What Is a Generic Biopharmaceutical? Biogeneric? Follow-On Protein? Biosimilar? Follow-On Biologic?

Part 1: Introduction and Basic Paradigms

by Ronald A. Rader

Terminology (and related taxonomy or classification and nomenclature) is of utmost importance to any industry. The concepts and paradigms involved and the words used to convey them provide a common framework for communication, understanding, and perceptions.

This is the first of two articles concerning generic biopharmaceutical paradigms, terminology, and nomenclature issues: how we think of, define, name, and regulate these products. Part 1 reviews background information and basic views, paradigms, and/or definitions. Part 2 will provide perspectives and further discuss nomenclature, legislation, and public controversies.

A great deal is at stake because most successful biopharmaceuticals will sooner or later face generic competition; and sooner or later, most successful biopharmaceutical companies will be involved or competing with biogenerics. The paradigms, taxonomies, terminology, and definitions to be adopted for biogenerics will profoundly affect the (bio)pharmaceutical industry, healthcare systems, and economies worldwide. New laws and regulations are needed for biogenerics and will be controversial, particularly in the United States. They will largely be rather predictable extensions of current generic drug and biologics regulations. The underlying concepts, terminology, and nomenclature used for such products, including those adopted by regulators, the medical community, and general public, are likely to cause the most controversy. As I will discuss in Part 2, these aspects, not approval mechanisms, will shape perceptions and more directly affect the marketing of these products.

Biopharmaceutical terminology has faced a certain degree of chaos and anarchy for years. In fact, the word *biopharmaceutical* itself continues to be subject to a wide variety of views, paradigms, and definitions, whether in relation to products, technologies, companies, or the industry (**1, 2**). The predominant definition (the "broad biotech" view) within the US industry is that *biopharmaceutical* refers to pharmaceuticals that are inherently biological in nature due to their manufacture using live organisms (biotechnology). The "new biotechnology" view, more common in Europe, restricts the term to

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genetically engineered products (recombinant proteins and monoclonal antibodies).

Many people, including much of the popular and financial press, companies, and major trade associations, ignore the products' biological nature and use of biotechnology and concentrate instead on business models. The "biotech business" view therefore considers biopharmaceutical products (and companies, and industry) as those involving anything pharmaceutical (including small-molecule drugs) associated with smaller, biotech-like

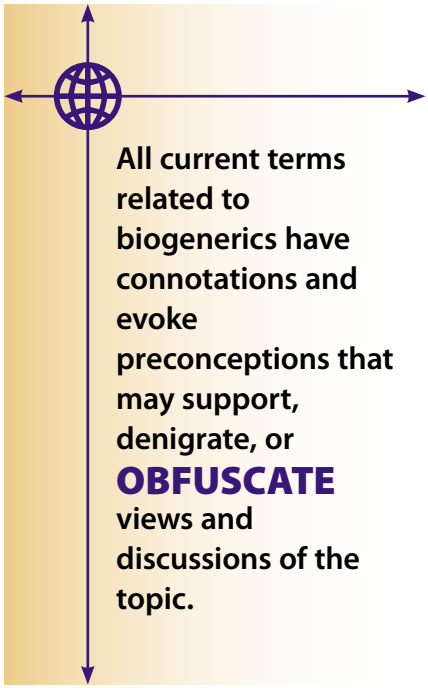
companies or that seem to be or can be portrayed as high-tech. The "pharma business" view simply considers all pharmaceuticals (and companies and industry) to now be biopharmaceutical. With *biopharmaceutical* itself so ill-defined and with the products so complex, it is easy to see why discussions of what is or isn't a generic biopharmaceutical are difficult to undertake.

There are no widely accepted or recognized definitions for *biogenerics, biosimilars, follow-on proteins and biologics, biocomparables, off-patent* or *multisource biopharmaceuticals*, and other terms for generic biopharmaceuticals. As discussed below, depending on the paradigm or definition used, there are none, just a few, or even hundreds of generic biopharmaceuticals in the world market, and they are either a new phenomenon and class of products or have been around for several hundred years. For purposes of this article, I adopt the "broad biotech" view (pharmaceuticals manufactured by biotechnology methods). This includes not just recombinant proteins and monoclonal antibodies, but also vaccines, blood and plasma products, nonrecombinant proteins, and cultured cellular and tissue products. I use the term *biogeneric* in this article to broadly include all generic biopharmaceutical-related terms.

Caution! Biases and Preconceptions Prevail

With no available consensual or accepted terminology, terms and definitions used for biogenerics often depend on their context and the intentions of their users, with such intentions often based on individual or corporate biases and vested interests. This does not even begin to take into account that most of what has been written on this topic has used terms inconsistently and rarely defined them.

All current terms related to biogenerics have connotations and evoke preconceptions that may support, denigrate, or obfuscate views and discussions of the topic. Even the term *generic* (and the terms *similar, comparable, follow-on*, and so on) in the context of biopharmaceuticals can have vastly different meanings and connotations. For some, *(bio)generic* is objectionable, rightly or wrongly evoking images of (bio)generics as inherently inferior and linking them to generic drugs and the generic drug industry, which has battled its own negative public perception problems. *Follow-on* implies to some that biogenerics are newer and better (incorporate newer or current rather than decades-old "innovator" technology); and *innovator*, referring to the original developer and product, implies to some that biogenerics are less or not innovative and of lower quality.



Basic Views, Paradigms, Definitions

Biogeneric-related concepts and terms are based on relationships (e.g., similarity, comparability, equivalence), taxonomies, and classifications concerning biopharmaceutical finished products and/or their active agents. The basic presumption underlying (bio)generics is that (bio)pharmaceutical active agents and/or finished products can be considered to be similar or even identical (for all practical purposes), allowing extrapolations of activity, safety, and efficacy among agents or products based on shared characteristics or similarities. Such similarities are often based on the entities (products and active agents); associated activities, both biological and clinical; regulatory approvals, and/or commercial characteristics. If agents and/or products appear to be substantially similar or identical and act in a substantially similar or identical way, they are considered generic (relative to each other). In the extreme, similarities may enable designation of therapeutic equivalence/substitution in the filling of prescriptions. To date, there are no precedents for biopharmaceuticals in major Western countries approved with formal designation of equivalence/substitutability similar to that granted to many generic drugs.

Table 1 summarizes three basic, underlying paradigms or ways to view and define generic biopharmaceutical products and relationships.

Entity-Based (Including Product = Process): Biogeneric products and relationships are usually based on consideration of their chemical and/or biological source, identity (structure), activities, manufacturing process, and specifications — the aspects that largely define and differentiate distinct biopharmaceutical products. Entity-based similarities are the most important because only these enable science-based comparisons and predictions of product safety and efficacy based on knowledge of one or more similar products.

Table 1: Views, paradigms, and definitions of biogenerics and associated number of marketed products

View or Paradigm	Basis for Similarities	US and EU Markets	World Market
Entity-based	Product = Process; CMC; structure, composition	Some	Many
Regulatory-based	Approval as biogeneric (usually in addition to entity-based)	Few (or none)	Some
Market-based	Any perceived similarities (e.g., similarly named, competing for same indication)	Many	Many

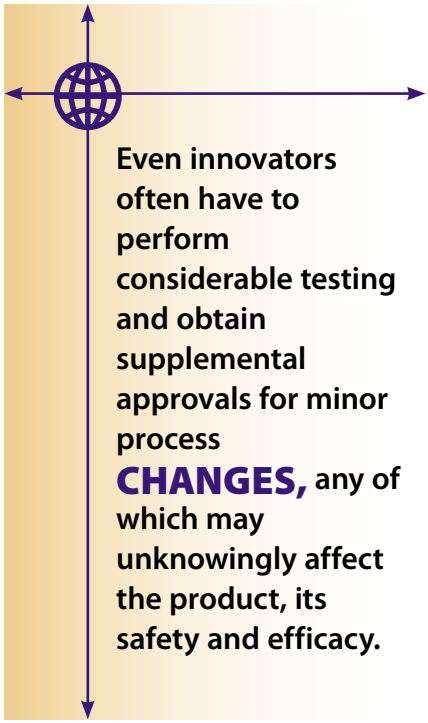
Many functional-, safety- and efficacy-related characteristics of an active agent, beyond its primary structure (e.g., sequence), depend on its manufacture. Examples include three-dimensional structure(s), presentation of epitopes (immunogenicity), attachment of variable polysaccharide side chains (glycosylation); intra- and interchain linkages, existence as multimers or noncovalent complexes of chains, and variable oxidation states.

To the extent that biopharmaceuticals can be defined and differentiated by their identity or source, methods of manufacture, and specifications, products and their active agent ingredients can be largely defined and differentiated on the basis of their manufacturing process. This is the classic "product, process, specifications" paradigm, often shortened to "process = product," promoted by many in the biopharmaceutical community, usually those associated with innovator companies (**3, 4**).

"Process = product" is much the same as the chemistry, manufacturing, and control (CMC) aspects of GMP manufacturing. Thus, a product from one manufacturer, made using consistent biological sources (e.g., genes, cell lines), a consistent set of processes, under a consistent set of conditions, using consistent in-process and other controls and assays, and with a consistent set of final specifications constitutes a unique biopharmaceutical product. In this context, regulatory approvals are secret pacts between a manufacturer and the regulatory agency concerning the associated ranges of allowable variations in each of these aspects.

Following that paradigm, because manufacturing processes are complex (and never fully publicly disclosed), biopharmaceuticals are considered impossible to exactly replicate by all but their licensed manufacturers (usually their innovators).

This has formed the basis for regulation of all but the simplest biopharmaceuticals and assertions that biogenerics (through abbreviated approvals) are inherently impossible or inappropriate. Even innovators often have to perform considerable testing and obtain supplemental approvals for minor process changes, any of which may unknowingly affect the product, its safety and efficacy. This requires biochemical, in-process, and sometimes even clinical testing, usually bioavailability comparison trials, to prove that different product iterations or versions can be considered comparable or identical.



It is far more difficult for a biogeneric company with its own manufacturing process, e.g., using a different genetic construct, cell line, or cell culture and purification process, to prove that its product is similar or comparable to the innovator product. This requires in-depth biochemical characterization of the final formulated biogeneric compared with the marketed final product, usually because only that will be available to the biogeneric developer. But comparisons of final products, with the active ingredient often very diluted and usually combined with stabilizers and other excipients, may be inadequate to prove sufficient similarity, and comparative bioequivalence trials may also be required. But even with these, regulators may not perceive sufficient similarity to support approvals based largely on comparisons, and some biogeneric developers may have to submit full(er) applications, including phase 3 like safety and efficacy trials (**5**).

The presumption is that only an approved manufacturer can replicate its own process (and the product), including proprietary source organisms (e.g., cell lines), hundreds of processing steps, in-process and other assays, reference standards, specialized equipment, and so on. Biopharmaceuticals are often so complex that even the same manufacturers often have problems making "comparable" (within acceptable ranges of variations) products from batch-to-batch.

The "process = product" paradigm is already understood by most people, particularly when analogies are made to wine, cheese, and other biotechnology products that are similarly variable based on their source or identity, processing, and specifications. Such products are often subject to regulation-defined generic standards of identity. Everyone appreciates that products such as cheddar cheese and red wine from different manufacturers are unique (e.g., in flavor or texture), yet they may be treated as the same (generic equivalents) and be assigned the same generic product name.

This paradigm provides a basis for defining and differentiating specific biopharmaceutical products (particularly, when combined with consideration of regulatory and commercial aspects) and recognizes each biopharmaceutical (active agent ingredient and finished product) as unique. However, the issues with biogenerics involve relationships and determining relevant similarities (such as comparability and equivalence), not uniqueness. The "process = product" paradigm does not rule out finding similarities among products and extrapolating properties from one agent or product to another. Can (and what) similarities allow knowledge of one product to be used to make judgments regarding another, particularly concerning safety and efficacy? Determining such relationships is more difficult and subjective than defining and differentiating products on the basis of their source or identity, manufacturing, and specifications.

Regulation-Based Views and Definitions

For many users and uses, the only biogeneric relationships and definitions that matter are those made by regulatory agencies, with many further restricting this to the United States and Europe. Regulation-based views and definitions of biogenerics start with entity-based (process = product) considerations, the underlying basis for regulation, and then add further regulation-based restrictions. Biogenerics are defined based on their approvals or plans for approvals as biogenerics (under an abbreviated testing and/or filing scheme), which may also involve designation of therapeutic equivalence. From a regulatory view, identifying biogenerics is very simple — just look at approvals and sponsors' plans for approvals.

Biogeneric filings and approvals, like those for generic drugs, generally involve a sponsor basing an application largely on knowledge (including published information and from comparative testing) of a previously approved (innovator) product. Besides biochemical studies, this often involves abbreviated clinical testing — notably bioequivalence and/or pharmacokinetic trials and other comparative clinical studies with the innovator product rather than traditional, large-scale, placebo-controlled phase 3 type clinical trials. The challenge is to prove sufficient similarities between the chemical composition, biological activity, and pharmacokinetic aspects of the products such that all relevant aspects concerning the biogeneric's safety and efficacy can be reliably predicted based on knowledge of the innovator product.

Cost and time savings in development are the main commercial advantages and reasons for biogenerics. In addition, designation of therapeutic equivalence can further reduce or eliminate marketing costs (e.g., pharmacies need only stock the generic, with negligible marketing, detailing, and advertising on the part of the marketing company). These aspects allow a biogeneric to, presumably, have a lower price than the reference product from the innovator company, which has invested much more in R&D and testing (including large safety and efficacy trials) and which has devoted considerable sums toward brand-name promotion.

Table 2: Some biopharmaceutical approvals as 505(b)(2) generic drugs

Entry	Name (Descriptive and Trade)	Companies
107	Calcitonin, rDNA (Forical)	Unigene, Upsher-Smith
152	Glucagon, rDNA (GlucaGen)	Novo Nordisk
171	Hyaluronidase, rDNA (Hylenex)	Halozyme Therapeutics; Baxter
527	Hyaluronidase, bovine (Amphadase)	Amphaster Pharmaceuticals
529	Hyaluronidase, ovine (Vitrase)	ISTA Pharmaceuticals
235	Somatropin, rDNA (Omnitrope)	Sandoz/Novartis

With the recent much-hyped section 505(b)(2) approval (**6**) of Omnitrope (recombinant *E. coli*–expressed somatropin) from Sandoz/Novartis as a generic drug (a follow-on protein version of Genotropin from Pfizer), FDA stated

> *Follow-on protein product*s generally refers to protein and peptide products that are intended to be sufficiently similar to a product already approved or licensed to permit the applicant to rely for approval on certain existing scientific knowledge about the safety and effectiveness of the approved protein product. Follow-on protein products may be produced through biotechnology or derived from natural sources. (**7**)

Unstated, this definition is restricted to those few simpler biopharmaceuticals regulated as drugs, including most peptide hormones (e.g., insulin, somatropin, and calcitonin). These are regulated as drugs under the Food, Drug, and Cosmetic Act, not as biologics regulated under the Public Heath Service Act of 1946 for which no generic approval mechanisms yet exist.

Unlike the United States, the European Union (EU) has adopted biogeneric regulations allowing approvals of "biosimilars" (primarily recombinant proteins and monoclonal antibodies) based on abbreviated, comparative testing. However, EU regulations never explicitly define "similar biotechnology medicinal products," commonly referred to as "biosimilars," other than as products approved or considered for approval under these regulations.

The FDA and other regulatory agencies have approved thousands of generics, nearly all of them drugs (chemical substances), based on comparison with and knowledge of earlier innovator products. But in terms of biopharmaceuticals, this has been restricted to smaller, simpler, or other active agents that in the United States, due to regulatory history, natural sources, and/or small-molecule nature, have already been regulated as drugs (rather than as biologics, involving much larger and more complex molecules, or even cells, tissues, and organisms). Omnitrope was approved based largely on comparisons with Genotropin from Pfizer derived from Hatch-Waxman Act–505(b)(2) generic drug regulations. The European Union approved Omnitrope and another recombinant *E. coli*–expressed somatropin (Valtropin) under its new biosimilar regulations based on comparisons with Genetropin and Humatrope (from Eli Lilly), respectively.

Table 2 shows recent examples of biogeneric-like FDA drug approvals. None of those has included formal recognition of equivalence and/or substitutability, a hallmark of most generic drug approvals, forcing each to be marketed as branded products — by trade name rather than by generic name. For people taking a restrictive Western (US, EU)- and regulatory-centric view, these are the only current biogeneric products.

Currently, no regulations exist in the United States for approval of biologics as generics based on comparative, abbreviated applications

(optionally, with designations of therapeutic equivalence). The FDA has signaled that it will leave this up to Congress to resolve, which is not expected until 2008 (**8**). A bill proposing generic biologics regulations was recently introduced in Congress (**9**), and other proposals are likely. The FDA has avoided issuing guidelines for even the simplest biopharmaceuticals regulated as drugs (follow-on proteins). Only after years of delay did the agency grant approval of Omnitrope, and only after being forced to act after having lost a lawsuit brought by Sandoz in federal court.

As will be discussed in Part 2 of this article, even though not approved as biogenerics, many current US- and EU biopharmaceuticals, including blockbusters (>$1 billion/year sales) are very similar — such that they would be labeled as biogenerics if currently in development — and a number of biopharmaceuticals are commonly considered therapeutically equivalent and/or substitutable.

In light of this topic, the European Union is much further ahead than the United States, having developed a new class of approvals for "similar biotechnology medicinal products" (biosimilars); issued related guidelines for a few classes of biopharmaceuticals (e.g., insulins and somatropins); and approved two "biosimilar" somatropin products. However, as in the United States, the European Union has yet to issue guidance concerning the great majority of more complex biopharmaceuticals, and it has avoided issues of therapeutic equivalence and official nomenclature to be used with biosimilars (whether to adopt unique or generic names for the products).

Commerce and/or Market-Based

For many users and uses, the only biogeneric relationships and definitions that matter are those that are based on commerce, markets, and related perceptions and preconceptions, often never defined and with little or no consideration of entity- or regulatory-based relationships. Thus, *biogeneric*, *follow-on protein*, and related terms are commonly applied to just about any biopharmaceuticals that appear competitive and similar (e.g., share some characteristics of structure or activity, commonalities of active agent name, compete for the same indication/market, or are similar in some other aspects).

Broad commerce-based views of biogenerics often include next and other later generation (follow-on) versions and variations of products, irrespective of how (dis)similar they actually are as entities. This can include products so dissimilar as to rule out bioequivalence trials, abbreviated applications, and approvals as biogenerics. For example, insulin products delivered by inhalation or other novel routes are commonly referred to as biogenerics (relative to injectable insulin), but how could they ever be approved based on bioequivalence trials? A newer term, *super biogenerics*, is used by some to refer to such follow-on biogenerics involving radical modifications — usually new and improved delivery systems.

Biogeneric Relationships Are All Relative

Generic drugs contain what are considered (approved) to be the same active agent, with such products often meeting pharmacopeial or other standards of identity (e.g., minimums for purity and potency). Such drugs (not biopharmaceuticals) are presumed to be and treated as substantially similar or identical for many or all practical purposes, with comparable dosage forms often considered therapeutically equivalent and substitutable, and with each generic drug assigned a common nonproprietary (generic) name based on its active agent. However, the simplicity and certainty that generic drugs (containing chemical, not biological, active agents) are comparable or identical for all practical purposes just does not apply to biopharmaceuticals.

Even seemingly rigorous entity-based views of biogenerics can variably include or exclude related products. For example, it might be proper to consider as biogeneric all new products containing injectable high-purity recombinant regular insulin with the same primary amino acid sequence, clinical activity (and so on), and a similar method of manufacture (e.g., *E. coli* expression) — similar to Humulin from Lilly, originally approved by FDA in 1982. But excluded from those would be similar products with different manufacturing processes: e.g., using different expression systems, having modified primary structures (muteins), undergoing molecular modifications (such as pegylation), using different formulations (such as particles for inhalation), or having different impurity or other analytical profiles.

Other people might take a broader entity-based view to consider all high-purity injectable regular insulins to be biogeneric or even the same (insulin is insulin), whether the insulin has been isolated from human pancreas, semisynthetically made from animal-derived insulin, or expressed by bacteria, yeast, plant, or some other recombinant expression system. The fact that many insulins are not bioequivalent and have not received US or other major market approvals as biogenerics does not figure into many peoples' views and definitions.

Factors Affecting Biogenerics: Temporal relationships are a common aspect of many views and definitions of biogenerics. Usually and, particularly, in regulatory contexts, a later biogeneric product is compared to an earlier, original product often termed the *innovator* (or reference) product, based on the presumption that its development involved original R&D and innovation and included full, not abbreviated, clinical and other testing (phase 3 type safety and efficacy trials). Related to temporal aspects, patents and other government grants of marketing exclusivity (such as orphan designation) figure prominently in the commercialization of biogenerics. As with generic drugs, biogenerics cannot be commercialized until relevant patents expire, and those are usually held by innovator companies. Because of variability in the issuance of patents and time in R&D and testing, marketing of most biogenerics will usually follow 10–20 years after launch of their innovator products.

Therapeutic equivalence (substitution and/or interchangeability) is another concept commonly applied to biogenerics, much the same as with generic drugs. In the extreme, this involves innovator and generic products being ruled sufficiently identical in terms of their active agents and bioequivalence and pharmacodynamics (from comparative trials) such that the generic may be substituted for the innovator in the writing and filling of prescriptions. This is the situation with most generic drugs, and the majority of drug prescriptions in the United States are now filled with generics. Although there are precedents for the FDA (and other regulators) approving biopharmaceuticals as generics based on abbreviated filings, these approvals have, to date, been restricted to the few relatively simple biopharmaceuticals regulated as drugs as described above.

FDA biogeneric-like drug approvals have so far not included official designation of therapeutic equivalence. However, in practice, a large number of biopharmaceuticals, including many complex biologics, are often treated as therapeutically equivalent and interchangeable. For example, many blood-derived products (such as albumin and red blood cells) from hundreds of licensed manufacturers are considered to be therapeutically equivalent. And various vaccines (e.g., influenza, hepatitis B, and DTaP vaccines) are considered sufficiently similar and bioequivalent that their approved indications recognize that a series of inoculations started with one product may be finished using another. Major pharmacopoeia and medical references commonly ignore making distinctions between such similar products and consider them as equivalent (in the same generic monograph). So in many respects, the medical community already has considerable experience with therapeutic equivalence and substitution with complex biologics.

Geographic considerations can profoundly affect views and definitions of biogenerics. For many users and uses, the only products that matter are those in the United States, European Union, and perhaps a few other major pharmaceutical markets (highly developed countries). However, untold hundreds of what are clearly biogenerics are already manufactured and marketed in lesser-developed countries, with these often being "knockoffs" considered to be exact copies approved for use in place of innovator products.

In fact, the majority of biopharmaceuticals in the world market may be considered generics. For most successful biopharmaceuticals developed and marketed in the United States and European Union, there are multiple copies in lesser-developed countries (where lack of granted patents and/or their enforcement allows). This includes copies of many newer products (e.g., recombinant proteins and monoclonal antibodies) and an even larger number of older, off-patent products (e.g., many vaccines and blood products). In the People's Republic of China alone, there are 17 or more manufacturers of recombinant granulocyle-colony stimulating factor (G-CSF; copies of Leukine from Amgen) and many other biopharmaceuticals. And more than 180 insulin products are reported to be in the world market.

How old are biogenerics? They are as old as whatever you consider to be biopharmaceuticals. For example, various live *vaccinia* virus–based vaccines for smallpox prophylaxis have been available and considered therapeutically equivalent for more than 200 years. On the other hand, biogenerics may be considered a recent phenomenon, with just a few on the market, if you take a rigorous regulatory view.

The "Proposed Biogenerics and Related Terms" box provides a short glossary of some common biogeneric and other terms (purely, from my perspective). I suggest some of those terms are suitable for adoption, whereas many are best avoided or their use limited to their specific, usually regulatory, contexts.

Diversity of Views Must Be Accommodated

There are obviously a wide variety of views, paradigms, and/or definitions for what is or isn't a biogeneric. For example, some people consider all later variations and versions of a recombinant protein to be biogenerics, despite variations in primary structure (amino acid sequence), glycosylation, multimers (linking of chains), major molecular modifications (such as pegylation), formulations (e.g., adjuvants, buffers, use of albumin or other stabilizers), packaging or delivery systems (e.g., liposomes, controlled release, transcutaneous), and so on. Some even naively presume these diverse products to be approvable with only abbreviated, comparative testing based on the large body of knowledge concerning the innovator product or its active agent. Some with a Western bias ignore or exclude the hundreds of biogenerics manufactured in lesser-developed countries. Some only consider recombinant proteins and monoclonal antibodies, ignoring or excluding most vaccines, blood, and other products.

On the other hand, most people taking a rigorous entity-based (or derivative regulatory) view would consider those to be clearly distinct, dissimilar products that cannot be compared with each other (particularly for regulatory approvals), negating any possibility of their being biogenerics. Others would simply say that if product names sound or seemingly involve similar active agents and biological and clinical activity, they are obviously biogenerics. Some consider only products involving improvements or technological advances to be later-generation or follow-on biogenerics — not including innovator products as biogenerics — whereas others consider all similar products to be biogenerics, including the innovator products (once a biogeneric is in development or approved).

There are obviously a wide variety of already established, divergent and often conflicting views and definitions of what is or isn't biogeneric. It is easy to dismiss some of these are simplistic, deficient, erroneous, or irrelevant. But these views and definitions are useful and represent reality for many of their users. Changing their preconceptions

to more consensual and/or rigorous views and definitions will be difficult or impossible.

The existence of so much diversity and the lack of consensus regarding basic terminology and definitions will sooner or later require development of a variety of new, more refined, and specific biogeneric-related paradigms and terms. They are likely to include different terms and definitions for scientific, regulatory, medical, and popular use, further complicating the situation. For example, I can foresee the need for multiple types or classes and degrees of entity-based relationships and similarities, for different types or classes and extents of therapeutic substitution or interchangeability, and terms to differentiate biogenerics developed as knockoffs (reverse-engineered copied of usually decades-old innovator products), including many in lesser-developed countries, from those (re)designed to be similar (for regulatory purposes) and/or manufactured using modern technologies. As can be seen in the glossary and to be further discussed in Part 2, regulatory terminology and definitions can be relied on to multiply and become more complex, convoluted, and unsuited for use other than within a regulatory context.

In the meantime, in the current chaotic situation, those writing and speaking about biogenerics should define the terms used or at least make them clear in context and be aware that those terms may well be interpreted much differently by others.

Looking beyond the current chaos and anarchy regarding biogenerics (e.g., do we call these products *biogeneric*, *follow-on*, *biosimilar*, or what?), biogenerics will involve many other terminological, nomenclature, and information-based issues that are likely to be even more complex and controversial. Most discussions of biogenerics to date have ignored or avoided posing and answering many questions that must be answered if we are even to rigorously define, name, track, and regulate biogenerics. Such questions include

- What information is needed to define specific biogenerics or biopharmaceuticals
- What common information or properties (similarities) make products similar, comparable, or identical,

Proposed Biogenerics and Related Terms

biocomparable: a common synonym for *biogeneric*; best avoided due to comparability guidelines that apply to manufacturing changes (see *comparability* below)

biogeneric: refers to any biopharmaceutical considered generic, based on any criteria (which should be stated or clear in context)

biologic(s): a type of FDA approval for biopharmaceuticals and other associated products (best used only to refer to products approved or on track for approval by this mechanism); generally includes all but the simplest biopharmaceuticals regulated as drugs by the FDA; the official definition is complex, unwieldy, developed decades ago, and based on analogies to terms and concepts at the time (e.g., viruses analogous to toxins, vaccines to serums, etc.)

biological product: an official synonym for *biologic* and best reserved for this use

biopharmaceutical: a pharmaceutical product or active agent that is biological in nature and manufactured using living organisms (biotechnology); note — this does not include small molecule or other drugs that are inherently chemical, not biological, in their nature and manufacture

biosimilar: short name (never actually officially defined) for "similar biotechnology medicinal product," a new type of generic biopharmaceutical approval in the European Union and associated products; best used to refer only to products approved or on track by this mechanism

comparability: refers to similarities, regulatory acceptability, and supplemental approvals of products incorporating a change in the manufacturing process by the product's current manufacturer or contractor (judgments of similarities between the same products, presumably, from the same manufacturer, incorporating a change in the manufacturing process; best used only in this context, not to refer to biogenerics

drugs: chemical, not biological pharmaceutical agents, and products manufactured using chemical, not biological methods, and including the vast majority of pharmaceuticals

follow-on: a synonym for *biogeneric*; often used to describe a later biopharmaceutical and often involving a more technologically advanced version of an innovator product; see also *later generation*; best avoided because the FDA has adopted the term *follow-on protein*

follow-on protein (FOP): a biopharmaceutical approved or on track for approval by the FDA as a generic drug, usually under section 505(b)(2), generally restricted to relatively simple proteins, including those with prior versions approved as natural products (best reserved for this use)

follow-on biologic (FOB): a biopharmaceutical approved or on track for approval by the FDA as a generic biopharmaceutical, a regulatory track that does not yet exist (best reserved for this use)

innovator: refers to original products, usually the first product to receive approval, and associated companies; such products are presumed to have involved original and extensive research and development (R&D) and full (not abbreviated) phase 3 type safety and efficacy testing

later generation: a biopharmaceutical similar to a prior product; it often involves technological advances or other modifications such that it may not actually be similar to prior innovator product(s); term recommended for adoption in place of *follow-on*

pharmaceutical: any medical product, particularly those products with therapeutic or in vivo uses; two major subsets are drugs and biopharmaceuticals

therapeutic biological product: a term adopted by the FDA for those simpler biologics regulated by the Center for Drug Evaluation and Research (CDER), not by the Center for Biologics Evaluation and Research (CBER, which regulates more complex biologics)

including suitable for therapeutic substitution?

• What differences (dissimilarities) between similar products make them unique or distinct for different purposes?

• What changes (e.g., in manufacture of formulation) require defining, naming, and tracking a product as a new, unique, or distinct (different) product, and is this a biogeneric version or *what* of the prior product iteration?

• What official names should be used for products approved as biogenerics — do we use the same active agent-based nonproprietary names for each, as is done with generic drugs, or must each product have its own name?

• What information resources are needed, and who will coordinate and disseminate information concerning biogeneric paradigms, terminology, and specific products?

These and other largely information-based issues, along with politics and regulations, will be discussed in Part 2.

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