

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

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Introduction - Preface

My perspective is primarily that of a pharmaceutical information specialist, an expert in competitive intelligence, technology/market assessment, etc., and author of a major biopharmaceutical reference

Most discussions of FOBs/biosimilars/biogenerics are way too simplistic (dichotomies) and ignore the complexity, diversity and history of existing biopharmaceutical products

- 1) Biogenerics are not new - most biopharmaceuticals are biogeneric in some, many or even all respects
- 2) CBER/FDA generic biologic-related precedents are many, but thoroughly inconsistent
- 3) basic underlying paradigms/definitions, e.g., 'biotech' and 'biopharmaceutical,' vary greatly
- 4) Much of the establishment favors the view that real biotech and biopharmaceutical products do not exist
- 5) basic terminology is undefined, chaotic
- 4) product nomenclature is extremely chaotic and will be very contentious and problematic
- 5) Most discussion of legislation is way too simplistic
 - a) near-term (fixated on a few recombinant proteins)
 - b) need to handle all biologics
 - c) illogical patent and exclusivity provisions
 - d) must define products - need reference points for comparison-based approvals and exclusivity

Four Basic Definitions/Paradigms/Views of What is Biopharmaceutical (and Biotech)

	Biopharmaceutical	Biotechnology	Pharmaceuticals	Drugs	Users
<i>[Objective - product-centric; science/technology-based industry]</i>					
Broad Biotechnology	All biotechnology-based pharmaceuticals	use of living organisms, bioprocessing	All medicinal products (all pharmaceuticals)	Chemical/non-biological source pharmaceuticals	Core biopharma industry, science (especially in U.S.)
New Biotechnology	Only new biotech (genetic engineered) pharmaceuticals (recombinant protein and Mab-based products)	Only "new" biotech (genetic engineering)	All medicinal products (all pharmaceuticals)	Chemical/non-biological source pharmaceuticals	Some in biopharma industry, science (especially in Europe); EMEA/EU
<i>[Subjective - image- and business model-centric; ignore consideration of products and technologies; no chem. vs. biol. dichotomy; often include non-industry research]</i>					
Biotechnology Business	All pharmaceuticals from biotech-like (small, R&D intensive) life sci. companies (plus high-tech pharm. including from Big Pharma)	All products from biotech-like cos. or life sci.-related and can be hyped as being high-tech; includes life sci. res.	All medicinal products (all pharmaceuticals)	Chemical/non-biological source pharmaceuticals	Business/financial communities; popular press; BIO
Pharmaceutical Business	All medicinal products (all pharmaceuticals are biopharmaceuticals); often adjective only	All products from pharmaceutical and biotech cos.; includes life sci. res.	Biopharmaceutical used as synonym for pharmaceutical (no subsets)	Term dropped from usage (now all biopharmaceuticals)	Big Pharma supporters; PhRMA; popular press

See my 2-part series, "What is a Biopharmaceutical?..." published in *BioProcess International*, available at www.biopharmacoepia.com

**PRODUCTS INCLUDED IN DIFFERENT DEFINITIONS OF
BIOPHARMACEUTICAL**

	BROAD BIOTECH	NEW BIOTECH	BIOTECH BUSINESS	PHARMA BUSINESS
PROTEINS, rDNA	X	X	X	X
MABS, rDNA	X	X	X	X
PROTEINS, NON-rDNA	X		X	X
MABS, NON-DNA¹	X		X	X
VACCINES	X		X	X
ENZYMES	X		X	X
TOXINS	X		X	X
CELLS/TISSUES	X		X	X
BLOOD PRODUCTS	X		X	X
SMALL DRUGS²			X	X
ALL DRUGS				X

1: Monoclonal antibodies, hybridoma cultured (in vitro or ascites methods)

2: Includes small and other nonbiological molecules

Remarks

- a) **Broad Biotech (pharmaceuticals manufactured using biotechnology)**
 - 1) best, recommended definition; parallels biologics vs. drug regulation
 - 1) predominant in U.S. industry and science
 - 2) includes products 100s of years old, e.g., smallpox vaccines
- b) **New Biotech (genetically engineered products subset of Broad Biotech)**
 - 1) what is "new," i.e., rDNA and Mabs, is now old (1970s technologies); other products in recent decades are more high-tech than these
 - 2) OK, but best avoided - unwieldy, arbitrarily leaves out many products
- c) **Biotech Business (if it's pharmaceutical and involves a biotech-like co. or can be hyped as high tech, it's obviously biopharmaceutical, with Big Pharma and generics optionally included/excluded)**
 - 1) predominant in business and financial communities, press, BIO, etc.
 - 2) used by BIO, which when asked, refuses to define 'biotechnology'
 - 3) major problems: totally subjective; small molecule drugs included
- d) **Pharmaceutical Business (everything pharmaceutical is now biopharmaceutical -- sounds much better than drug, pharmaceutical, etc.)**
 - 1) biotech. and biopharma industry are part of and serve Big Pharma
 - 2) used by PhRMA, including in core industry studies, annual reports
 - 3) "myth of convergence" - biotechnology has merged into the pharm. industry; purely PR claims
 - 4) no distinctions/subsets (e.g., biopharmaceuticals); adj. only
 - 5) major problems: totally subjective; small molecule drugs included
- e) **Trade associations (BIO; PhRMA) follow their PR-driven vested interests; Biopharmaceutical industry (\$100 billion) lacks its own trade association!**

What is 'biopharmaceutical?' and what is 'drug?' [my views]

pharmaceutical - medicinal products with therapeutic or prophylactic indications, and diagnostics administered systemically or in vivo;
two subsets - ***biopharmaceutical*** and ***drug***

biopharmaceutical - involves pharmaceutical products inherently biological in nature manufactured using biotechnology (live organisms; usually some obvious bioprocessing/biotransformation) [Broad Biotech definition]

drug - involves pharmaceutical products inherently chemical in nature manufactured using chemical methods

Correlaries:

- a) **Small molecule and other drugs are not biopharmaceuticals?**
[If one can draw structure without resorting to symbols for subunits, it's almost certainly a drug]
- b) **Natural (biological source) products derived by chemical methods are drugs** (e.g., heparin, collagen, hyaluronic acid, taxol)
- c) **Manufacture must retain biological nature of product**
(e.g., avoid extremes of heat, pH, solvents, etc.)
- d) **Live organisms includes animals and humans (e.g., blood products)**

Biopharmaceutical revenue will be \geq \$100 billion in 2007!

2006 Worldwide Biopharmaceutical Revenue by Product Class (\$ millions)

Recombinant proteins (rDNA)	65,300*
Monoclonal antibodies, rDNA	19,500
Insulin Products (nearly all rDNA)	8,300
Monoclonal antibodies, non-rDNA	300*
Vaccines	9,500
Vaccines, non-rDNA	8,000*
Enzymes, non-rDNA	500*
Toxins (Botulinum)	1,050*
Cultured cells/tissues	100*
Blood Products (human and animal)	15,000*
Plasma-derived proteins	9,300
Cellular components	5,700
Borderline/grey area biopharmaceuticals	800*
Misc. foreign biogenerics, knock-offs, etc.	2,000*
Total	~\$94,300

*Indicates number used in total

What is a generic biopharmaceutical, biogeneric, biosimilar, biocomparable, follow-on biologic or protein, subsequent entry biologic...?

All current terms have connotations and evoke preconceptions that may support, denigrate, or obfuscate views and aspects of the topic.

For convenience, I use biogenerics to broadly encompass these terms/concepts.

All terms have problems!

biogeneric - linked to generic drugs (negative connotations) and presumptions of therapeutic equivalence

follow-on biologic - implies to some that biogenerics are newer and better (vs. decades-old innovator products)

biosimilar - already has specific meaning in context of EU regulations

biocomparable - linked too closely to comparability, with its own regulatory-based definition

subsequent entry biologic - unwieldy

copy-cat biotech drug - too derogatory

Three basic views, paradigms or ways of defining biogenerics [How to define a unique/distinct biopharmaceutical product]

- 1) **Entity-based** - look at the active agent and finished product; can't avoid process = product paradigm, with manufacturing methods determining product characteristics
 - a) from this perspective, most biopharmaceuticals in commerce are biogenerics (similar and even interchangeable), e.g., most vaccines, blood/plasma products and even some rDNA proteins
 - b) there already are biogeneric versions of most every successful innovator product, particularly in lesser-developed countries
- 2) **Regulatory-based** - look at approvals (FDA, EU, etc.) with each full (non-supplemental) approval being a unique, distinct product
 - a) from this perspective, a few biogenerics in U.S. market, e.g., 505(b)(2) approvals of recombinant and cultured proteins
 - b) many more in foreign markets, with many countries approvals and markets being inherently biogeneric
- 3) **Market-based** - look at product in the marketplace; subjectively define unique, distinct products, e.g., biogenerics defined based on having similar names, same/similar indications, belonging to same product class, having same/similar biological activity, or whatever

Example: Are Xyntha and ReFacto (both from Wyeth) the same, similar or totally different products?

ReFracto - approved in 2000 with orphan designation; B-domain deleted CHO-expressed rDNA Factor VIII; approved based on bioequivalence (n = ~100) with full-length (human equiv.) recombinant Factor VIII [is ReFracto a FOB/biosimilar?]

Xyntha is replacing ReFracto in the marketplace, with products used the same.

Xyntha - submitted sBLA, full BLA granted in Feb. 2008; exact same Factor VIII (FDA); also approved based on bioequivalence with human analog rDNA Factor VIII; manufacturing process has major changes (updated) - eliminated use of animal products in cell culture, purification uses immobilized custom peptide ligands (vs. immobilized Mabs), animal products (albumin) removed from formulation

Entity-based view - unclear

Same, from active agent perspective

Unique/different, considering product and its manufacture

Regulatory view - absolutely different (full BLAs)

Market-based view

Same, from most sales and use perspectives (updated, rebranded new version)

Unique, based on manufacturer's claims (new name, better)

What is the relationship? What do we call these products?

Is Xyntha new? -- Should it get orphan and/or proposed full exclusivity?

Is Xyntha a new biogeneric version, variation or (what) of ReFracto?

What new and unique names should be used for Xyntha, and what old ones, e.g., generic and active agent names, should be carried over from ReFacto?

Example:

Are Epogen and Procrit the same/identical or different products?

Amgen manufactures bulk active agent (recombinant erythropoietin, EPO) used in both finished products (which have the same/similar formulation).

Products are same from an active entity-based, process = product view.

Both Epogen and Procrit are covered by the same approvals, granted to Amgen. Each product is actually approved for all approved indications (with licensing splitting up which company markets for which indications).

Products are same from a regulatory-based view.

Products are marketed as distinct, unique products. Epogen is marketed by Amgen for kidney-related indications. Procrit is marketed by Ortho/J&J for other (cancer) indications. Both are blockbusters (>\$1 billion in sales/year in U.S.).

Products are totally different from a market-based view.

What do we call these types of products?

If the same products, is Procrit an authorized, simply relabeled, generic of Epogen (which came first, from the innovator)?

If different products, are Epogen and Procrit examples of fully substitutable, interchangeable, identical, true, etc. biogenerics?

Some biosimilarity problems and fallacies:

- 1) Biologics are black boxes - only bits and pieces about source/identity, manufacture, specifications (process=product aspect) in the public domain**
 - a) neither manufacturers/marketers nor FDA disclose information**
 - b) products are essentially impossible to replicate (which is OK)**
 - c) no substantive basis for comparisons by anybody**
 - d) No substantive basis for public oversight or trust!**
- 2) Biogenerics are new (false). Most biologics worldwide are biogenerics. Interchangeability is common, e.g., vaccines and blood/plasma products.**
- 3) Biogenerics will cost less than the products they emulate (maybe). Innovators have 1-2 decades experience manufacturing; world class, unbeatable economies-of-scale; and many will gladly undercut prices of their products to maintain market share (which is often more important than sales, with many companies bundling products for indications, often including their own next-generation products)**
- 4) Even if we agree on rigorous entity-based definitions of unique (and biogeneric) products, there is no agreement on how to apply this. E.g., is a product unique/distinct or similar/comparable, if its active agent has the same primary and even tertiary structure, but is manufactured differently, e.g., using a different expression system/host cell line? [Canadian proposed regs rule out such "nonanalogous" manufacture].**

Questions/issues everyone ignores, but that need to be resolved:

- Products need to be defined, both for regulatory comparisons and the granting of exclusivity
- FDA biologics approvals have no relationship to whether products are the same, similar, or new/different. BLAs do not necessarily define products, with biologics (same product) receiving multiple BLAs, e.g., for a new indication; and major changes in products often result in sBLAs (no consistency!).
So, using BLAs, e.g., granting exclusivity based on BLAs, will fail!
- Should manufacturers (or FDA) issue substantive (but nonenabling) summary descriptions of their products identity/source, manufacture and specs (process = product aspects) upon approval? If not, how will anyone be able to compare products. Should this be mandated in legislation? Or, is transparency, public information and public confidence something to be ignored?
- Similarity is relatively simple (subjective/relative judgements), but
What differences (dissimilarities) between similar products make them unique or distinct for various, different purposes (approvals, naming, marketing)?
- What changes (e.g., in manufacture) require defining and naming a product as a new, unique, or distinct (different) product? Is this new product a biogeneric version or what, relative to the prior product?

So, what is a unique biopharmaceutical? And, what changes or differences result in a product becoming a new, distinct product?

In the real world, when considering products, one must consider all aspects -- entity-, regulatory- and market-based. Biopharmaceuticals, like other commercial products, cannot be defined from a single perspective!

At the most basic level, a unique biopharmaceutical is a specific finished product, containing a specific active agent, with its own approval, unique name(s), and manufactured/marketed by a single company.

But agents, products, manufacturing, approvals, companies, and marketing change and evolve; and regulatory approvals often have no relationship as to whether products are the same, similar, or new/different.

Any changes define a new product (from someone's perspective).

Even changes in a product not defining a new product must be public information and tracked (need to know more about sBLAs)

Biopharmaceutical and Biogeneric Nomenclature

Nomenclature, particularly official names (used for marketing and prescriptions) will be contentious, probably more so than regulations, since names directly affect product marketing, positioning, etc.

Nomenclature goals - unique, unambiguous and usable names

These goals are impossible with biopharmaceuticals! Nomenclature involves compromises. And what about generic names, indicative of commonalities?

Unique names - facilitate safety, post-marketing surveillance

Generic names - facilitate substitution (cost-savings), confound surveillance

Major nomenclature types:

- a) **systematic** (chemical) - IUPAC, CAS - based on active agent, not product
largely useless - designed for indexing chemical substances in the literature
with biopharmaceuticals, use the same (generic) names; names too long
- b) **compendial (official product names)** - arbitrary; inconsistent; too long
- b) **proprietary** - trade names (trademarks); an option for unique names
largely useless - change with whim of marketer; common use would make
everything into advertising (companies would game the system)
- c) **nonproprietary** (often called generic, based on active agent) - USAN, INN
largely useless - systems designed for drugs, particularly generic drugs
assigned by WHO, which already has stated will not change system
- d) **trivial** - common names; nonsystematic; no authority; short; familiar
- e) **proper** - CBER/FDA generic names for biologics; inconsistent, no rules

Product names will likely be more controversial than regulations for biogeneric approvals -- affects or even controls marketing

Biopharmaceutical and biogenerics, like everything else, need names. But what type of names, how many names should there be, should names reflect characteristics of the product or be totally arbitrary?

Adequate description of a biopharmaceutical involves lengthy text — useless as a name or identifier.

(Interferon 1000-2a, a trivial name for a mythical product, as an example

If unique names are to be the official ones (for marketing and prescribing);

- a) Should this be trademark (Millenniferon)?
- b) totally arbitrary and meaningless to make unique (Zixamarpostuff)?
- c) Should it be partially descriptive, e.g., of class or function (Blablablaferon)
- d) Should it be the generic, e.g., USAN name, with identifiers appended
(interferon-1000-2alfa/xyz company or interferon 1000-2alfa/Millenniferon)

If (bio)generic names are to be used

- a) Should name be based on similarity of structure, biological activity, indications, or what (cancerkineferon-delta)?

What if products are substitutable or interchangeable?

- a) Do similar products use the same active agent-based nonproprietary name (like generic drugs)?
- b) Will the innovator be forced to drop use of his trade names and only use the biogeneric name?

Based on chemical/pharmaceutical information science/practices and common sense.

- 1) Many types of names are needed for biopharmaceuticals, including both unique, (bio)generic and descriptive names.
Officially designating just one name per product will fail.
- 2) In real-world, many different users have their own needs and views (FDA and other countries, marketers, pharmaceutical references, formularies, insurers, physicians, pharmacists, general public).
- 3) Most everyone will revert or prefer to use biogeneric or descriptive names, irrespective of approvals (no reason to change)
- 4) Someone needs to track products, names and define what each name actually refers. None of the usual organizations (FDA, WHO, USP, ASHP, ASTM, CAS/ACS, IUPAC, IUB, BIO, PhRMA, etc.) want to get involved, and most can't.

The biopharmaceutical industry is maturing and must grow up!

Biogenerics, like generic drugs, are just part of the business, and must be rationally integrated, with appropriate information and information resources available for many user communities (medical, pharmacy, formulary, insurance companies, general public, etc.), each of which has unique information needs.

New paradigms, terminology, taxonomy and nomenclature systems are needed for biopharmaceuticals, particularly ones that include biogenerics.

Both unique/unambiguous and (bio)generic names are needed! The need for both for diverse uses and users is obvious. E.g., insurers will ignore pronouncements about non-interchangeability/non-substitution and switch people to the cheapest similar product. So, should there be a system up-front to handle this? And, what about every other country, most of which will adopt (bio)generic/INN names?

What organization will track products (approvals) and coordinate names associated with each product? Who will propose/assign unique and generic names?

What is needed?

- a) Industry should self-regulate, rather than have Congress and FDA making a mess of things. Example - *CTFA Dictionary* of cosmetic ingredient names, put together by CTFA, and recognized by FDA for labeling.
- b) *U.S. BIOPHARMACOPEIA Registry of Biopharmaceutical Products* - proposed by this author; see www.biopharmacopeia.com

Exclusivity

What is to be rewarded and the criteria to be used are ill-defined! Do we consider:

- 1) innovation, novelty, classically determined by patents;
Do we extend patents? If so, which one(s)?
- 2) new approvals - grant full (e.g., 12 years) exclusivity to all full BLAs (ignore patents)?

Do we leave this up to FDA or specify criteria in legislation? Is this to be automatic/predictable, e.g., based on approvals or patents, or will FDA make judgements?

Many presumptions/justifications are unconfirmed

- 1) no studies of actual patent-based exclusivity for current biopharmaceuticals - all based on drugs
- 2) Why no generic drug-life calculations, e.g., extending patents based on time in trials and at FDA?

Patents are a mine field

- 1) Biopharmaceuticals almost always protected by a large number of patents - composition-of-matter, use/indications, process, formulation, administration, etc.
If patents are to be extended, do we consider all of these?
- 2) Must innovator disclose patents it intends to assert?
But what about exclusively licensed technologies?

Further information (authored by this speaker):

1) *Biopharmaceuticals in the U.S. and European Markets*, the only biopharmaceuticals reference book (and database); visit www.biopharma.com, and check out the free public database.

1) www.biopharmacopeia.com - includes links to articles listed here, along with more information about nomenclature issues and the *U.S. BIOPHARMACOPEIA Registry of Biopharmaceutical Products*.

2) www.biosimilars.com (also www.followonbiologics.com) - miscellaneous news and commentary from this author

3) "What Is a Generic Biopharmaceutical? Biogeneric? Follow-On Protein? Bio-similar? Follow-On Biologic?... Part 1: Introduction and Basic Paradigms," and "Part 2: Information, Nomenclature, Perceptions, and the Market" - 2-part series in *BioProcess International*, March and May 2007.

4) "What is a Biopharmaceutical? Part 1: (Bio)Technology-Based Definitions," and "Part 2: Company and Industry Definitions - 2-part series in *BioExecutive*, March and May 2005.