Biologics Are Not Chemical Drugs

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As soon as you go into any biological process in any real detail, you discover it's open-ended in terms of what needs to be found out about it.

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Nobel Prize winner, 1925–2008

Abstract

It is shown that in the eyes of both the FDA and the EMA, biologics are definitely different from chemical drugs. This is not a perception, but a reality, and it is reflected by the statements on their websites and in the wording of the regulatory guidances that they issue. Also, as is shown in this chapter, the three major differences between biologics and chemical drugs are discussed: (1) use of living source materials to produce the biologic, (2) increased complexity of biologic manufacturing processes, and (3) increased complexity of the biologic molecules themselves. Finally, in this chapter, an explanation is presented of why biosimilar biological products are best viewed as similar biologics and not as true generics.

Keywords

Biosimilars • Generics • FDA • EMA • WHO • Health Canada • ICH • NDA • ANDA • BLA • Abbreviated BLA

In my conversations with senior management, especially those who have moved recently from the chemical drug side of the pharmaceutical industry into the biologics side, I am asked whether biologics are really different than chemical drugs or is it just a perception that they are different. And the question is understandable if one has limited understanding of the challenges imposed by these products. Biologics, when directly compared to chemical drugs, (1) take more staff to operate and control the manufacturing processes, (2) have more demanding and expensive QC release and stability tests, and (3) have an extensive number of batch and testing records for QA to review which takes QA longer to release each batch of product.

Probably the strongest argument that biologics are different than chemical drugs is from the statements made by the regulatory authorities themselves. As is shown in this chapter, in the eyes of both the FDA and the EMA, biologics are definitely different from chemical drugs. This is not a perception, but a reality, and it is reflected by the statements on their websites and in the wording of the regulatory guidances that they issue. Also, as is shown in this chapter, the three major differences between biologics and chemical drugs are discussed: (1) use of living source materials to produce the biologic, (2) increased complexity of biologic manufacturing processes, and (3) increased complexity of the biologic molecules themselves. Finally, in this chapter, an

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explanation is presented of why biosimilar biological products are best viewed as similar biologics and not as true generics.

2.1 Regulatory Authorities Agree

The FDA and EMA regulatory authorities clearly see the reality that biologics are not chemical drugs. A glance at the statements on their websites and a review of the wording in their regulatory guidances for these products show this. Furthermore, the ICH consensus guidance documents add support to this regulatory acceptance that biologics are different than chemical drugs.

2.1.1 FDA's Viewpoint on Differences

FDA embraces the reality that biologics are not chemical drugs. On its introduction to biological products website, the FDA openly discusses some general differences between these two classes of drugs [1].

> Most drugs consist of pure chemical substances and their structures are known. Most biologics, however, are complex mixtures that are not easily identified or characterized. Biological products differ from conventional drugs in that they tend to be heat-sensitive and susceptible to microbial contamination. This requires sterile processes to be applied from initial manufacturing steps.

The FDA website also has a location for frequently asked questions about regulating biologic products. On that website, one question that the FDA addresses is as follows: "How do biologics differ from conventional drugs?" [2]

> 10. How is the manufacturing process for a biological product usually different from the process for drugs? Because, in many cases, there is limited ability to identify the identity of the clinically active component(s) of a complex biological product, such products are often defined by their manufacturing processes. Changes in the manufacturing process, equipment or facilities could result in changes in the biological product itself and sometimes require additional clinical studies to demonstrate the product's safety, identity, purity and potency. Traditional drug products usually consist of pure chemical substances that are easily analyzed after manufacture. Since there is a significant difference in how biological products are made, the production is monitored by the agency from the early stages to make sure the final product turns out as expected.

Two guidance documents issued by FDA on CMC content for Investigational New Drug (IND) clinical applications, one for human gene therapy [3] and the other for cell-based biologics [4], reinforce the reality of the differences between biologics and chemical drugs:

> In order to deliver a safe and effective product, human somatic cell therapies present many manufacturing challenges. Some of these challenges include the variability and complexity inherent in the components used to generate the final product, such as the source of cells (i.e., autologous or allogeneic), the potential for adventitious agent contamination, the need for aseptic processing, and the inability to "sterilize" the final product because it contains living cells. Distribution of these products can also be a challenge due to stability issues and the frequently short dating period of many cellular products, which may necessitate release of the final product for administration to a patient before certain test results are available.

Thus, from the FDA viewpoint, biologics are different from chemical drugs due to (1) the use of living source materials to produce the biologic, (2) increased complexity of the manufacturing processes, and (3) increased complexity of the products themselves.

2.1.2 EMA's Viewpoint on Differences

The EMA embraces the reality that biologics are not chemical drugs. The EU GMP Annex 2 guideline on manufacture of biological medicinal substances and products openly discusses the differences between biologics and chemical drugs [5]:

> The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and the processes. The ways in which biological medicinal products are manufactured, controlled and administered make some particular precautions necessary.
>
> Unlike conventional medicinal products, which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of biological medicinal substances and products involves biological processes and

materials, such as cultivation of cells or extraction of material from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products may be variable. As a result, quality risk management (QRM) principles are particularly important for this class of materials and should be used to develop their control strategy across all stages of manufacture so as to minimise variability and to reduce the opportunity for contamination and cross-contamination.

Since materials and processing conditions used in cultivation processes are designed to provide conditions for the growth of specific cells and microorganisms, this provides extraneous microbial contaminants the opportunity to grow. In addition, many products are limited in their ability to withstand a wide range of purification techniques particularly those designed to inactivate or remove adventitious viral contaminants. The design of the processes, equipment, facilities, utilities, the conditions of preparation and addition of buffers and reagents, and training of the operators are key considerations to minimise such contamination events.

A 2005 guidance document issued by EMA on similar biological medicines reinforces the reality of the differences between biologics and chemical drugs [6]:

Biological medicinal products are usually more difficult to characterise than chemically derived medicinal products. In addition, there is a spectrum of molecular complexity among the various products (recombinant DNA, blood or plasma-derived, immunologicals, gene and cell-therapy, etc.). Moreover, parameters such as the three-dimensional structure, the amount of acido-basic variants or post-translational modifications such as the glycosylation profile can be significantly altered by changes, which may initially be considered to be 'minor' in the ;the monitoring of quality aspects.

Thus, the EMA, consistent with the viewpoint of the FDA, agrees that biologics are different from chemical drugs due to (1) the use of living source materials to produce the biologic, (2) increased complexity of the manufacturing processes, and (3) increased complexity of the products themselves.

2.1.3 ICH's Position on Differences

While ICH is not a regulatory authority, the tripartite guidances that are issued under this title are consensus guidance documents accepted by the FDA, EMA, and the Japanese Ministry of Health Labor and Welfare (JMHLW). As the ICH has attempted to develop consensus guidances, they have had to face the reality of the differences between biologics and chemical drugs.

ICH has issued two consensus guidance documents entitled "Specifications: Test Procedures and Acceptance Criteria"; one is specific for chemical drugs (ICH Q6A) and the other is specific for biological products (ICH Q6B). Owing to the differences between chemical drugs and biologics, each document makes a strong point of indicating in its scope that it applies either only to chemical drugs or only to biological products:

ICH Q6A [7]
This guideline addresses only the marketing approval of new drug products (including combination products) and, where applicable, new drug substances; it does not address drug substances or drug products during the clinical research stages of drug development. This guideline may be applicable to synthetic and semi-synthetic antibiotics and synthetic peptides of low molecular weight; however, it is not sufficient to adequately describe specifications of higher molecular weight peptides and polypeptides, and biotechnological/biological products.

ICH Q6B [8]
The principles adopted and explained in this document apply to proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or nonrecombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures. The principles outlined in this document may also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids. To determine applicability, manufacturers should consult with the appropriate regulatory authorities.

A separate ICH Guideline, "Specifications: Test Procedures and Acceptance Criteria for New Drugs Substances and New Drug Products: Chemical Substances" addresses specifications, and other criteria for chemical substances.

ICH has also issued two consensus guidance documents entitled "Stability Testing," one for chemical drugs (ICH Q1A(R2)) and one for biological products (ICH Q5C). Owing to the differences between chemical drugs and biologics,

each document makes a strong point of indicating in its scope that it applies either to chemical drugs only or biological products only:

> *ICH Q1A(R2)* [9]
> The guidance addresses the information to be submitted in registration applications for new molecular entities and associated drug products.
> Further guidance on new dosage forms and on biotechnological/biological products can be found in ICH guidances Q1C Stability Testing for New Dosage Forms and Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products, respectively.
>
> *ICH Q5C* [10]
> The guidance stated in this annex applies to well-characterised proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues, body fluids, cell cultures, or produced using rDNA technology. Thus, the document covers the generation and submission of stability data for products such as cytokines (interferons, interleukins, colony stimulating factors, tumour necrosis factors), erythropoietins, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulins, monoclonal antibodies, and vaccines consisting of well-characterised proteins or polypeptides. In addition, the guidance outlined in the following sections may apply to other types of products, such as conventional vaccines, after consultation with the appropriate regulatory authorities. The document does not cover antibiotics, allergenic extracts, heparins, vitamins, whole blood, or cellular blood components.

2.2 Three Major Differences of Biologics

The regulatory authorities do indeed state clearly that biologics are not chemical drugs. The differences that they identify will obviously be reflected in the way that the regulatory authorities evaluate and regulate the control of the biologics. An understanding of the three major differences gives an appreciation of why regulatory authorities manage the biologics so differently than chemical drugs: (1) use of living source materials, (2) impact of the manufacturing processes on the produced biologic, and (3) complexity of the produced biologic molecules themselves.

2.2.1 Use of Living Production Systems

Unlike the use of nonliving chemical reagents in the synthetic manufacture of chemical drugs, living systems (whether bacteria, yeast, animal or human cells; viruses; transgenic animals or plants) are used in the production of biologics. Unlike the use of harsh environments to carry out the synthesis of chemical drugs (e.g., organic solvents, high temperatures and pressures), biologic production is carried out under aqueous controlled-temperature conditions that must be protected from ongoing risk of contamination by other living microorganisms in the environment. For living systems to produce a biologic, the living system must be kept alive, must be happy, and must be healthy:

- Living systems must be kept alive. Around the clock, 24/7, for as long as needed to produce the biologic. Dead cells do not produce biologics. In the frozen state of a stored cell bank, the dormant cells must retain their viability upon thawing. During the cell culturing process, maintaining an adequate amount of viable cells is a critical quality attribute affecting not only the total amount of biologic produced but also the amount of process-related impurities present (i.e., dead cells lyse releasing their host-related impurities into the medium). Lower product yield coupled with higher impurity levels can challenge the purification process capability.
- Living systems must be kept happy. The manufacturing process must be appropriately controlled to provide adequate nutrients and a friendly environment of an appropriate oxygen and carbon dioxide gas concentrations, pH, and temperature. These process parameters can impact several cellular functions and properties such as cell metabolism, protein glycosylation, and protein synthesis. Biologic manufacturers go to great care and expense into designing their biologic production process to ensure that the cells are maximized for overproduction of the desired biologic.
- Living systems must be kept healthy. An adventitious agent is defined as a microorgan-

ism—including bacteria, fungi, mycoplasma/spiroplasma, mycobacteria, rickettsia, viruses, protozoa, parasites, and TSE agent—that is inadvertently introduced into the production of a biological product. Once it contaminates a living production system, the biologic process and product have a serious problem. It is a nasty world outside of the sterile environment of a bioreactor, and multiple barriers must be erected around the control of the manufacturing process to protect the living system from these adventitious agents during the production of the biologic.

Since life generates life, it is also important to know the heritage of the living system being used in biologic production. Cells, due to past exposures to viruses, may have a latent virus infection which may be transmitted vertically from one cell generation to the next, since the viral genome persists within the cell. Upon stress of the living production system (such as due to cell aging and nutrient depletion), a latent viral contaminant can be shocked into activity, producing infectious particles [11]. An illustration of a latent virus concern in a living system is children exposed to chickenpox virus. After suffering 1–2 weeks of misery, children recover from the initial virus infection. After the initial attack of chickenpox, however, the chickenpox virus lies dormant in certain nerves in the body. For reasons that are not fully understood, the chickenpox virus can reappear in the form of shingles, more commonly in people with weakened immune systems and with aging. Shingles is characterized by a rash of blisters, which generally develop in a band on one side of the body and can cause severe pain that may last for weeks and, in some people, for months or years after the episode.

2.2.2 Impact of Manufacturing Process on the Product

For chemical drugs, the manufacturing process can frequently be uncoupled from the product, which is the basis for the generics chemical drug industry. But this is not so for biologics.

Molecular conformation, the three-dimensional (3D) structure of the biologic, results from folding of the molecule due to many complex interactions: amide bonding (i.e., covalent bonding forming the amide amino acid linkages in the protein chain), disulfide bonding (i.e., covalent bonding between sulfur atoms of the cysteine amino acids), hydrogen bonding (i.e., joining hydrogen atoms with close oxygen atoms), and nonbonded interactions (i.e., hydrophobic and van der Waals interactions). Molecular conformation of biologics can be readily impacted by subtle changes in the environment (some proteins are only marginally stable, impacted by even ~10 kcal/mol energy shifts). Environmental events such as temperature increases (e.g., holding a biologic solution at room temperature versus refrigeration), sheer forces (e.g., strong agitation of liquid solutions), and even exposure to light can impart enough energy into a solution to cause a molecular conformation shift. Although some tests methods (such as X-ray crystallography) are available to analyze molecular conformation, such methods are not applied routinely to biologics. Without this analysis, it is most difficult for a manufacturer to know if the biologic molecular conformation has been impacted by the manufacturing process, and if impacted, whether it has returned to its original 3D state.

Subtle manufacturing process changes can also have major impact on the biologic produced. For example, although nutrient-deficient culture media are used as a selection mechanism in certain cases, culture media deficient in certain amino acids may cause substitutions in the protein produced. When recombinant *E. coli* cells are starved of methionine and/or leucine while growing, the organism will synthesize norleucine and incorporate it in the amino acid position normally occupied by methionine, yielding an analogue of the wild-type protein. The presence of these closely related products will be difficult to separate chromatographically [12]. As another example, the recombinant Chinese hamster ovary (CHO) cells used to manufacture the monoclonal antibody Rituxan (rituximab) produce a biopharmaceutical that has varying levels of galactose at the termini of the carbohydrate chains attached to

the protein molecule. A small molar shift in the number of galactose molecules on the protein molecule profoundly impacts the biological potency of the produced molecule, resulting in either a reduction in potency to 80 % (when there are 0 mol galactose/mole of protein) or an increase in potency to 150 % (when there are 2 mol galactose/mole of protein) [13]. Carefully controlling a complex manufacturing process to control the amount of specific carbohydrate moieties attached to the protein can be a major challenge facing biologic manufacturers.

2.2.3 Complexity of the Produced Biologic

Looking at a recombinant DNA-derived protein or a monoclonal antibody, the complexity of the biologic molecule is due to (1) the possible modifications to amino acids on the intact protein, (2) the varying carbohydrate moieties attached to the protein, and (3) the possible higher-order molecular structures (i.e., conformational changes).

The DNA central theorem states that the DNA sequence should translate directly into the final protein sequence; however, modifications to the desired protein can occur on both the N-terminus and the C-terminus ends of the protein (e.g., truncation of amino acids). The amide peptide bonds can undergo hydrolysis. Amino acids are not "rock solid"; they can also undergo changes such as oxidation of methionine, disulfide scrambling of cysteine, and deamidation of glutamine and asparagine.

Glycan moieties (i.e., the carbohydrate moieties) attached to different sites on the protein present considerable heterogeneity: different types of monosaccharides present and linked in different sequences, length, and branching of carbohydrate chains, etc.

Taken together, if one assumes that all possible variations to the amino acids and to the glycan moieties can occur, it has been estimated that approximately 100 million possible molecular variants of a monoclonal antibody molecule could occur [14]. And these possible molecular variants cannot be taken lightly, since there are potential clinical safety concerns associated with them [15]:

> Biotechnology-derived analogs to human endogenous proteins may trigger an immune response due to variations in the amino acid sequence or changes to the protein structure as a result of posttranslational modifications, physical, chemical or enzymatic degradation and/or modification e.g. deamidation, oxidation and sulfatation during all steps of the manufacturing process and during storage. Fusion proteins composed of a foreign and self-protein are of particular concern because of the potential of the foreign moiety to provoke an immune response to the self-protein (epitope-spreading). Identification of the antigenic moiety of the fusion protein is advisable. Glycosylation is a frequent posttranslational modification of biotechnology-derived therapeutic proteins. These modifications may differ in the number and position of glycosylation sites as well as sequence, chain length and branching of the attached oligosaccharide.

The size of the biologic molecule along with the close similarity with other similar proteins increases the challenge for Quality Control (QC) to develop appropriate test methods for analysis of these products. Take, for example, the need of a specific fingerprint identification test. For a chemical drug, infrared (IR) spectral analysis is a suitable fingerprint identification test. The test is specific, identifying functional groups on the molecule, and appropriate for many chemical drugs. According to the United States Pharmacopeia (USP) <197> Spectrophotometric Identification Tests: "the IR absorption spectrum of a substance, compared with that obtained concomitantly for the corresponding USP Reference Standard, provides perhaps the most conclusive evidence of the identity of the substance that can be realized from any single test" [16]. Such an IR fingerprint identity test, performed under current good manufacturing practice (cGMP), takes less than a half a day to complete for a chemical drug. However, for a biologic protein or monoclonal antibody, the IR fingerprint identity test is not effective; instead, a peptide mapping fingerprint identification test is necessary. According to USP <1047> Biotechnology-Derived Articles—Tests, Peptide Mapping: "peptide mapping is an identity test for proteins … it is a powerful test that is capable of identifying single amino acid changes

resulting from events such as errors in the reading of complementary DNA (cDNA) sequences or point mutations" [17]. A peptide mapping fingerprint identity test, performed under current good manufacturing practice (cGMP), takes from several days to up to a week to complete for a biologic protein (e.g., Insulin Human USP peptide mapping identity test requires a 6-h enzymatic incubation followed by a 90-min chromatographic gradient program for each sample to be tested [18]).

The enhanced sophistication in the testing required by QC for a biologic, across many of the tests that must be performed (e.g., biological functioning potency assays and residual host cell process impurity tests), explains why QC resource is much more intensive for biologics than for chemical drugs.

2.3 Biosimilar, Not "Biogeneric"

A chemical drug can be approved as a generic drug product. However, a biosimilar biological product (also referred to as subsequent entry biologics or similar biotherapeutic product) is best viewed as a similar biologic and not as a generic.

A generic chemical drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use. Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24–36 healthy, volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug. A chemical drug generic application expedites the availability of less costly drugs because the regulatory authority can approve an application to market a generic version of a brand-name reference listed drug (RLD) without conducting costly and duplicative clinical trials. Both the U.S. FDA [19] and EMA [20] approve generic chemical drugs for market release.

A similar biologic is not pharmaceutically equivalent to a brand-name reference listed drug (RLD). A similar biologic is not a generic, as clearly stated by the regulatory authorities:

> *EMA* [21]
> It should be recognised that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established.

> *Health Canada* [22]
> The term, subsequent entry biologic, was chosen as an alternative to "biogeneric" or "generic biologic" in order to clearly distinguish between the regulatory process (and product characteristics) for SEBs and that which is currently used for generic pharmaceutical drugs.

> *World Health Organization (WHO)* [23]
> The term 'generic' medicine is used to describe chemical, small molecule medicinal products that are structurally and therapeutically equivalent to an originator product whose patent and/or data protection period has expired. 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. However, the approach established for generic medicines is not suitable for development, evaluation and licensing of SBPs since biotherapeutics consist of relatively large, and complex proteins that are difficult to characterize.

A similar biologic relies not just on CMC comparability but also on nonclinical and clinical comparability generated by the manufacturer.

2.3.1 EMA: Biosimilar Medicines

The EMA has a matured pathway for similar biologics, having released the first guidelines in 2005. In principle, the concept of similar biolog-

ics could be applicable to any biologic; however, in practice, the success of such an approach depends upon the ability to thoroughly characterize the molecule and demonstrate the similar nature to the reference listed drug. Thus, the EMA currently limits biosimilars to highly purified products, such as the biotechnology-derived medicinal products.

At present, the following biologics are listed by EMA as too difficult to thoroughly characterize and to be considered for biosimilars [24]:

- Biological substances arising from extraction from biological sources
- Vaccines
- Plasma-derived proteins (and their recombinant alternatives)
- Gene and cellular therapy products

For approval as a biosimilar, (1) full CMC information must be provided in a MAA submission, (2) an acceptable reference listed drug must be used as the comparator, and (3) extensive state-of-the-art characterization studies must be applied to the similar biological and reference medicinal products in parallel at both the active substance and the medicinal product levels to demonstrate with a high level of assurance that the quality of the similar biological medicinal product is comparable to the reference medicinal product. The quality of the biosimilar does not have to be identical to the reference listed drug, but it must be highly similar, and any differences identified need to be justified [25].

But, also most importantly, for approval as a biosimilar, both nonclinical and clinical comparability studies must be considered [26]:

> The Marketing Authorisation (MA) application dossier of a biological medicinal product claimed to be similar to a reference medicinal product already authorised shall provide a full quality dossier. Comparable clinical efficacy and safety has to be demonstrated.

The EMA has published a number of product-specific biosimilar guidances that provide case-by-case recommendations for these nonclinical and clinical comparability studies (see Table 2.1).

Table 2.1 EMA nonclinical/clinical biosimilarity guidelines (Information obtained from the EMA Human Medicines Multidisciplinary: Biosimilar website; www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002958c)

Product type
Recombinant granulocyte-colony-stimulating factor (2006)
Somatropin (recombinant human growth hormone) (2006)
Recombinant interferon-alpha (2009)
Recombinant erythropoietins (2010)
Recombinant follicle stimulation hormone (2013)
Recombinant interferon-beta (2013)
Recombinant human insulin and insulin analogs (2012)
Monoclonal antibodies (2012)

2.3.2 Health Canada: Subsequent Entry Biologics

A subsequent entry biologic (SEB) is a biologic drug that enters the market subsequent to a version previously authorized in Canada and with demonstrated similarity to a reference biologic drug. A subsequent entry biologic relies in part on prior information regarding safety and efficacy that is deemed relevant due to the demonstration of similarity to the reference biologic drug and which influences the amount and type of original data required.

Submission requirements for SEBs are determined on a case-by-case basis by Health Canada. These requirements include the following [27]:

- A complete chemistry and manufacturing data package for the SEB
- A rationale for the choice of the innovator biologic as the comparator and extensive published information on its safety and efficacy
- Sufficient characterization information to demonstrate both chemical and biological comparability of the SEB to the innovator product chosen as the comparator
- Sufficient comparative animal toxicity and toxicological data, where appropriate
- Pharmacodynamic data to demonstrate comparable bioactivity based on parameters or surrogate markers that are clinically relevant and validated
- Pharmacokinetic data to demonstrate comparable bioavailability of the SEB to the innovator product based on suitable validated pharmacokinetic parameters

- Data characterizing the immunogenic profile of the SEB in humans and its potential impact on safety and efficacy
- A clinical package which demonstrates the safety and efficacy of the SEB including comparative studies between the SEB and innovator products, and data for the innovator product in the public domain

A final determination of similarity is based on a combination of analytical testing, biological assays, and nonclinical and clinical comparability data. However, to be considered a SEB by Health Canada, the weight of evidence needs to be provided by the CMC comparability.

2.3.3 WHO: Similar Biotherapeutic Products

The WHO guidelines cover ROW (rest-of-the-world) countries, or have been stated MOW (most-of-the-world) countries, and as such provide important guidance to many national competent authorities (NCAs). The WHO employs the term "similar biotherapeutic product" (SBP) for a biotherapeutic product which is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product. Decision making by the NCAs regarding the licensing of SBPs is based on scientific evidence. The onus is on the manufacturer to provide the necessary evidence to support the application for licensing.

At present, the following biologics are excluded by the WHO for consideration as an SBP:

- Vaccines
- Plasma-derived proteins (and their recombinant alternatives)

The CMC comparison showing molecular and biological functional similarity between the SBP and the RBP (Reference Biotherapeutic Product) is indispensable. But it is the totality of CMC and nonclinical and clinical comparability data that will determine if the SBP can ultimately be approved [28]:

> In addition to the quality data, SBPs require non-clinical and clinical data generated with the product itself. The amount of non-clinical and clinical data considered necessary will depend on the product or class of products, the extent of characterization possible undertaken using state-of-the-art analytical methods, on observed or potential differences between the SBP and the RBP, and on the clinical experience with the product class (e.g. safety/immunogenicity concerns in a specific indication). A case by case approach is clearly needed for each class of products.

Table 2.2 Three regulatory approval pathways within the FD&C Act

505(b)(1) NDA pathway	Standard approval mechanism for new drugs—full CMC, safety and efficacy studies, new drug stands on the merits of its own data
505(b)(2) NDA pathway	This in an abbreviated approval mechanism that permits an applicant to rely on published literature or on the agency's finding of safety and effectiveness for a referenced approved drug product to support approval of a proposed product. The applicant must demonstrate that reliance on the previous finding of safety and effectiveness is scientifically justified and must submit whatever additional nonclinical and clinical data are necessary to establish that the proposed product is safe and effective
505(j) ANDA pathway	This is the abbreviated approval mechanism for duplicates of drugs already approved under section 505 of the Act—chemical generics

2.3.4 FDA: Follow-On Protein Products

The FD&C Act permits the FDA to approve biological products regulated under this law using the 505(b)(2) abbreviated NDA pathway (see Table 2.2).

Janet Woodcock, Deputy Commission of the FDA, in 2007, presented the following summary of how the FDA uses this 505(b)(2) NDA abbreviated pathway for "follow-on proteins" (FOPs) [29]:

> Even though protein products are more complex than small molecules, FDA has applied its expertise and experience to approve certain follow-on protein products in applications described in section 505(b)(2) of the FDC Act. Some examples of products approved in this manner are: Hylenex (hyaluronidase recombinant human), Hydase

(hyaluronidase), Fortical (calcitonin salmon recombinant) Nasal Spray, Amphadase (hyaluronidase), GlucaGen (glucagon recombinant for injection), and Omnitrope (somatropin [rDNA origin]).

Omnitrope is a human growth hormone product derived from recombinant DNA processes. Human growth hormone is a single-chain, 191 amino acid, nonglycosylated protein. Its amino acid sequence is well known and physicochemical tests are able to determine the complex folded structure of human growth hormone products. There are also clinically relevant bioassays and validated biomarkers (laboratory indicators of effect) available to assess the performance of human growth hormone products. Human growth hormone has a long and well-documented clinical history as replacement therapy for growth failure in pediatric patients due to endogenous growth hormone deficiency, and its mechanism of action and toxicity profile are well established. Some marketed human growth hormone products are approved for other uses, such as therapy for growth failure associated with chronic renal insufficiency and replacement of endogenous growth hormone in adults with growth hormone deficiency. The original marketed versions of human growth hormone were derived from the pituitary glands of human cadavers. The first recombinant version was approved in 1985. Since then, several more recombinant human growth hormone products have been approved under section 505(b)(1) of the FDC Act (i.e., each product approval relied on original clinical data developed specifically for that product, not an abbreviated pathway).

Omnitrope is the first recombinant human growth hormone product approved through the abbreviated pathway described by section 505(b)(2) of the FDC Act. It was approved for (1) long-term treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous growth hormone and (2) long-term replacement therapy in adults with growth hormone deficiency (either childhood or adult onset). The approval of Omnitrope was based on new data specific to Omnitrope (but less new data than would be needed to support an approval under section 505(b)(1)) and also relied on the approval of Genotropin (a previously approved version of rDNA-derived somatropin) for the same indications proposed. Specifically, the approval was based on the following:

- Physicochemical testing that established, among other things, that the structure of the active ingredient in Omnitrope is highly similar to the structure of the active ingredient in Genotropin;
- New non-clinical pharmacology and toxicology data specific to Omnitrope;
- Vast clinical experience and a wealth of published literature concerning the clinical effects (safety and effectiveness) of human growth hormone;
- Pharmacokinetic, pharmacodynamic, and comparative bioavailability data that established, among other things, that Omnitrope and Genotropin are highly similar based on pharmacokinetic parameters and pharmacodynamic responses;
- Clinical efficacy and safety data from controlled trials comparing Omnitrope to Genotropin and from long-term trials with Omnitrope in pediatric patients; and
- FDA's conclusions that Genotropin is safe and effective for the indications for which approval was sought in the Omnitrope application and that Omnitrope is highly similar to Genotropin.

Omnitrope has not been rated by FDA as therapeutically equivalent (that is, substitutable) to any other approved human growth hormone product.

2.3.5 FDA: Biosimilar Biological Products

Modification of the PHS Act by the Biologics Price Competition and Innovation (BPCI) Act of 2009 finally permits the FDA to approve biopharmaceuticals and biologics regulated under this law using an abbreviated BLA pathway (see Table 2.3).

FDA employs the term "biosimilar biological product" for a biological product which is similar in terms of quality, safety, and efficacy to an already PHS Act-licensed reference biological product. At present, only the therapeutic protein biologics (recombinant proteins and monoclonal antibodies) are under consideration as possible biosimilar biological products.

FDA also employs two terms, "biosimilarity" and "interchangeability" [30]:

> Biosimilarity to mean that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that '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
>
> To meet the higher standard of 'interchangeability', an applicant must provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once

Table 2.3 Two regulatory approval pathways within the PHS Act

BLA pathway 351(a)	Standard approval mechanism for new biologics—full CMC, safety and efficacy studies, new biologic stands on the merits of its own data
Abbreviated BLA pathway 351(k)	A sponsor may seek approval of a "biosimilar" product under new section 351(k) of the PHS Act A biological product may be demonstrated to be "biosimilar" if data show that the product 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 safety, purity, and potency In order to meet the higher standard of interchangeability, a sponsor must demonstrate that the biosimilar product can be expected to produce the same clinical result as the reference product in any given patient and, for a biological product that is administered more than once, that the risk of alternating or switching between use of the biosimilar product and the reference product is not greater than the risk of maintaining the patient on the reference product. Interchangeable products may be substituted for the reference product by a pharmacist without the intervention of the prescribing health-care provider

> to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the 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

The CMC comparison showing molecular and biological functional similarity between the biosimilar biological product and the reference biological product is indispensable. But it is the totality of CMC and nonclinical and clinical comparability data that will determine if the biosimilar biological product can ultimately be approved [31]:

> In evaluating a sponsor's demonstration of biosimilarity, FDA will consider the totality of the data and information submitted in the application, including structural and functional characterization, nonclinical evaluation, human PK and PD data, clinical immunogenicity data, and clinical safety and effectiveness data. FDA intends to use a risk-based, totality-of-the-evidence approach to evaluate all available data and information submitted in support of the biosimilarity of the proposed product.

2.4 Never Say Never

When I entered the biologic industry 35 years ago, the dogma of the regulatory authorities was as follows: "the biologic process defines the biologic product." Unlike chemical drugs which had a risk-based assessment for allowing manufacturing process changes, biologics at that time had a fixed high risk which required regulatory authority preapproval for almost all manufacturing process changes. Then, between the 1980s and 1990s, the regulatory authorities had the opportunity to review numerous recombinant DNA-derived protein and monoclonal antibody biologics for market approval. This helped shape their current regulatory authority dogma which is as follows: "the biologic process may impact the biologic product." Today, a biologic manufacturing process change is now also based on a risk-based assessment review. And it is now the responsibility of the biologic manufacturer to demonstrate to the regulatory authority what impact, if any, a manufacturing process change might have on the biologic product.

Might the future dogma of the regulatory authorities be the following: "the biologic process can be separated from the produced biologic product?" Currently, no regulatory authority accepts biologics as generics (i.e., completely uncoupling the manufacturing process from the biologic produced). But who knows what changes in regulatory authority dogma the future holds. Already, EMA has raised this discussion point in a concept paper [32]:

> Discussion is needed to clarify if in exceptional situations, e.g. where a very simple biological fully characterised on the quality level, a biological medicinal product could be authorised based on a bioequivalence study only combined with an extensive quality comparability exercise.

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