processes that allow for replication, and produce equivalent versions of the drug that are identical to the originator drug.[5]

Question 3

A pharmaceutical company has developed a biosimilar product to treat patients with psoriatic arthritis. Which one of the following choices describes the purpose of the biosimilar regulatory pathway and data that manufacturers must submit to the US FDA to establish biosimilarity?

A. Demonstration of safety and efficacy of the biologic molecule; therefore, a full report of safety and efficacy investigations must be submitted
B. Demonstration of bioequivalence; therefore, safety and efficacy data showing equivalence in pharmacokinetics must be submitted
C. Demonstration of identity to an approved product; therefore, only studies comparing the structure and function must be submitted
D. Demonstration of comparability to an approved product; therefore, analytical data showing high similarity in physicochemical/functional characteristics and clinical studies showing the absence of clinically meaningful difference from reference product must be submitted

The correct answer is D.

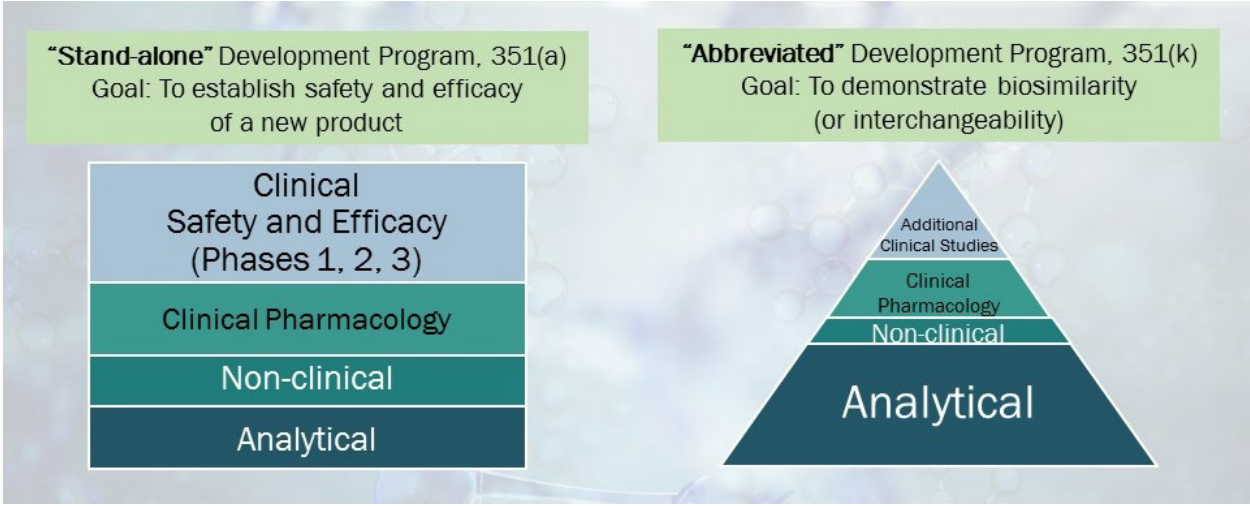
Rationale

In contrast to the regulatory approval pathway for originator drugs, the pathway for biosimilar drug approval requires that applicants submit a global data package to demonstrate that the biosimilar is first: analytically, functionally, pharmacologically, and then subsequently clinically (efficacy, safety, immunogenicity) similar to the reference product. Applications for a Biosimilar Biologics License in the United States have an abbreviated pathway for approval under the Biologics Price Competition and Innovation (BPCI) Act of 2009, and rely for approval on the prior approval of the reference product. Manufacturers must show that the biosimilar is "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that, for the intended condition or conditions of use, there are no "clinically meaningful differences in terms of the safety, purity, and potency of the product as compared with the reference product."[10] The global data package is largely focused on analytic data, including the structure of function, the preclinical pharmacology assays, the clinical pharmacology program, and pharmacokinetics and pharmacodynamics studies (Figure 1).

The process for biosimilar approval requires demonstration of comparability in quality, efficacy, and safety between the biosimilar and reference product. The demonstration of comparability is taken in a stepwise fashion that entails analytic comparison of a biosimilar and its reference product in terms of functional and biological activity and of nonclinical in vivo studies.[9] In vitro studies identify the physiochemical similarities between the biosimilar and the reference product, and determine if in vivo studies are required. Clinical pharmacokinetic and pharmacodynamics studies must demonstrate similarity of pharmacologic profile and assess comparability between the biosimilar candidate and its reference product before or instead of clinical efficacy trials. The goal of comparability studies is not to demonstrate safety and efficacy, but rather that the biosimilar candidate is not meaningfully different than the reference drug, both analytically and clinically, in a sensitive indication.[11]

Small-molecule drugs are approved under the US Food, Drug, and Cosmetic Act, and are required to submit a full report of efficacy and safety as a New Drug Application.[10] Generic products follow an abbreviated approval pathway under the Drug Price Competition and Patent Term Restoration Act of 1984 that relies to some extent on prior safety and efficacy findings of the reference product. Approval of a generic does not require efficacy and safety data, but does require demonstration of pharmaceutical equivalence and bioequivalence to these data. Biologics are generally approved under the Public Health Service Act (PHSA), which requires a Biologics License Application.[10] Like small molecules, the pathway to approval for biologics requires a full report of efficacy and safety.

Figure: Goals of stand-alone vs biosimilar development



Question 4

One of the unique characteristics of the regulatory process for biosimilar products is that they can be FDA-approved for an indication for which the reference product is approved without the biosimilar being required to be directly compared with the reference product for that indication. Which one of the following FDA review processes justifies such approval?

A. Immunogenicity
B. Pharmacovigilance
C. Substitution
D. Extrapolation

The correct answer is D.

Rationale
Extrapolation refers to the process through which a biosimilar is approved for one or more clinical indications that the reference product is approved for despite the absence of head-to-head clinical comparison. There is no need to conduct a biosimilar clinical trial for each indication, if the structure of the biosimilar is highly similar to the reference product. Extrapolation is assessed after the confirmation of biosimilarity, and the approval of an indication for a biosimilar through the extrapolation process eliminates the need for further clinical studies.[12] The scientific justification for extrapolation is based on review of the totality of evidence, including not only the clinical data but also the analytical, functional, and nonclinical data that support the approval application.[12] The extrapolated indication(s) should be based on similarity in mechanism of action as well as similarities in pharmacokinetic and pharmacodynamics (PK/PD) and immunogenicity.

In order to extrapolate the clinical data from one indication to another, clinical evaluation of the efficacy of a given biosimilar must consider the sensitivity of the study population, that is, whether the population being studied is appropriate and whether any differences between the biosimilar and the reference would translate into differences to the target population under consideration for extrapolation. Evaluation of clinical efficacy must also consider other data, such as the measures of response.[12] For instance, although clinical efficacy for the reference product may be demonstrated in one inflammatory disease (eg, rheumatoid arthritis), this does not necessarily predict its effectiveness in another inflammatory disease (eg, ulcerative colitis) if different response measures are used, and if identified differences in a proposed biosimilar and reference could potentially affect the biodistribution of the proposed biosimilar in the indication being considered for the extrapolation.

The Food and Drug Administration (FDA) will view extrapolation as valid when the mechanism of action, pharmacokinetics, immunogenicity and safety of the biological molecule (based on the reference product experience) are similar in both the clinically tested indication and in the extrapolated indication.[13] If there is uncertainty within these characteristics within the extrapolated indication, the FDA requires additional evidence to show that the biosimilar is likely to be similar in its efficacy and safety in the extrapolated indication, despite not being clinically tested for that indication. This data could be in the form of assessing bioactivity, pharmacokinetics or biodistribution, or additional safety/immunogenicity safety studies. For instance, there is currently considerable debate on the extrapolation to inflammatory bowel disease of anti-tumor necrosis factor biosimilar drugs, because they have primarily been clinical tested in patients with rheumatoid arthritis.[12]

Immunogenicity refers to the ability of a substance to trigger an immune response or reaction (eg, development of specific antibodies, T cell response, or allergic or anaphylactic reaction).[13] These responses can translate to clinically meaningful events such as acute anaphylaxis or serum sickness, or compromise treatment efficacy. Pharmacovigilance via collection of post-marketing data is an important safety assurance component in the abbreviated regulatory pathway for biosimilar products, since not all safety issues will be evident in the totality of evidence used to evaluate clinical efficacy and safety for biosimilar drugs.[14] Substitution occurs when a pharmacist selects and dispenses a drug product that is identical to the branded product in terms of active ingredient, strength, concentration, dosage form, and administration route. A biosimilar has to be designated "interchangeable" in order for a pharmacist to substitute it for a reference drug.[15]

Question 5

The pharmacy department in your hospital has decided to place a biosimilar drug on its formulary for treating patients with inflammatory diseases and has brought this suggestion to the Pharmacy and Therapeutics (P&T) committee for discussion.

As you review the materials circulated by the P&T committee prior to the meeting for this biosimilar, you realize that no phase 3 clinical trial data has been included. In order to evaluate whether this biosimilar drug should be added to a hospital's formulary, which of the following materials should the hospital's Pharmacy and Therapeutics committee review?

A. Phase 3 clinical data on efficacy and safety for the biosimilar drug
B. Pharmacokinetic, pharmacodynamics, and toxicological studies for the biosimilar drug
C. Comparative analytical, functional, nonclinical, clinical, pharmacokinetic/pharmacodynamic, efficacy, safety, and immunogenicity studies for both the biosimilar drug and its reference product
D. Interchangeability data for the biosimilar product

The correct answer is C.

Rationale

The issue before the P&T committee is that there is a difference between the indication for the biosimilar and its likely use in the hospital; therefore, it is important to consider the FDA's extrapolation for on-label indications. The clinical trial to establish biosimilarity is to demonstrate that there are no meaningful differences from the reference product. Safety and efficacy of the drug were established by the reference product. Extrapolation to other indications already approved for the reference product is granted when it can be scientifically justified; this determination is largely based on shared mechanism of action, pharmacology and pharmacokinetics in clinically studied population.

The P&T committee should review the in vitro and in vivo bioanalytical, pharmacokinetic, pharmacodynamic, and toxicological studies for both the biosimilar drug and its reference product. This "totality of evidence" constitutes the evidence on which biosimilar approval was based and is publically available via the Food and Drug Administration website.[16] The paradigm of evaluating phase 3 randomized controlled trials does not apply to biosimilars. Manufacturers must establish the biologic similarity of the biosimilar product with its reference product by comparing their analytic, preclinical, and clinical properties, since they are structurally related molecules, and not identical. Therefore, regulatory review of biosimilarity in the United States is based on a global data package that consists of analytic data (eg, structural and physiochemical tests, functional and biological assays), analysis of the mechanisms of action, and review of non-clinical, pharmacokinetic and pharmacodynamics, immunogenicity, and clinical efficacy and safety data. The actual data package of study design and endpoints depends on the complexity of the molecule and degree of analytical similarity.

The goal of this clinical data review is to identify potential differences between the biosimilar and its reference product that might arise in the production process and to confirm comparable clinical performance. The FDA requires a pharmacokinetic/pharmacodynamic (PK/PD) study in humans and at least 1 randomized clinical trial to demonstrate clinical/therapeutic equivalence between the biosimilar and reference product, as well as immunogenicity and comparable safety of the biosimilar and its reference product. Before biosimilar drugs are clinically evaluated, nonclinical studies examine comparability.[16] For instance, the nonclinical testing for infliximab biosimilar CT-P13, which was the first monoclonal antibody biosimilar approved in Europe and in the United States, involved examination of molecular structure, product stability and quality, and binding affinities for soluble monomeric and trimeric forms of tumor necrosis factor-alpha and transmembrane tumor necrosis factor-alpha.[17] The pharmacokinetic and toxicity profiles of the biosimilar CT-P13 were also studied in animal populations. Regulatory approval for biosimilar CT-P13 was based on studies that confirmed the pharmacokinetics and clinical equivalence of CT-P13, and included 2 randomized, double-blind trials, a phase 1 pharmacokinetics study in patients with ankylosing spondylitis, and a phase 3 efficacy study in patients with active rheumatoid arthritis.[18-20]

Question 6

Within a community pharmacy setting, the insurers have been setting lower reimbursement rates for biologic therapies in a range of disease states. The pharmacy is exploring the potential for dispensing the lowest-cost, therapeutically equivalent product. Which FDA designation applied to biosimilars allows pharmacists to substitute a biosimilar for a reference product without having to notify the prescriber?

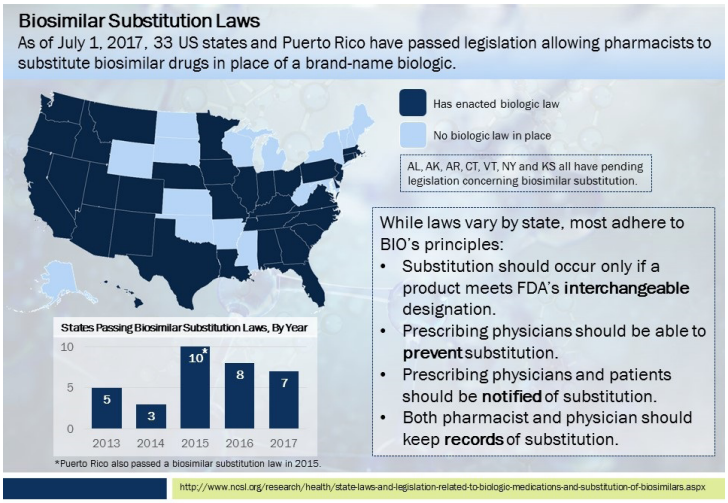
A. Identical
B. Immunogenic
C. Extrapolated
D. Interchangeable

The correct answer is D.

Rationale

In addition to approving biosimilar drugs as "highly similar" to their reference products, the FDA may make an additional determination and designate a biosimilar product as "interchangeable." Patients being treated with a reference drug can be switched to an "interchangeable" biosimilar without loss of efficacy or safety, and without the intervention of the provider who prescribed the reference product.[21] Biosimilarity itself does not guarantee interchangeability. In order to receive a designation of interchangeability, the approval pathway requires higher standards than for approval of a biosimilar as "highly similar."[22] The 2009 Biologics Price Competition and Innovation (BPCI) Act defines an "interchangeable biosimilar" as one that is expected to produce the same clinical results in any given patient, and, for a product that is administered more than once, that there is no additional risk to safety or efficacy as a result of switching to the biosimilar drug.[22] To date, the Food and Drug Administration has not designated interchangeability to any currently approved biosimilar.[23]

Substitution occurs when a pharmacist selects and dispenses a drug product that is identical to the branded product in terms of active ingredient, strength, concentration, dosage form, and administration route.[24] In practice, individual state laws already regulate substitution, and give pharmacists the authority to make this substitution within reason.[22] Many state pharmacy practice laws tie this substitution to the interchangeability designation. This is analogous to the "AB" therapeutic equivalence rating that generic products have. However, if a biosimilar drug has an interchangeability designation, it may be considered appropriate for substitution by pharmacists without the intervention of the prescriber. Extrapolation refers to the process through which a biosimilar is approved for 1 or more clinical indications that the reference product is licensed for, despite the absence of head-to-head clinical comparison. The approval of an indication for a biosimilar through the extrapolation process eliminates the need for further clinical studies. Immunogenicity is the ability of a substance to trigger an immune response or reaction in a human or animal (eg, development of specific antibodies, T cell response, allergic or anaphylactic reaction).[21]



Question 7

Comparative clinical efficacy studies of biosimilar products should be designed to evaluate safety. A critical component of preapproval safety evaluation of a biosimilar requires review of data for which one of the following?

A. Anti-drug antibody development or cytokine release
B. Identification of novel adverse effects not experienced by the reference
C. Statistically equivalent profiles in rare but serious adverse effects
D. That there is no risk of dispensing or medication errors compared to the reference

The correct answer is A.

Rationale

Immunogenicity is a measure of the ability of a substance to trigger an immune response or reaction (eg, development of specific antibodies, T cell response, allergic or anaphylactic reaction). These responses or antidrug antibodies correlate with toxicity and efficacy, and can translate to clinically meaningful events such as acute anaphylaxis or serum sickness, or compromise treatment efficacy. The risk of immunogenicity is a concern with any biologic drug, and a substantial proportion of patients treated with biopharmaceuticals develop antidrug antibodies, regardless of whether they received a biosimilar or the reference product.[25] The goals of preclinical safety assessments and risk mitigation strategies are to assess whether the incidence of antidrug antibodies in the biosimilar differs from the reference product. For instance, in trials of CT-P13 (infliximab biosimilar), the development of antidrug antibodies was similar in patients who were treated with the biosimilar drug vs those treated with reference infliximab, or who switched from reference infliximab to biosimilar CT-P13.[26, 27] Many factors affect immunogenicity (eg, route of administration, co-medications); therefore, the US FDA recommends collecting additional immunogenicity data through post-marketing surveillance of biosimilar products.[28]

The likelihood of novel adverse effects not experienced by the reference product is low and is not the purpose of the regulatory exercise. The safety analysis is based on what is already known about the reference product. The numbers for rare but serious adverse effects are too small to identify in pre-approval studies. Therefore, a post-approval pharmacovigilance program will identify whether there are issues in real-world settings. Although the pre-approval immunogenicity assessment mitigates most of these concerns, post-approval surveillance provides additional security. The risk of dispensing or medication errors is beyond the purview of the FDA. Such errors are a practice concern, and institutions need to set their own policies to prevent the risk of occurrence.

Question 8

A 40-year-old man with moderate-to-severe Crohn's disease is being treated with mesalamine 3 g/day. The patient complains of increasingly persistent diarrhea, rectal bleeding, and abdominal pain, and his Crohn's Disease Activity Index (CDAI) score is 236.

Which one of the following biosimilar products is FDA-approved to treat this patient?

A. Rituxumab-abda
B. Infliximab-dyyb
C. Filgrastim-sndz
D. Etanercept-szzs

The correct answer is B

Rationale
Infliximab-dyyb was the first biosimilar monoclonal antibody (mAb) that the FDA approved for the treatment of adults and children older than 6 years with moderate-to-severe active Crohn's disease (CDAI 220-450) who have had an inadequate response to conventional therapy. It is also approved for treating adults with ankylosing spondylitis, moderate-to-severe active rheumatoid arthritis in combination with methotrexate, active psoriatic arthritis, and chronic severe plaque psoriasis.[29] In 2 clinical trials, infliximab-dyyb was compared to reference infliximab in patients with rheumatoid arthritis and ankylosing spondylitis.[30, 31]

Rituxumab-abda is approved in Europe for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis. This agent is not yet approved in the United States. Filgrastim-sndz is a human granulocyte colony-stimulating factor that was FDA-approved in 2015 to reduce the risk of infection in patients being treated with chemotherapy.[32] Etanercept-szzs is FDA-approved for the treatment of rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, and ankylosing spondylitis.[33]

Question 9

A 67-year-old woman with HER2-positive metastatic breast cancer is considered a candidate for treatment with a HER2-directed monoclonal antibody. Based on recently published clinical comparative data, which one of the following biosimilar agents, if approved, could be considered an appropriate treatment option for this patient?

A. Myl-1401O
B. ABP 980
C. SB3
D. BCD-022

The correct answer is A.

Rationale

Trastuzumab is a humanized monoclonal antibody used in the adjuvant and metastatic setting to treat patients with breast cancer. Data show that treatment with trastuzumab significantly improves outcomes for patients with HER2–positive metastatic breast cancer when combined with chemotherapy.[34] However, its patent will expire in 2019, and several biosimilar drugs are currently being investigated. The efficacy and safety of trastuzumab biosimilar Myl-1401O were initially evaluated using a stepwise analysis of physicochemical and biological characterization, nonclinical, pharmacokinetic, and pharmacodynamic studies. The last step in this review was a phase 3 confirmatory clinical study to demonstrate similarity in the efficacy, safety, and immunogenicity of biosimilar trasuzumab to its reference product.[35] The trial involved 500 women with metastatic HER2-positive breast cancer who were randomized to trastuzmab plus a taxane, or to biosimilar trastuzuamb plus a taxane, and was designed as an equivalence study with a primary outcome of overall response rate (ORR) at 24 weeks, defined as complete or partial response. The overall response rate to the proposed biosimilar plus a taxane at 24 weeks was 69.6% (95% CI, 63.62%-75.51%) compared with 64.0% (95%CI, 57.81%-70.26%) for trastuzumab plus a taxane, which was within predefined equivalence boundaries.

Other trastuzumab biosimilar candidates are currently undergoing investigation, including ABP 980 and SB3. A phase 1 bioequivalence trial has been published for ABP 980 showing comparable pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity to trastuzumab in healthy volunteers,[36] while no data are currently available for SB3.[37] Phase 1 clinical data for BCD-022 showed similar pharmacokinetics and safety to trastuzumab in patients with HER2-positive metastatic breast cancer.[37]

Question 10

Myl-1401O has been tested as a potential biosimilar treatment option for patients with HER2-positive metastatic breast cancer. Recently published clinical data confirmed the efficacy and safety equivalence of this biosimilar to the reference product trastuzumab based on which one of the following clinical endpoints?

A. Overall survival
B. Progression-free survival
C. Overall response rate
D. Patient reported outcomes

The correct answer is C.

Rationale

The pharmacologic action of reference trastuzumab is well documented, as are response rates and overall survival in HER2-positive breast cancer. The goal of comparative clinical studies is to identify whether there is a clinically different effect of a proposed biosimilar compared to the reference, if a difference actually exists. The efficacy and safety of the reference product have been previously established.[38] Proposed biosimilar agents must be comparable to the reference drug in phase 1 studies, especially with regard to pharmacokinetics, pharmacodynamics, and immunogenicity. The guidance is that the phase 3 trial be conducted in a suitably sensitive indication to identify differences between the biosimilar and the reference product. Therefore, phase 3 studies for biosimilar candidates typically involve evaluating a disease and indication for which the reference product has been approved; the aim is to demonstrate clinical and safety equivalence. Efficacy endpoints for an innovator trial may differ from the endpoints used in evaluation of a biosimilar candidate often emphasizing short-term endpoints felt to be sensitive enough to reveal clinically meaningful differences between a biosimilar candidate and a reference drug.

In oncology trials of biosimilar products, progression-free survival (PFS) is a delayed endpoint, and overall survival (OS) can be confounded by subsequent therapy. In these studies, response endpoints such as: overall response rate; complete response rate; pathological complete response; and molecular response, are often used.[38] PFS is a common secondary endpoint to confirm the result established by the response endpoint, but the sample may be underpowered for the PFS endpoint.

Although pharmacokinetic and pharmacodynamics studies for a biosimilar can be conducted with healthy volunteers, an equivalence trial design for a biosimilar should be conducted in a sensitive population of patients with a disease for which the reference product is licensed.[39] Sensitive means that if a difference existed, it could be readily identified in this population. This means that this disease should have a measurable near-term metric. This trial design strategy ensures that any differences in efficacy, safety, and immunogenicity are likely to be attributed to the biosimilar drug vs the patient population.[39] A clinical trial to confirm biosimilarity should also be designed with an equivalence margin for the clinical endpoint that is based on a meta-analysis of previous clinical trials involving the reference product.[39] For instance, in the recently published clinical trial comparing trastuzumab biosimilar with reference trastuzumab, the pre-established equivalence margins were set to be between 0.81 to 1.24 of the effect ratio. For biosimilar trastuzumab, the 90% confidence interval for the overall response rate ratio (proposed biosimilar/trastuzumab) was between 0.974 to 1.211, well within this boundary and thus considered to be equivalent.[40] Patient-reported outcomes is not considered a clinical endpoint.

Question 11

Following approval of a biosimilar, and in order to ensure the accurate attribution of safety events to the product that caused the event, which one of the following processes is used to document procedures for data collection, data processing, and mandatory safety reporting for biosimilar products after FDA approval?

A. Biovigilance
B. Risk management
C. Pharmacovigilance
D. Pharmacomanagement

The correct answer is C.

Rationale

Biosimilar pharmacovigilance involves procedures that monitor drug safety to detect, evaluate, and prevent adverse events after drug approval. The FDA assesses the safety of biosimilar products using the same parameters that are used to evaluate the reference product, and in a clinical relevant, large enough population to compare adverse event frequencies.[41] In general, clinical studies of biosimilars have demonstrated adverse event profiles that are comparable to the reference product class.[42] However, not all safety issues will be evident in the totality of evidence used to evaluate clinical efficacy and safety for biosimilar drugs, in part because a limited number of patients are typically involved in studies that constitute the totality of evidence.[43] Pharmacovigilance is therefore an important safety assurance component in the abbreviated regulatory pathway for biosimilar products.

For pharmacovigilance to be effective, biosimilar drugs must be named uniquely to differentiate them clearly from the reference product. The FDA has published guidance on naming that recommends using an international nonproprietary name (INN) followed by a unique, 4-letter suffix that is devoid of meaning.[44] The rationale for this approach is to create a common lexicon that electronic health systems can use to group similar biologics, as well as to support the traceability and identification of the drug associated with an adverse event.[43] Strategies for effective pharmacovigilance include designated staff with responsibility for pharmacovigilance; documented procedures for data collection, processing, and mandatory reporting of adverse events to the FDA or manufacturer, and electronic databases to support systematic reporting.[45]

Question 12

A 36-year-old woman with rheumatoid arthritis being treated with a recently approved biosimilar product develops cellulitis. Which of the following regulatory requirements is considered essential by the US FDA for reporting this adverse event and for facilitating the post-marketing surveillance of biosimilar products?

A. A fingerprint-like analysis
B. Unique names that distinguish between products
C. A totality of evidence review
D. A stepwise analysis

The correct answer is B.

Rationale

When adverse events are reported, the event must be attributed to the specific product that caused the event. With the increase of multi-source biologics, identifying a product linked to an adverse event by its generic name (eg, filgrastim) is insufficient. A recent retrospective analysis of claims data assessed the capability of active and passive safety surveillance systems to track product-specific safety events in the USA for branded and generic enoxaparin.[46] The study reviewed heparin-induced thrombocytopenia (HIT) incidence in patients newly treated with enoxaparin. The study also reviewed the attribution of enoxaparin-related reports to specific manufacturers using the FDA Adverse Event Reporting System. The study found no clinical difference between the products and the incidents of HIT. After the originator product's loss of exclusivity, only 5% of spontaneous reports were processed by generic manufacturers; reports attributable to specific generics were approximately 9-fold lower than expected, based on market share. Authors concluded that the current spontaneous reporting system is unlikely to distinguish product-specific safety signals for products distributed by multiple manufacturers, including biosimilars. Therefore, the FDA has developed specific guidance on naming biosimilars in order to facilitate pharmacovigilance and to enable clinicians to report the specific product linked to post-marketing adverse events. The FDA is instituting a random 4-letter suffix to all biologic drugs (both the biosimilar and its reference product). The FDA has published guidance on naming that recommends using an international nonproprietary name (INN) followed by a unique 4-letter suffix that is devoid of meaning.[47] Current approved naming examples include rituxumab-abda, infliximab-dyyb, filgrastim-sndz, and etanercept-szzs. The rationale for this approach is to create a unique name for each product that facilitates the tracing and identification of the drug associated with an adverse event.[48]

Stepwise analysis refers to the process of reviewing preclinical studies, followed by phase 1 then phase 3 studies as part of the regulatory pathway. The totality of evidence is also referred to as fingerprint similarity.[49]

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