What is a *Biopharmaceutical*?

Part 1: (Bio)Technology-Based Definitions

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Biopharma(ceutical) and related terms are so misused and abused that they are losing their meaning. If the industry does not use biopharmaceutical terminology consistently, it may well lose its identity.

The terms *biotechnology* and *biopharmaceutical* describe many complex and important products, technologies, R&D, and industries. Most people, particularly those within the industry, presume that a *biopharmaceutical* involves biotechnology, but this connection is often ignored or rejected. That causes problems in communication and public perception.

This article examines *biopharmaceutical* terminology and ramifications for the industry. There are four major views of *biopharmaceutical*—the intersection of *biotechnology* and *pharmaceuticals*—based on different views of *biotechnology*. (See Models of Biopharmaceutical Terminology.)

Part I examines why terminology is important and discusses technically grounded definitions based on underlying (bio)technologies and historical and regulatory definitions, including the *broad biotechnology* view of biopharmaceutical as pharmaceuticals manufactured using biotechnology and the *new biotechnology* view restricted to genetic engineering.

Part 2 will look critically at how terms are being redefined by industry sectors and the press (trade and popular) based on business models (company type). In that view, *biopharmaceutical* is no longer linked to biotechnology, and small molecule drugs and companies with no biotechnology involvement are included. That discussion will include the *biotechnology business* view, which considers *biotechnology* to include any small, R&D-intensive life-science company, and the newer *pharmaceutical business* view that simply redefines *pharmaceutical*, including all drugs and big pharma, as *biotechnology* and *biopharmaceutical*.

WORDS MATTER

Terminology (and related taxonomy and classification) is of utmost importance to any industry. The words we use and the concepts they convey provide the framework for communication, understanding, and perceptions at both individual and societal levels. Definitions of *biotechnology* and *biopharmaceutical*, particularly what is included/excluded, define entire industries at the most basic level. Increasingly, *biopharmaceutical* is being (mis)used to encompass all pharmaceutical R&D or the entire pharmaceutical industry—both drugs and biopharmaceuticals.

Traditional, mainstream sources for resolution of terminology—dictionaries—are of little help. Nearly all of the more comprehensive and authoritative English language and even sci-tech and medical dictionaries lack any entry for *biopharmaceutical* despite decades of widespread use. In a Google search, a good indicator of general usage, *biopharmaceutical* retrieves about 442,000 entries.

Misuse of terminology, particularly at the level of what is or isn't considered a biotechnology or biopharmaceutical product, can only contribute to problems,

Paradigms of Biopharmaceutical Terminology

	Biopharmaceutical	Biotechnology	Pharmaceutical	Drugs	Users
Broad Biotechnology	All biotechnology-based pharmaceuticals	Living organism/ bioprocessing source	All medicinal products (all pharmaceuticals) savvy sources; FDA	Chemical/non-biological source pharmaceuticals	Core biopharma industry (especially in United States); many tech-savvy sources
New Biotechnology	Only new biotech (genetic engineered) pharmaceutcals (primarily rDNA protein and monoclonal antibody-based)	Only new biotech (genetic engineered) products	All medicinal products (all pharmaceuticals) savvy sources; FDA	Chemical/non-biological source pharmaceuticals	Some in biopharma industry (especially in Europe); some tech-savvy sources; EMEA
Biotechnology Business	All pharmaceuticals from biotech-like (small, R&D intensive) life sci. companies (plus biopharmaceuticals from Big Pharma)	All products from biotech-like companies (plus biotech products from large companies)	All medicinal products (all pharmaceuticals) savvy sources; FDA	Chemical/non-biological source pharmaceuticals	Business/financial communites; popular press; BIO
Pharma Business	All medicinal products (all pharmaceuticals are biopharmaceuticals)	All products from pharma ceutical and biotech companies	Biopharmaceutical used as synonym or pharmaceutical	Term often dropped from usage	Some Big Pharma supporters

At least four conflicting paradigms of biopharmaceutical terminology are in common use: Broad Biotechnology, New Biotechnology, Biotechnology Business, and Pharma Business. Part 1 of this article considers the first two paradigms. Part 2 of this article will discuss the second two.

Biopharmaceutical:

noun: a pharmaceutical product manufactured by biotechnology methods (involving live organisms; bioprocessing); *adjective*: relating to biopharmaceutical products, technologies, companies, or industry

misunderstanding, and frustration within industry and among the general public. Pity the reporter or student trying to make sense of industry products, size, total sales, or other seemingly basic parameters. The prevailing chaos concerning terminology and information organization in biotechnology was reported nearly two decades ago [1, 2]. The situation has only gotten worse since then. Inconsistencies and problems in terminology often extend to scientific terminology such as the technical definition of a *gene* and terms such as a gene's or protein's *structure* and *function* [3].

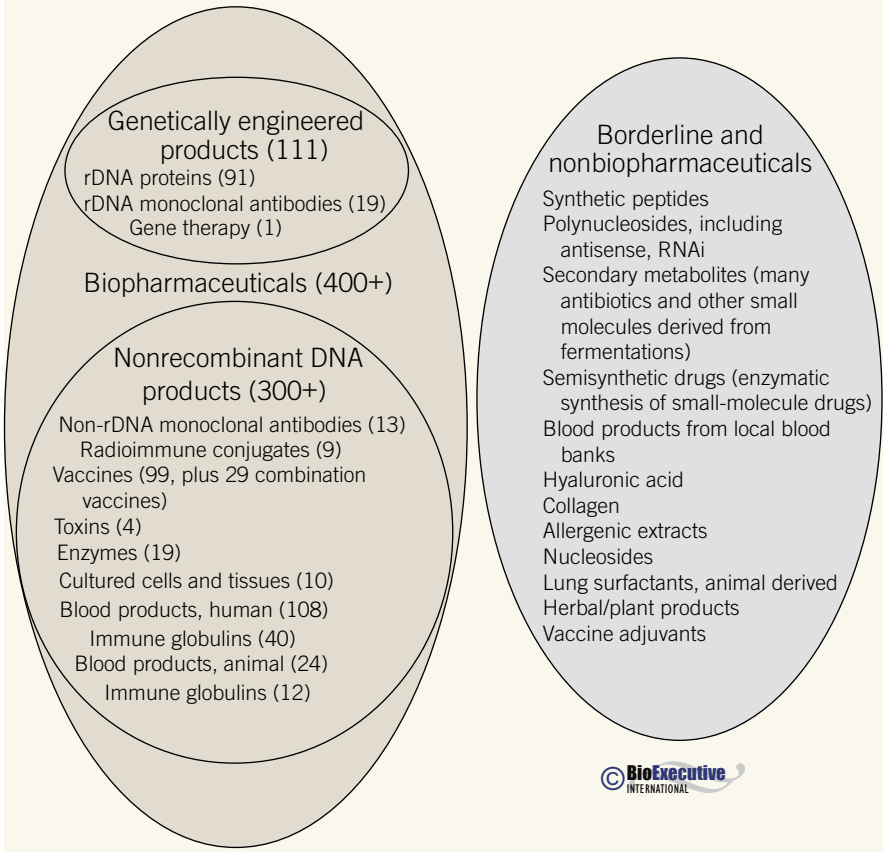
Not only are *biopharmaceutical* and *biotechnology* defined differently by industry, the financial sector, the general public, and the trade and popular press, legal and regulatory definitions further confound the situation. Terminology is an important factor influencing technical, legal, and political battles such as the one over generic biopharmaceuticals—an area involving even more complex, chaotic, and undefined terminology. Because the term *biopharmaceutical* is used inconsistently, other pharmaceutical sectors—including the R&D services and mainstream drug (Big Pharma) industries—are co-opting it for their own uses. Seemingly authoritative sources such as major trade associations are of little help. Even those that actually define the terms they use often misapply them, particularly when referring to companies and industry instead of to products and technologies. These aspects are discussed further in Part 2.

There is no consensus on the use of *biopharmaceutical* or related terms in the scientific community. Those concerned with biopharmaceuticals are divided among a large number of scientific and industrial disciplines and professional associations. None have taken a visible position concerning terminology.

Misapplication of terms can have profound implications, such as wide variations in reporting of biopharmaceutical product approvals, total sales, and other aspects of the industry. Are total biopharmaceutical revenues about $40 billion, as is commonly reported—including only recombinant proteins and monoclonal antibodies? Or are revenues more on the order of $70–80 billion—including other pharmaceutical products manufactured by biotechnological methods such as vaccines, plasma-derived proteins, nonrecombinant cell culture–derived proteins, enzymes, toxins, and other products?

A basic distinction can be made between *biopharmaceuticals*, manufactured by biotechnology methods and involving complex biological molecules, and *drugs*, manufactured by chemical (nonbiological) means and involving small molecules and other chemical substances. Another basic premise is that *biotechnology* and *biopharmaceutical* refer to inherently commercial and industrial activities (bioprocessing). Thus, these terms do not apply to noncommercial scientific research, disciplines, and organizations. In this view, life sciences research, generally performed by the public sector, forms the knowledge base for biotechnology. That

Major Classes of Biopharmaceutical Products



This visual representation shows how biopharmaceutical products are arranged by this author, including the number of major marketing and near-market products in each category. ©2005 *BioExecutive International*

includes bioinformatics, drug design, proteomics, and other state-of-the art research often referred to as *biotechnology* or *biopharmaceutical*. Thus, NIH and universities are negligibly involved in the *biotechnology* and *biopharmaceuticals* industry.

Because biological systems are involved, biotechnology and biopharmaceutical products are almost always highly complex, often defying short, simple description and analytical characterization. Unlike chemical substances and drugs, few biopharmaceuticals are composed of single, readily describable chemical structures. A biopharmaceutical's description is dependent on its identity (source), manufacture (bioprocessing) and specifications (the product–process–specifications paradigm used in the context of discussing generic biopharmaceuticals) ~4. But irrespective of method of manufacture, if an active agent's structure can be portrayed atom-by-atom (instead of using symbols for components, as with proteins), it is almost certainly a chemical substance or drug—usually a small-molecule drug—and not a biological substance nor a biotechnology or biopharmaceutical product. Thus, small molecule drugs are not biopharmaceuticals.

Broad Biotech

Many different definitions, taxonomies, classification schemes and paradigms can be applied to the word *biopharmaceuticals*. No simple definition has been universally accepted. In the United States, the term is most commonly used to refer to all therapeutic, prophylactic, and in vivo diagnostic products manufactured using live organisms or derived functional components. Thus, a *biopharmaceutical* involves *bioprocessing*; and can therefore be defined as the intersection of *pharmaceutical* and *biotechnology*. It is thus synonymous with *biotechnology pharmaceutical* and *pharmaceutical biotechnology* products. Usage in this manner follows the general paradigm of linking descriptions of products, technologies, companies, and industries to methods of manufacture and materials involved and is consistent with the common understanding of the prefix *bio* to indicate biotechnology.

By this definition, *biopharmaceuticals* includes a broad range of products (see "Major Classes of Biopharmaceutical Products"):

- Recombinant and other cell culture–derived proteins
- Antibodies, both mono- and polyclonal, and cell and in vivo ascites cultured and blood-derived
- Antibody-based radioimmune conjugates
- Blood/plasma products, both human and animal-derived
- Enzymes
- Cultured cells/tissue products.

Other definitions of biopharmaceutical include different groups of products. (See "Products Included in Different Definitions of Biopharmaceutical.")

This broad biotechnology-based definition has been in use since the early to mid-1980s. See, for example, the biotechnology patent abstract periodical, *BioINVENTION* ~5, and based on that, the analyses of US biotechnology patents issued in the late 1980s by the Pharmaceutical Manufacturers Association (PMA, now PhRMA) ~6.

As early as 1984, a landmark report by the US congressional Office of Technology Assessment (OTA) recognized that *biotechnology* is a set of methods useful in many industrial sectors, particularly for manufacture of products ~7. The idea that *biotechnology* involves many biotechnologies is now predominant. At least in the United States, *biopharmaceutical* is thus often considered to include products manufactured by both "new" technologies (recombinant DNA and monoclonal antibody/hybridoma) and "old" technologies (fermentation, nonrecombinant cell culture–derived proteins, vaccines, and other products from live organisms including blood/plasma products). Despite the

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-DNA[1]	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 drugs[2]			X	X
All drugs				X

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

2: Includes small and other nonbiological molecules

commonality of such a broad definition, many people still perceive biopharmaceutical products and technologies as involving only genetic engineering.

European usage generally follows the US paradigm of defining biopharmaceuticals as biotechnology-based pharmaceuticals with genetically engineered products as a subset, but it uses different terminology. *Biopharmaceutical* is defined as involving only new biotechnologies (genetic engineering): "a protein or nucleic acid based pharmaceutical substance used for therapeutic or in vivo diagnostic purposes, which is produced by means other than direct extraction from a native (non-engineered) biological source," explains Walsh ~8, 9. He further notes that "general consensus, initially formed in the 1980s, seems to be that biopharmaceuticals are a class of therapeutic product produced by modern biotechnological techniques, i.e., by recombinant DNA technology, or by hybridoma technology in the case of murine monoclonal antibody based products." Unlike the broad definition widely used in the United States, this definition excludes all products from nonengineered organisms.

Europeans use a broader term, *biotechnology medicines* (or *products of pharmaceutical biotechnology*) to denote "all [pharmaceutical] products produced in part or in full by biotechnological means, either traditional or modern" ~8, 9. The broad class of biotechnology medicines is also considered to include some classes of products not considered by most people (including this author) to be biotechnology products, such as chemical substances extracted from plants; secondary metabolites from microbial culture (many antibiotics); fully synthetic peptides; and antisense and other oligonucleotides. Although it may seem strange to consider *biopharmaceuticals* as a subset of *biotechnology medicines*, it is essentially the same paradigm commonly held in the United States, but using different terms and definitions.

Whatever definition is used, what is or isn't considered a biopharmaceutical is often in the eye of the beholder, particularly at the boundaries. Antisense oligonucleotides, aptamers, RNAi, and so on, may be considered biopharmaceuticals (because they mimic biological molecules), drugs (because they are almost always synthetic), or both. There are also many valid reasons to exclude, class as borderline or gray area, or give secondary consideration to some products and technologies. Many people exclude relatively low-tech products manufactured by local blood banks such as red blood cells, plasma, and antihemophilic factor (Factor VIII) cryoprecipitate. One reference book considers those products to be biopharmaceuticals but does not include the same depth of coverage and indexing as provided for other products ~10.

Old vs. New: As shown in "Models of Biopharmaceutical Terminology," the new biotechnology view restricts biotechnology and biopharmaceuticals to genetic engineering. The time has come to eliminate classifications based on old or new technology. Biotechnology now emcompasses a variety of evolving technologies, and as the industry matures, distinctions among them have become less clear and relevant. Even genetic engineering, which origninated in the 1970s, could now be considered "old." It is inappropriate to label as "old" many non-genetic–engineering products and technologies developed in recent decades, some of which involve more complex and modern technologies than many recombinant protein and monoclonal antibody products. The end products and methods of manufacture are most important, not particular technologies used to obtain source organisms. Most recombinant protein products are still mimics of naturally occurring proteins anyway. With modern technology better able to characterize products both genetically engineered and not, there is much less need to make distinctions based on crude characterizations of the age of technologies used to obtain source organisms.

So far, this discussion has centered on terminology in the context of products and technologies. The situation gets more complex when considering regulatory terminology and applying it to companies and industry.

Regulatory Convolutions

The US Food and Drug Administration (FDA) has no useful definition of *biopharmaceutical*, *biologic*, or similar terms. The official term *biologic* has a brief definition: "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man." A lengthy, official definition (see 21 CFR 600.3) defines products on the basis of analogies or similarities to a virus, serum, toxin, or antitoxin, using those terms as defined over a century ago in 1902 when the Virus-Toxin Law initiating the regulation of biologics was enacted. That definition ignores terms in use as long

Reference

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~2 Rader RA. The Status of the Infrastructure of Information Resources Supporting U.S. Biotechnology. *Impact of Chemistry on Biotechnology.* (ACS Symposium Series No. 362) American Chemical Society: Washington, DC, 1988; Chapter 32; pp. 375–85. Related presentations available at www.biopharma.com.

~3 Atwood TK. The Babel of Bioinformatics. *Science* 220 October 20, 2000: 271–2.

~4 Webster C, et al. Biologics: Can There Be Abbreviated Applications, Generics, or Follow-On Products? *BioPharm International* July 1, 2003: www.biopharminternational.com/biopharm/article/articleDetail.jsp?id=73785.

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~8 Spada S, Walsh G. *Directory of Approved Biopharmaceutical Products.* CRC Press: Boca Raton, FL, 2004.

~9 Walsh G. Biopharmaceuticals and Biotechnology Medicines: An Issue of Nomenclature. *European J. Pharm. Sci.* 15(2) 2002: 135–8.

~10 Rader RA. *BIOPHARMA: Biopharmaceutical Products in the U.S. Market.* Biotechnology Information Institute: Rockville, MD, September 2004; www.biopharma.com.

~11 Frequently Asked Questions. Center for Biologics Evaluation and Research, FDA. www.fda.gov/cber/faq.htm.

~12 FDA To Consolidate Review Responsibilities for New Pharmaceutical Products. Press release. www.fda.gov/bbs/topics/NEWS/2002/NEW00834.html.

~13 Federal Food, Drug, and Cosmetic Act. Public Law 95-532, section 201(g). 21 USC § 321(g).

~14 *Council Regulation (EEC) No 2309/93 of 22 July 1993 Laying down Community Procedures for the Authorization and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Agency for the Evaluation of Medicinal Products*, http://pharmacos.eudra.org/F2/eudralex/vol-1/REG_1993_2309/REG_1993_2309_EN.pdf .

~15 *Council Directive 75/318/EEC of 20 May 1975 on the Approximation of the Laws of Member States Relating to Analytical, Pharmacotoxicological and Clinical Standards and Protocols in Respect of the Testing of Medicinal Products*. http://pharmacos.eudra.org/F2/eudralex/download/volpdf/vol1/vol1en.pdf .

ago as three or more decades, such as *virus*, *protein*, *antibody*, *gene*, and *DNA/RNA* and makes no reference to the involvement of bioprocessing.

Thus, *biologics* can include proteins and blood-derived products based on similarity to serum; virus-, bacteria-, and other microorganism-derived products—vaccines and gene therapies—based on similarities to filterable pathogens (a definition of virus predating a basic understanding of viruses or DNA/RNA and encompassing all microorganisms); and antibodies based on similarities to antitoxins. In current practice, *biologics* includes "a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins" ~11.

Because it is linked to long-forgotten terminology and has been inconsistently applied by the FDA over the years, *biologics* is not an optimal term for common use. For example, *biologics* includes some simple organic drugs such as arsphenamine and other organic arsenic compounds. In practice, intended use may also be taken into account by the FDA to classify and regulate a product as a biologic (rather than as a drug or medical device). Some in vitro diagnostics, such as HIV antigen (infection) detection kits, are regulated as biologics based on their use for testing (release) of other biologics, mostly blood-derived products. Also, many outside the regulatory community use *biologics* to include all biopharmaceuticals. Even the FDA has avoided using the term: The Center for Biologics Evaluation and Research (CBER) website includes use of the more descriptive *biological products*.

Most *biopharmaceuticals* (using the prevailing US definition) are classed and regulated by the FDA as *biologics*. However, some are regulated as drugs or medical devices, with different laws, definitions, and regulations applying to each class. Some proteins, particularly those substantially similar to products originally regulated as drugs such as recombinant protein equivalents of animal-derived drugs—insulin and somatropin (human growth hormone)—continue to be regulated as drugs (not biologics) by the Center for Drug Evaluation and Research (CDER). This has profound implications for the development of regulations for *generic biopharmaceuticals*, terminology that is still undefined.

Regulatory-related classifications are complicated by changes in intra-FDA authority over biologics. As of June 2003, many of the more readily characterizable biologics, particularly many recombinant proteins and monoclonal antibodies, have been transferred to CDER, which continues to regulate and approve them under biologics regulations ~12. That has left CBER regulating the more complex biologics—vaccines and blood-derived, cellular, and gene therapy products. Thus nearly all biologics with therapeutic/prophylactic indications can be considered biopharmaceuticals; and biopharmaceuticals/biologics are now regulated by both the biologics and drugs divisions of the FDA. Only a few biopharmaceuticals are regulated as medical devices.

Further confounding regulatory terminology, the Federal Food, Drug, and Cosmetic (FD&C) Act defines *drugs* as all "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "articles (other than food) intended to affect the structure or any function of the body," particularly those described in officially recognized pharmacopeias ~13. Thus essentially all products regulated as biologics (and also drugs and medical devices) could also be

considered drugs by the FD&C definition. That may be the source for terms such as *biologic drugs* and *biotech drugs* to refer to *biologics* and *biopharmaceuticals*. Fortunately, in practice this FD&C-derived view defining all pharmaceuticals (biologics, drugs, and medical devices) to be *drugs* has been rarely used. The term *drugs* is best used to refer to nonbiologic, chemical-based pharmaceuticals.

European Union (EU) regulations define *biotechnological processes* as those involving "recombinant DNA technology; controlled expression of genes coding for biotechnologically active proteins in pro- and eukaryotes, including transformed mammalian cells; monoclonal antibody technology" ~14. Thus, *biotechnology* is largely restricted to recombinant and monoclonal antibody products (new biotechnologies). EU pharmaceutical regulators (EMEA) use the term *biological medicinal products* to refer to nonrecombinant pharmaceuticals manufactured using biotechnological processes. Although European biological medicinal product regulations include mention of "vaccines, serums, toxins, allergen products and medicinal products derived from human blood or plasma," in practice the term has been largely restricted to genetically engineered and monoclonal antibody-based products ~9, 15.

Obviously, US and EU regulatory terminology differ vastly from each other. The US term *biologics* includes recombinant and nonrecombinant microbial and cultured products, vaccines, and blood products, whereas the European terminology is largely restricted to recombinant and monoclonal antibody products.

Not Over Yet

Defining *biopharmaceuticals* is not easy. Many different views and definitions are in use. Much terminology in common use, including by industry sources and regulators, varies and often conflicts. But at least it is solidly based on links to biotechnology—including broad biotechnology, new biotechnology, and official US and EU definitions.

The link to biotechnology is simply ignored by the biotechnology business and pharmaceutical business definitions. Part 2 will discuss those definitions; how the trade and popular press, financial community, companies, and trade associations use and misuse terminology; and strategic considerations and recommendations for the biopharmaceutical industry to preserve its identity and links to biotechnology. ~

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