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,
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. 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.

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.

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### Paradigms of Biopharmaceutical Terminology

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

### Products Included in Different Definitions of Biopharmaceutical

<table>
<thead>
<tr>
<th></th>
<th>Broad Biotech</th>
<th>New Biotech</th>
<th>Biotech Business</th>
<th>Pharma Business</th>
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<tbody>
<tr>
<td>Proteins, rDNA</td>
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<tr>
<td>Mabs, rDNA</td>
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<tr>
<td>Proteins, non-rDNA</td>
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<tr>
<td>Mabs, non-DNA</td>
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<td>Vaccines</td>
<td>X</td>
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<td>Enzymes</td>
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<td>Toxins</td>
<td>X</td>
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<tr>
<td>Cells/tissues</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Blood products</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Small drugs</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>ALL drugs</td>
<td>X</td>
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1: Monoclonal antibodies, hybridoma cultured (in vitro or ascites methods)  
2: Includes small and other nonbiological molecules

**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 encompasses a variety of evolving technologies, and as the industry matures, distinctions among them have become less clear and relevant. Even genetic engineering, which originated 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 as...
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, allergens, 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 biologic 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 busi-