(Re)defining biopharmaceutical

Ronald A Rader

Vested interests are redefining, rebranding and co-opting what is 'biopharmaceutical'. This is not just a matter of semantics—the core identity of the biotech industry and its products is at stake.

The industry sector involved in 'biopharmaceutical' development, manufacture and marketing is now over 25 years old (or several hundred years old, depending on the definition used), with over 350 marketed products (or thousands, depending on the definition used). This includes over 125 recombinant proteins currently approved in the United States or European Union[1]. And yet, there is still considerable confusion over what is and what isn't biopharmaceutical[2,3]. The term is widely used, but is hardly ever defined by its users. Definitions of biopharmaceutical in common use vary greatly, ranging from those based on the biological source and nature of products and their manufacture to those based purely on business models, perceptions and public relations. These definitions include pharmaceuticals manufactured using living organisms (biotechnology), only the subset of these pharmaceuticals involving genetic engineering, or simply all pharmaceuticals (including small-molecule drugs), with everything 'pharmaceutical' now 'biopharmaceutical'. In many respects, these diverse definitions parallel different definitions for 'biotechnology' (e.g., whether this concerns just products manufactured using living organisms, the subset of these involving genetic engineering, or now encompasses everything involving biotechnology-like companies and/or much or all pharmaceutical and other life sciences–based R&D and industries).

The result is a Babel-like situation with terminological chaos and anarchy confounding communication, comparative and industry analyses, understanding and regulation. With the industry maturing, including generic biopharmaceutical (biogeneric, biosimilar, follow-on biologic) approval regimens being implemented sooner or later in the United States, Europe and other regions, defining basic terms and talking about biopharmaceuticals as a distinct class of products is a necessity. But perhaps a more serious problem is that the biopharmaceutical industry risks loss of its core identity to related industries that covet and are actively co-opting its good will and name to apply to themselves.

How the word 'biopharmaceutical' is defined and applied in common usage affects not only public perceptions but also the reliability and comparability of statistics gathered on companies, their products and the industry.

Ronald A. Rader is at the Biotechnology Information Institute, 1700 Rockville Pike, Suite 400, Rockville, Maryland 20852, USA. Further information related to this article is available at http://www.biopharmacopeia.com/. e-mail: ron@biopharma.com

First principles

Any examination of recent articles, presentations or studies discussing biopharmaceutical topics reveals a wide variety of divergent paradigms/definitions in use, along with a variety of terms less frequently used as synonyms (e.g., biotechnology drugs, biotechnology medical products, biotherapeutics and biologicals). Most English language dictionaries, including those considered the most authoritative, simply lack any entry for biopharmaceutical. This occurs despite the word being in common use—a Google search of the Internet retrieves over 4 million entries.

The classic view, in use for decades, is that the term pharmaceutical concerns medicinal products, technologies, related R&D and companies, with two major subsets: biopharmaceutical and drug. Note, with no recognized or authoritative definitions, various synonyms may be substituted for biopharmaceutical and other terms used in this article, but the core concepts and distinctions remain the same. For example, some may prefer drug as the broader term, with pharmaceutical and biopharmaceutical being the two major subsets. However, the basic distinction remains that one subset involves inherently biological products with manufacture involving biological sources and processes, whereas the other involves chemical (nonbiological) medicinal products manufactured using chemical sources and processes.

The classic definition, also used in science and industry, is that biopharmaceutical refers to pharmaceuticals (medicinal products, therapeutics, prophylactics and *in vivo* diagnostics) with active agents inherently biological in nature and manufactured using biotech. I present this and other simple, classic definitions for various terms in **Box 1**. These definitions of biopharmaceutical and drug parallel US regulatory definitions of biologic and drug. Biopharmaceutical involves the inter-

Box 1 Glossary: author-recommended definitions of basic terms

Pharmaceutical. *noun* A medicinal product (both active agents and formulated products), including therapeutics, prophylactics and *in vivo* diagnostics; two major subsets are drugs and biopharmaceuticals. *adjective* Relating to pharmaceutical products, technologies, companies and industries.

Biotechnology. *noun* The manufacture of products by or from living organisms, usually involving bioprocessing. *adjective* Relating to biotechnology, for example, products, technologies, companies and industries.

Biopharmaceutical. *noun* A pharmaceutical inherently biological in nature and manufactured using biotechnology. *adjective* Relating to biopharmaceuticals, for example, products, technologies, companies or industries.

Drug. *noun* A pharmaceutical inherently chemical (not biological) in nature and manufactured using chemical methods. *adjective* Relating to drugs, for example, products, technologies, companies and industries.

Biopharmaceutical company. A company primarily (or otherwise substantially) involved in biopharmaceuticals (e.g., research, development, manufacture and/or marketing).

Biopharmaceutical industry. Those companies and other organizations primarily (or otherwise substantially) involved in biopharmaceuticals (e.g., research, development, manufacture and/or marketing).

section of biotechnology and pharmaceutical, and drug involves the intersection of chemical and pharmaceutical. To make matters even more complicated, 'biopharmaceutics' refers to the scientific discipline concerned with the chemical and physical properties of pharmaceuticals in relation to their bioavailability and pharmacokinetics.

Using these classic definitions, distinctions between biopharmaceuticals and drugs are usually obvious when looking at products' active agents and their manufacture. Some agents/products may fall into gray areas and be considered biopharmaceuticals, drugs or both. For example, antisense oligonucleotides, aptamers, RNA interference, synthetic peptides and others may be viewed as biopharmaceuticals (because they are similar to, or mimic, biological molecules), as drugs (because they are almost always synthetic) or as both. Drugs manufactured using enzymes and certain animal- and plant-derived natural products may also be variably classified. No matter what criteria are used, there will be differences of opinion regarding classification of some products. But like organic versus inorganic chemicals and chemistry, the core paradigm and dichotomy between biological- and chemical-based entities and processes remains. Despite the long use, simplicity, utility and logic of this biological versus chemical dichotomy, many people now ignore or refuse to follow this paradigm, and define biopharmaceutical from perspectives ignoring science (consideration of products or agents) and technology (methods of manufacture). For example, small-molecule drugs and much or all biomedical R&D (e.g., anything involving molecular or cellular biology with relevance to human/mammalian systems) are now often classed as biopharmaceutical.

Biopharmaceutical, like biotechnology and pharmaceutical, is both a noun and adjective referring to an inherently industrial activity (that is, involving products and commerce), and it does not generally apply to scientific research, disciplines or to organizations not significantly involved with biopharmaceuticals in a commercial context. An analogy may be made with pharmaceutical versus pharmacology; the former involves products and industry, whereas the latter involves a scientific discipline. In this context, life sciences research, generally performed by the public sector, provides the knowledge base for, but is not, biotechnology; and there is relatively little academic or other public sector biopharmaceutical research.

Industries (and certainly products) have always been primarily characterized and named based on the nature of their commercial products and related manufacturing technologies, not the science and technologies that happen to be used for R&D. For example, integrated circuit companies are dependent upon and conduct much solid state physics and materials research, but neither these products, companies nor the industry are referred to using these terms; and a company primarily concerned with using bioinformatics or biologically based screening for small-molecule drug discovery is a drug, not a biopharmaceutical, company.

Biopharmaceuticals are distinct from chemical-based drugs

Essentially all aspects of biopharmaceuticals are distinct from those of drugs, most of which are small molecules or other synthetic chemical substances. The inherent differences between these two classes include product and active agent sources, identity, structure, composition, manufacturing methods and equipment, intellectual property, formulation, handling, dosing, regulation and marketing.

Small-molecule and most other drugs have structures composed of relatively few atoms, such that their structures can generally be portrayed by diagrams showing linkages of specific atoms. Drugs can generally be manufactured with high consistency and using rather standardized chemical processes, usually involving conditions and materials (e.g., heat and solvents) that kill most organisms and inactivate biological molecules. Most drugs are manufactured from chemical precursors, and some considered natural products are derived chemically (e.g., extracted from nonliving biological sources). The purity and contents of drug active agents and finished products can generally be readily analyzed and demonstrated. Drugs and chemical substances with high purity, including those composed of multiple isomers and complex natural products, can generally be presumed to be similar or even identical for all practical purposes (including generic substitution). In contrast, biopharmaceuticals are much larger and more complex, such that they make structural representation at the atomic level much harder. Compared with drugs, biopharmaceuticals are composed of many more atoms—with molecular masses usually two or three orders of magnitude greater—and involve many additional levels of structural complexity (e.g., forming polymeric chains with varying and diverse structures and chemical modifications). Most biopharmaceuticals involve proteins or other biopolymers comprising many, usually hundreds or thousands, of chemical subunits or monomers (e.g., amino acids or nucleotides), with each subunit a potential site for structural variation.

Biopharmaceuticals, due to their biological source and manufacture, involve inherent diversity, randomness and complexity, often defying rigorous (bio)chemical analysis and terse textual descriptions. Even biopharmaceuticals (e.g., from different manufacturers), indistinguishable using state-of-the-art analytical technologies, may be substantially different, including having different efficacy and safety profiles (e.g., immunogenicity), which is a major factor complicating regulation of generic biopharmaceuticals (e.g., biogenerics, biosimilars, follow-on proteins). In contrast, drugs and other chemical substances offer relative simplicity and certainty. Describing the nature and identity of a biopharmaceutical requires information on its biological source and processing, whereas the source for pre-

cursors and intermediates and manufacturing processes of small-molecule drugs generally need not be known. Unlike drugs, many structural-, functional-, safety- and efficacy-related characteristics of biopharmaceutical active agents, beyond primary structure (e.g., amino acid sequence), are highly dependent on their methods of manufacture (further discussed below). This includes three-dimensional conformation, the size and folding of polymeric chains, formation of multimers or complexes of chains, variable oxidation states, self-aggregation of molecules, intra- and inter-chain disulfide linkages, amidation, attachment of variable polysaccharide side chains (glycosylation) and other post-translational modifications[4] (see **Box 2**).

Most biopharmaceuticals, including seemingly simple well-characterized and specified recombinant proteins, involve considerable (micro)heterogeneity, with the active agent actually a complex mixture of molecular subspecies with a range of variations in structural aspects (e.g., due to amino acid substitutions, twists and turns in chain structures, intra- and inter-chain linkages, side-chain modifications and aggregation). Some biopharmaceuticals are not single molecules, or even single macromolecules; they are therapies comprising cells or organisms (e.g., vaccines composed of whole microorganisms or cultured skin) that are impossible to fully characterize at a molecular level. And, the finished products also entail a number of characteristics distinct from those of drugs[5]. This applies to most biopharmaceuticals: administered systemically rather than orally or otherwise (due to their digestion, and large size inhibiting movement across membranes); requiring complex systems for stabilization (e.g., addition of albumin or sugars); being temperature sensitive and requiring cold storage; being subject to different legal/regulatory regimes; having no generic competition; and not being sold through the usual pharmacy outlets, with most being expensive specialty items and only a few being cheap commodity items, such as some pediatric vaccines.

Distinctions between biopharmaceuticals (and biotechnology) and drugs (and chemicals/chemistry) are also evident in terms of intellectual property, particularly patents. Biopharmaceuticals are usually protected by patents involving biological entities and/or information (e.g., gene/protein sequences, vectors and other genetic constructs, cell lines, often embodied in culture collection deposits), whereas drugs are primarily protected by patents covering chemical structures. Much more than drugs, biopharmaceuticals are also often protected by a mass of other patents (or trade secrets) concerning processes, uses (diseases/indications), and reference standards and assays.

Biopharmaceutical manufacturing methods, equipment, testing and the infrastructure required are much different, more complex and costly than for drugs/chemical substances. Biopharmaceuticals are generally manufactured using active agent-customized, proprietary bioprocessing methods, equipment and biological sources. Quality control and product specifications are much different. Unlike drugs, biopharmaceuticals generally must be manufactured under sterile conditions and the final products must be free (have acceptable levels) of diverse biological impurities, including contaminating bacteria, viruses and prions, and host or source DNA/RNA, proteins and cellular debris.

The distinctions between biopharmaceutical and drug carry over to the organizations, usually companies, involved in the discovery, development and marketing of these products. Compared with firms with drug products, biopharmaceutical companies generally have staff with different training and expertise, higher costs of goods, greater investment in different types of manufacturing facilities and more product-dedicated marketing/sales organizations. As discussed below, distinctions between biopharmaceutical and drug companies are beginning to blur as successful companies of both types diversify, but the products, technologies and industry identities remain distinct.

Process equals product

Unavoidably, due to their manufacture by or from living organisms or cells, biopharmaceutical products and their active agents are largely defined and differentiated from one another by their identity and/or source, methods of manufacture and composition and other specifications. This is the classic 'product, process, specifications' paradigm, often shortened to 'process equals product'[6,7] and is much the same as the chemistry, manufacturing and control (CMC) aspects of good manufacturing practice (GMP). In contrast, high purity drugs (chemical substances) can usually be differentiated and identified simply by referring to their name or structure.

Following the process-equals-product paradigm, a unique biopharmaceutical product (or active agent) is a product/agent from one

Box 2 Problems defining specific biopharmaceuticals

Defining particular biopharmaceutical agents or products is more difficult than defining the term. There are as yet no adequate methods to assign either unique or generic nomenclature (names and other identifiers) to biopharmaceutical agents and products, particularly names that are unique and unambiguous, yet informative and useable for communication. Similarly, from rigorous process-equals-product and chemical and/or pharmaceutical information perspectives, most references to biopharmaceuticals are imprecise and ambiguous, including in the scientific literature. Defining specific biopharmaceuticals involves the same issues as defining biogenerics (biosimilars, follow-on proteins and biologics)[24,27,28].

Complicating defining specific or unique biopharmaceuticals is their nature as commercial products, which adds complexities beyond biological identity, manufacturing processes and specifications. As commercial products, biopharmaceuticals cannot simply be defined from a single perspective. In the real world, defining and differentiating particular biopharmaceuticals requires consideration of their entity (scientific/technological; process equals product), regulatory (approvals) and commercial/market aspects. Depending on the use and user, a difference or change in any of these aspects may define a distinct, new and different product (e.g., changes in the product and/or agent, manufacturing processes, approvals, companies involved, trade names). Taking a very simple example: is a product repackaged and marketed by different companies the same product or two different products? Recombinant erythropoietin (epoetin alfa; EPO) manufactured by Amgen (Thousand Oaks, CA, USA) is marketed in the United States as Epogen by Amgen and marketed for different indications in the United States as Procrit by Ortho/Johnson & Johnson (Bridgewater, NJ, USA). Each branded product has billions of dollars in sales annually in the United States. Only one FDA original approval covers both Epogen and Procrit (a biologics license application approved for Amgen). Concentrating on either active agents and products or approvals, these products are the same, whereas any consideration of commercial aspects requires viewing these as two distinct products.

Box 3 Regulatory definitions of biopharmaceuticals

Most regulatory agencies, including the FDA, subscribe to the broad biotechnology view (see main text), whereas the European Union has largely adopted the new biotechnology view. However, the FDA and regulators in many other countries have no useful definition of 'biopharmaceutical' or related terms. The official FDA definition of 'biological products' or 'biologics' can be summarized as "any virus, therapeutic serum, toxin, antitoxin or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man"[29]. Similarly, the lengthy, official definition (codified in 21 CFR 600.3) vaguely defines biologics on the basis of analogies (that is, products similar to viruses, serums, toxins and antitoxins, as defined in 1902 when the US Virus-Toxin Law initiating the regulation of biologics manufacture was enacted). This definition avoids terms and concepts in use for generations (e.g., proteins, antibodies, genes, microbes, cells, viruses and DNA/RNA). In 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"[30]. Most biopharmaceuticals (using the broad and new biotechnology paradigms) are classed and regulated by FDA as biologics. However, due to their similarity to products historically regulated as drugs, some simpler biopharmaceuticals are regulated as drugs, mostly recombinant hormones, for example, insulin and human growth hormone, and a few products are regulated as medical devices, with different laws and regulations applying to each class. Because of its specific link to regulation by FDA and complex definition, 'biologics' is best used only in its regulatory context.

European Union regulations define 'biological medicinal products' as "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 (nonengineered) biological source"[2,9]. This corresponds to the new biotechnology view (that is, by elimination, it is largely restricted to recombinant and mAb products). The terms 'biotechnology medicines' and 'biological medicinal products' are used to broadly refer to all biopharmaceuticals (by the broad biotechnology view). Although these terms are commonly used, European Union use is generally restricted to biological medicinal products (genetically engineered and mAb-based products). As with 'biologics,' these terms are best used only in their specific regulatory context.

manufacturer, manufactured using consistent biological sources (genes, cell lines), a consistent set of processes, under a consistent set of conditions, using consistent in-process and other controls, and with a consistent set of final specifications. This is the classic view taken by the US Food and Drug Administration (FDA) and regulators in other developed countries, and forms the basis for regulation of all but the very simplest biopharmaceuticals (**Box 3**).

A corollary of process equals product is that biopharmaceuticals manufactured differently are each distinct and unique. Furthermore, as the identity, source, methods of manufacture and composition and other specifications for biopharmaceuticals are so complex and almost never fully disclosed, each agent or product from each manufacturer is inherently unique; and comparable products from different manufacturers, sometimes even different batches from the same manufacturer, are inherently and often detectably unique. This is recognized beyond the industry and by the public. Everyone realizes that beer, wine, cheese and other food products manufactured by biotechnology processes by different companies each have noticeable variations (e.g., taste, color and texture), yet the products may be treated as identical, including having the same generic name (e.g., cheddar cheese or Chardonnay). Some cite process equals product and manufacturer-based uniqueness to assert that biogeneric approvals are inherently impossible (but this misses the point of basing these approvals on the similarities between products and/or agents). Also, because the full identity or source, manufacturing methods and specifications for biopharmaceuticals are hardly ever publicly disclosed, other than their manufacturers (and associated marketers) and regulators, no one ever knows what they actually are. Thus, in many respects, biopharmaceuticals (and their approvals) are enigmas or black boxes.

Process equals product exemplifies the power and successful popularization of a biopharmaceutical-related paradigm and terminology. Just about every discussion of biogenerics now cites this. Process equals product appears to have originated with well-established (innovator) companies as an argument against biogenerics-enabling legislation and regulations[6,7]. In this context, it has served the interests of its original promoters very well.

Definitions currently in use

Four paradigms or ways of defining biopharmaceutical are in common use and can be readily observed in the trade, scientific, regulatory, financial and popular literature[2,3]. These are summarized in **Table 1**. Two of these are entity- and technology-based and use rigid criteria (that is, are based upon products/active agents and manufacturing methods). The other two are business model or product- and company image–based, with criteria not based on the product/agent or technology. Use of each paradigm/definition is often linked to the world view, employment or audience of the user.

Broad biotech. This definition of biopharmaceuticals follows the classic one grounded in objective consideration of product/agent sources and their manufacture—biopharmaceuticals are pharmaceuticals that are biological in nature and manufactured by biotechnology methods. This includes products manufactured both by what some label as 'new' technologies (e.g., monoclonal antibodies and recombinant proteins; involving genetic engineering) and 'old' technologies (e.g., proteins and vaccines derived from nonengineered organisms as well as blood/plasma-derived products). Regulatory definitions of biopharmaceutical are generally based on the broad biotechnology definition, but often use other terms with their own convoluted definitions (e.g., 'biologics' in the United States; see **Box 3**).

This broad view remains the predominant one in the United States and the industry itself. For example, in a July 2005 poll of *Bioprocess International* readers, 85% agreed with this definition[8]. Usage of biopharmaceutical in this manner also follows the traditional linking of characterizations of companies and industries (and products) to the nature of their commercial products and methods of manufacture, and it is consistent with the common understanding of the prefix 'bio' indicating biotechnology or biological. From this view, worldwide biopharmaceutical revenue in 2006 was ~$93 billion, and will likely top $100 billion in 2007 (ref. 1); and biopharmaceuticals have been around for over 200 years (e.g., smallpox vaccines using live vaccinia virus from cows were first introduced in the late 1700s).

New biotech. This definition is a restricted version or subset of the broad biotechnology view, defining biopharmaceuticals more narrowly as just those based on 'new(er)' technologies (that

is, recombinant proteins, monoclonal antibodies (mAbs) and other products produced using genetic engineering). This view reflects the current market dominance of recombinant proteins and mAbs; the emphasis placed on new(er) technologies and products is prevalent in Europe[9]. Following this paradigm, many product classes considered as biopharmaceuticals according to the broad biotechnology model (e.g., nonrecombinant proteins, vaccines and blood/plasma derivatives) are classed as old and are thus excluded or ignored. From this view, 2006 worldwide biopharmaceutical revenue was about $65 billion; and biopharmaceuticals have been around since the early 1980s (starting with recombinant insulin approved in 1982)[1].

Limiting biopharmaceuticals to those genetically engineered is not optimal but is acceptable, provided this is defined or otherwise made clear. Even so, there seems to be little rationale to arbitrarily single out genetically engineered versus other products (e.g., recombinant versus native proteins), although this is sometimes done for regulatory purposes, particularly in Europe. Labeling biopharmaceuticals (and biotechnologies) as either old or new is arbitrary and unwieldy because much of what is considered new may now be old and vice versa. Recombinant proteins and mAbs are based on technologies that may now deserve to be considered old—invented in the 1970s and commercialized in the 1980s. Among nonrecombinant products are many that incorporate newer and more complex technologies than many marketed recombinant proteins and mAbs. For example, Prevnar, approved in 2000, is a vaccine against pneumonia involving partially hydrolyzed capsular (outer coat) antigens from seven *Streptococcus pneumoniae* bacteria serotypes individually cultured, purified and chemically conjugated to a bacterial carrier protein (with sales now over $2 billion/year)[10]; Vivaglobulin, approved in 2006, is the first human plasma–derived immune globulin product of sufficiently high purity to be administered subcutaneously; and Epicel, approved in October 2007, is sheets of skin cultured from the patient's own keratinocytes. In terms of science, (bio)technologies, complexity, patents, difficulty in manufacture, approvals and other parameters, these and many other nongenetically engineered biopharmaceuticals are just as new as (or newer and higher tech than) many recombinant protein and mAb products.

Criteria for what is biotechnology and biopharmaceutical are unfixed, subjective, adaptable to the needs of the moment, presumed to be continually evolving and rarely defined.

Biotechnology business. This business model–and product image–centric definition of biopharmaceutical generally includes not only biopharmaceuticals by either of the above definitions but also anything involving pharmaceuticals, including research R&D, and/or biotech-like (generally smaller, entrepreneurial, R&D-intensive) companies and related research. This is often extended to include anything that is remotely pharmaceutical-related or that seems or can be portrayed as involving biomedical R&D (which is considered as biotech). Simply stated, biopharmaceutical can be used—even without the need for any involvement or use of actual biotech—if a biotech-like firm is connected with a pharmaceutical product, technology or organization in any way; or if a pharmaceutical-related product, technology or organization can be portrayed as involving high-tech life sciences R&D. Small-molecule drug research, discovery and development and related services companies are included, even where these involve purely chemical and/or drug technologies. Some simplify or modify this definition with everything pharmaceutical-related now being biopharmaceutical, optionally including anything related to biomedical R&D, except for that associated with big pharma (large multinational pharmaceutical companies with multi-billion dollar R&D budgets and sales).

Thus, for many of those concerned with companies, communications, investments, financing, pitching stories and media relations, biotechnology and biopharmaceutical have become business models, metaphors or even states of mind, no longer linked to the biological nature of products and their manufacture. Those commonly expressing this view include many in the press and financial community, stock analysts, the Biotechnology Industry Organization (BIO; Washington, DC) and many of the most respected reviews/studies of the biotechnology and (bio)pharmaceutical industries. Criteria for what is biotechnology and biopharmaceutical are unfixed, subjective, adaptable to the needs of the moment, presumed to be continually evolving and rarely defined. This works well for many uses and users, enabling them to classify anything related to life sciences, biomedicine or pharmaceuticals, particularly regarding companies, as they see fit. Using these definitions, the size of the market and other parameters regarding the biopharmaceutical industry vary greatly among different sources, and when the industry began is similarly unclear.

The biotechnology business view is often evident in discussions of products and/or approvals. For example, the latest listing of approved (US) 'biotechnology drugs' from BIO, part of its 'Guide to Biotechnology', includes "biologics developed by biotechnology companies and pharmaceutical companies,

Table 1 Common paradigms or ways of defining 'biopharmaceutical'

Paradigm	Industry size	Industry age	Biopharmaceutical criteria/definition
Broad biotech	$90–100 billion/year	200+ years old	Objectively defined; based on active agents/products made using live organisms and/or bioprocessing.
New biotech	$60–70 billion/year	25+ years old	Subset of above; involves genetic engineering and other new(er) biotechnologies (recombinant proteins and mAbs).
Biotech business	Size uncertain	Age uncertain; varies greatly	Rarely defined or definable; based on business models and/or perceptions or public relations. Involves biotech-like (small, R&D-based) companies or all pharmaceuticals and/or life sciences or biomedical R&D, particularly anything that can be portrayed as high tech[a].
Pharma business	$650+ billion/year	Age uncertain; varies greatly	Rarely defined/definable; based on business models and/or perceptions or public relations. Everything pharmaceutical is now biopharmaceutical, with everything biotech (by the above description) now subsumed into or serving the biopharmaceutical industry[a].

[a]Includes biopharmaceuticals as defined by the broad and new biotech paradigms.

as well as small-molecule products developed by biotechnology companies [members], and other selected small-molecule or tissue-engineered products"[11]. Examination shows that 100 (39%) of the 254 products listed are synthetic drugs mostly from BIO member companies. And, in its 2006 annual review covering worldwide public biotechnology companies (n = 703; revenue $73 billion/year), concentrating on biopharmaceutical and excluding big pharma companies, industry consultant Ernst & Young repeatedly cites "industry's success" in 2006 as including 36 approvals by FDA, including 25 new drug applications, nearly all of which were for synthetic drugs or chemical substances[12].

Pharma business. This second business model- and image-centric definition of biopharmaceutical simply considers the term to cover everything pharmaceutical-related, including small-molecule drugs, often including all of the biomedically oriented biotechnology industry (or all biotechnology). Biopharmaceutical is thus used as a synonym for pharmaceutical and drug (with the term including actual biopharmaceuticals). Essentially, the pharmaceutical industry is now the biopharmaceutical industry. By this definition, worldwide biopharmaceutical (pharmaceutical) revenue in 2006 was about $650 billion, and it remains entirely unclear when this 'industry' began. This definition is sometimes limited to innovator (that is, based on original R&D) products and companies, with unstated exclusion of generic drugs ($54 billion/year in the United States in 2006). Typically, medicinal chemistry, the foundation of the pharmaceutical (drug) industry, and its contributions are ignored or slighted.

The pharma business paradigm is linked to what this author terms the 'myth of convergence' and associated mainstream pharmaceutical (drug) industry efforts to lay the foundation to reengineer its image, rebrand itself and now be perceived as 'biopharmaceutical' (which evokes more positive images than pharmaceutical or drug). This is exemplified in various studies, notably those funded and issued by the Pharmaceutical Research and Manufacturers Association (PhRMA; Washington, DC) and other presumed authoritative studies, that assert that the pharmaceutical industry has recently morphed or transformed itself into the biopharmaceutical industry as a result of the 'convergence' or merging of the pharmaceutical and biotechnology industries and technologies and the development of close relationships (primarily outsourcing, in-licensing and acquisitions) with smaller biotechnology firms, and that this transformed biopharmaceutical industry has assimilated much or all of the biotechnology industry[13–15]. As stated by PhRMA, "Biotechnology + Pharmaceutical = Biopharmaceutical," with "+" designating union or the merging of everything (not the classic view of biopharmaceutical involving intersection)[16]. PhRMA has even retitled its annual industry review and now refers to its members as "America's research-based biopharmaceutical companies"[17].

> How and when did business models and public relations–based imagery come to define the nature of products and industries?

Flaws in business- and image-based definitions

Both business- and image-centric definitions of biopharmaceutical generally seek to encompass as much innovative R&D as possible. The biotechnology business view takes a bottom-up view broadly including all remotely pharmaceutical- and other biomedical R&D. The pharma business view takes a top-down view, concentrating on the relatively few large pharmaceutical companies that conduct the vast majority of pharmaceutical R&D, with most of the biotechnology industry and biomedical R&D included in a subservient capacity. These views are exemplified by BIO, which welcomes all as members, including diverse service and supply organizations, whereas PhRMA membership is restricted to large companies (that is, their US operations) involved in developing and marketing pharmaceuticals. Many using business- or image-based paradigms avoid ever providing definitions or criteria (e.g., for what is or isn't 'biopharmaceutical'). For example, when recently asked by this author, PhRMA refused to respond at all regarding its definition, whereas BIO stated that it currently does not recognize a definition for 'biotechnology'.

The two business- and image-centric definitions of biopharmaceutical are flawed on many levels. First, they ignore established principles for naming industries (and products), which are generally defined and named according to their commercial products or methods of manufacture, not by their R&D methods, business models or subjective views about what seems to be high tech or in vogue.

Second, biotechnologies (including *in vitro* and *in vivo* assays and screening) have formed much of the basis for pharmaceutical (drug and biopharmaceutical) R&D for decades, if not since the start of the modern industry, so convergence and the drug industry relying on biotechnologies and the life sciences for R&D are not new. If anything, the argument could be made that most recent major advances in pharmaceutical R&D involve chemistry, not biology, and/or advances in computers and information processing. The chemical screening, molecular modeling and other data-intensive drug design technologies cited as 'transforming' the pharmaceutical (drug) industry into the biopharmaceutical industry have been in use since the 1970s, and much of what is cited as biopharmaceutical R&D involves purely chemical-based discovery of small-molecule drugs and medicinal chemistry. The transformation of the pharmaceutical industry into the biopharmaceutical industry is a myth, often promulgated by authors and those with vested interests seeking an advantage by using the term in place of pharmaceutical, drug or other appropriate but less attention-grabbing or trendy terms.

Third, biopharmaceutical products and technologies remain readily identifiable and distinguishable from drug or chemical products and the technologies that produce them. All one has to do is look at the nature of products and their manufacture. Likening a biopharmaceutical product or technology to that of small-molecule drugs, usually synthetic, is like comparing apples and oranges. Many of the publications, studies and proponents adopting business- or image-based views often avoid using any term for actual biopharmaceutical products or agents or make up their own terms. Following their views that most everything pharmaceutical is now merged with and indistinguishable from biotechnology, business- and image-based users often refuse to acknowledge any product-centric, science- or technology-based subsets of what is 'pharmaceutical' and 'biotechnology'; for example, use of 'biopharmaceutical' and synonyms is avoided. Along these lines, PhRMA takes care to only use 'biopharmaceutical' as an adjective to refer to companies, R&D and the industry (its members), and never to refer to products.

And fourth, there is simply no body of information or documentation (e.g., peer-reviewed or other articles) supporting redefining biopharmaceutical and the industry based on either the biotechnology or pharma business models. These paradigms are useful and have their place (e.g., in economic, stock and company analyses), but lack technical rigor and are best avoided outside of these contexts. Proponents and users of these views almost universally fail to explain or cite support for their underlying criteria. Until someone proposes

rational answers to some basic questions, these paradigms and definitions should be avoided, particularly by the scientific community, the biopharmaceutical industry and governments and others intending to gather statistics on industry. How and why should small-molecule drugs be considered biopharmaceuticals? How and when did business models and public relations–based imagery come to define the nature of products and industries? How and when did the pharmaceutical and biotechnology industries converge or merge (or is this still happening)? Why should long-accepted terms, paradigms and definitions based on considering the nature (science) and manufacture (technology) of products and/or agents be abandoned (particularly, when no alternative working definitions are proposed)?

Obfuscating, co-opting and expanding what is biopharmaceutical in many respects are shrewd moves on the part of those with vested interests seeking benefits from such. However, this does not make this terminology worthy of use outside of the public relations, hype and image-spinning contexts for which it was designed.

Industry continues to evolve

If anything, it is biopharmaceutical and drug companies, not products, technologies or industries, whose R&D, business models and commercial activities are starting to converge or merge[18]. Besides being part of the pharmaceutical industry, both biopharmaceutical and drug companies now often use much the same product discovery and research technologies, and many companies, particularly the more profitable ones, are diversifying. Some drug companies are becoming more active in biopharmaceuticals, and some biopharmaceutical companies are becoming more active in small-molecule drugs. Large international drug companies (big pharma) face severe pipeline problems and continue to buy up or into smaller biopharmaceutical and drug companies[19].

There is even a new industry of pharmaceutical discovery, design and screening companies, most of which are oriented to making small-molecule drugs and serving the needs of big pharma, which outsources much discovery and early-stage R&D to them. There may be more companies in this estimated $7 billion industry than there are biopharmaceutical companies. Companies involved in predominantly chemical and chemistry-based drug discovery, design and screening or using bioinformatics or other high-tech life sciences R&D to discover or design drugs (not biopharmaceuticals) are drug (or pharmaceutical), not biopharmaceutical, companies.

Biopharmaceuticals remain a small and distinct subset (generally ~15%) of the pharmaceutical industry, whether considered in terms of products, R&D, companies, revenue or other parameters. For example, worldwide annual biopharmaceutical revenues using the broad biotechnology definition are now about $100 billion, compared with $650+ billion for all pharmaceuticals. The worldwide annual sales of vaccines and blood products are each less than $15 billion, comparable to that of sales of the leading pharmaceutical, Lipitor (atorvastatin calcium; Pfizer, NY).

The number, percentage and sales of biopharmaceuticals relative to drugs and all pharmaceuticals are growing, but neither this nor adoption of newer R&D methods changes the underlying nature of the pharmaceutical industry, which will remain primarily concerned with small-molecule drugs (not biopharmaceuticals). Even among those largest pharmaceutical (drug) companies most active in biopharmaceuticals, these are a minority of R&D and sales, most of these products have been licensed in or acquired, and few companies have themselves developed or manufactured more than just one or a few biopharmaceuticals.

The deleterious consequences of miscommunication in relation to the term biopharmaceutical are not limited to public and political perceptions.

Biopharmaceutical industry beware!

By failing to differentiate biopharmaceutical from other types of pharmaceutical research, development, technologies, products and companies, the industry focused on these products risks losing its unique identity and the ability to differentiate itself from the much older and established drug sector. This is important for several reasons.

In recent years, big pharma and the drug industry have been plagued by scandals, product withdrawals, ailing new product discovery and development, and commercial practices that have caused public opinion to plummet. Pharmaceutical firms now rank at the bottom in terms of public esteem, along with tobacco and oil companies[20]. The moves by large drug companies to rebrand themselves as the biopharmaceutical industry takes advantage of the positive public perception of the groundbreaking products produced by innovative biopharmaceutical firms and products, often for unmet medical needs and niche markets ignored by these larger companies. The downside for biopharmaceutical firms is, of course, that they will be conflated with big pharma in the public's mind, and the latter's image problems may well carry over to the biopharmaceutical industry.

If the positive contributions of biopharmaceuticals to healthcare are muddied by the poor image of big pharma, the industry is going to face a much steeper uphill battle in convincing the public and politicians that its products—which include some of the most expensive therapies—are worth the outlay and should not be subject to price controls. And company financing will become more difficult and regulations more strict. These trends may already be occurring.

Although the industry is currently held in esteem, the positive views of biopharmaceuticals and the industry may be tenuous and could easily be lost in the future. Let us not forget that many much-hyped classes of biopharmaceuticals (e.g., gene therapies, DNA vaccines, antisense therapeutics, immunotoxins, stem cells and vaccines for HIV) and even genomics-based drug discovery have generally not yet delivered useful products; and that other than the top five to seven surviving companies, very few biopharmaceutical companies have achieved, or will likely ever achieve, commercial success[21]. The CEO of Genentech (S. San Francisco, CA, USA), Arthur D. Levinson, recently noted, "Since 1976…the biotechnology industry has lost $90 billion in aggregate. I think it's the biggest money-losing industry of all time"[22]. Besides many people losing on their investments, many others have negative opinions about biopharmaceuticals, such as vaccines; many strongly oppose genetic engineering; and biopharmaceuticals can and have caused considerable harm (e.g., the recent withdrawal of Trasylol (aprotinin) purified from human blood plasma due to serious adverse events or the delays in implementing donor screening and viral inactivation processes, which resulted in thousands of hemophiliacs and other blood/plasma products recipients worldwide becoming infected with HIV or hepatitis C virus). 'Science held hostage', with biotechnology commercial progress halted by "negative public perception and policies" and "bio-gridlock," where the industry collapses due to failure to live up to expectations (e.g., cure diseases that will affect aging baby boomers) are two of four possible scenarios projected for 2020 by Schoemaker & Tomczyk[23]. The former may already be happening in Europe.

The deleterious consequences of miscommunication in relation to the term biopharmaceutical are not limited to public and political

perceptions. The industry itself remains in limbo while undefined. Already it is very difficult to find consistency in reports of industry revenue, employment and other basic parameters. Is worldwide biopharmaceutical industry annual revenue ~$50–70 billion, $80–100 billion or $650+ billion; and have biopharmaceuticals been around for centuries or just a few decades? Each of these is valid, depending on the definition used. With criteria often varying, including from year-to-year and analyst-to-analyst, and hardly ever stated, much of what has been written about the biopharmaceutical industry is highly suspect.

Last, but by no means least, with generic biopharmaceuticals starting to enter major markets and new laws to handle these needed in the United States and many other countries, even the simplest discussions about biogenerics will be very difficult or impossible if the most basic underlying concepts and terminology remain undefined. What is and is not a biopharmaceutical needs to be understood, and it is critical to begin to define and develop a consensus regarding this and related terms[24]. It is interesting to note that, when the subject is biogenerics, major proponents and users of business- or image-based definitions (e.g., BIO and PhRMA) readily switch to using either of the two product- and process-based definitions for what is biopharmaceutical. In fact, in the context of biogenerics, established (bio)pharmaceutical companies and their trade associations all vigorously assert the process-equals-product paradigm and the distinctive nature of biopharmaceuticals versus drugs, citing biopharmaceuticals' inherent manufacture-related biological complexity as the main reason why there should be no biogenerics approval mechanisms whatsoever[6,7,25]. Clearly, these organizations are adopting whatever terminology and definitions of biopharmaceutical best suit their particular message and audience.

Conclusions

The popular and scientific literatures have already been substantially polluted. Much of the diversity of definitions of biopharmaceutical may be attributed to the success of the industry, the desire to associate with the industry, the need for companies to get attention, associated nonstop media coverage (hype) and the failure of those (mis)using the term to define what they actually mean. Many authors, executives and companies persist in using the business- and image-based paradigms and definitions of biopharmaceutical in publications, presentations and press releases, reflecting their primary interests in business and public imagery. Much of this may be unintentional, simply following the pack, reflecting self-reinforcing (mis)use of terminology in the masses of press releases and corporate hype issued daily, and repeated in media coverage. This often involves spinning interesting or compelling stories for technologically illiterate audiences, or otherwise trying to get attention and maintain interest. As a buzzword, biopharmaceutical (and other terms prefixed with 'bio') attracts more attention and evokes more positive feelings and high-tech images than other terms, such as 'drug' and 'pharmaceutical'. Companies, trade organizations and authors often care more about attracting attention and exploiting positive images than proper use of terminology, and prefer to ignore potential damaging implications. Neither relevant trade associations nor many analysts, authors and companies now consistently use or recognize any useful term(s) for actual biotech-based biopharmaceuticals in their public communications. Despite being a well-established, high-tech industry with worldwide revenue expected to soon surpass $100 billion, the biopharmaceutical industry lacks a trade association solely devoted to its interests. Contrary to its origins, biopharmaceutical companies are now a distinct minority among BIO members.

Major proponents of business- or image-based definitions refuse to recognize biopharmaceuticals as a subset of pharmaceuticals, preferring to lump together and use the term to apply to all pharmaceuticals, associated R&D, companies and industry.

The industry will continue to mature and undergo dramatic changes in coming years as biogenerics enter the major markets and as the United States and other countries implement new laws and regulations for these. New and more specific terms concerning biopharmaceuticals will very soon be needed to accommodate discussions and public debates regarding similarities among agents and products and the regulation and marketing of biogenerics. The present terminological chaos at the most basic levels will confound and delay discussions and the implementation of regulations, the ability to reach consensus and the education of the healthcare industry and public concerning biogenerics. This could well be or, perhaps, already is being exploited by the established (innovator) biopharmaceutical firms threatened by biogenerics.

I strongly recommend that the scientific and industrial communities adopt biopharmaceutical and the broad biotechnology paradigm and/or definition (see **Box 1**). That is, biopharmaceutical products involve pharmaceuticals derived by biotechnology methods (from or using live organisms); a biopharmaceutical company is a company with these predominant among its products or activities; and the biopharmaceutical industry is the industry made up of only these companies. Other paradigms, particularly those that ignore the nature of products (science) and their manufacture (technology) are problematic and best avoided. Regulatory terms have specific, convoluted definitions and are best used only in this context. Those using biopharmaceutical to encompass all high-tech pharmaceuticals and related R&D, everything pharmaceutical and biotechnology (union, not intersection), and/or all pharmaceutical discovery and R&D services should realize that this conflicts with decades of prior use.

Major proponents of business- or image-based definitions refuse to recognize biopharmaceuticals as a subset of pharmaceuticals, preferring to lump together and use the term to apply to all pharmaceuticals, associated R&D, companies and industry. The upshot will be we will be left with no useable terms for what is actually biopharmaceutical. Obviously, business- and image-centric definitions are not appropriate for scientific or technical communications. Definitional dysfunction—where technical terms are divorced from their basis in science and technology and made ambiguous through doublespeak from industry and government leaders—can only cause problems, as it has for the agricultural/food biotechnology industry[26]. Already, biopharmaceutical paradigms, terms and definitions are in play or up for grabs, perhaps, by those with the best public relations effort.

With no established institutions taking an interest in terminology (other than co-opting it for their own purposes), this leaves these issues to concerned individuals and organizations. Along these lines, I have proposed the *US Biopharmacopeia Registry of Biopharmaceuticals* project to develop and propose new, integrated terminology, taxonomy and nomenclature systems and a registry for biopharmaceutical products, including biogenerics[24].

Use it or lose it! Those using biopharmaceutical, particularly those who view this as involving actual biotech, should use and define these terms (or make their use clear in context) in publications and presentations. Those concerned should express their views and educate

the scientific community and those in industry, trade associations and the media about what they consider proper and improper. Otherwise, vested interests will inevitably generalize, redefine and co-opt the core definitions of biopharmaceutical and the industry as they see fit.

1. Rader, R.A. *Biopharmaceutical Products in the US and European Markets*, 6th ed., 2 vols., (BioPlan Associates, Rockville, MD, 2007). <http://www.biopharma.com/>
2. Rader, R.A. *BioExecutive Intl.*, March, 60–65 (2005). <http://www.biopharma.com/BioExec_pt1.pdf>
3. Rader, R.A. *BioExecutive Intl.*, May, 42–49 (2005). <http://www.biopharma.com/BioExec_pt2.pdf>
4. Walsh, G. & Jefferis, R. *Nat. Biotechnol.* **24**, 1241–1252 (2006).
5. Akers, M.J. *BioProcess Intl.* **4**, 36–43 (2006).
6. Webster, C. *et al. BioPharm Intl.* July, 1 (2003).
7. Copmann, T. *et al. BioPharm Intl.* March, 14–24 (2001).
8. Scott, C. *BioProcess Intl.* **3**, 80 (2005). <http://www.bioprocessintl.com/default.asp?page=article_display&docid=61200511&display=full/>
9. Walsh, G. *Eur. J. Pharm. Sci.* **15**, 135–138 (2002).
10. Eby, R.J. *et al. The Story of Prevnar* (Pharmaceutical Research and Manufacturers Association, Washington, DC, 2008). <http://www.innovation.org/index.cfm/StoriesofInnovation/InnovatorStories/The_Story_of_Prevnar/>
11. http://www.bio.org/speeches/pubs/er/biotechguide.pdf
12. Ernst & Young. *Beyond Borders: Ernst & Young Global Biotechnology Report 2007* (Ernst & Young, New York, 2007).
13. DeVol, R. *et al. Biopharmaceutical Industry Contributions to State and US Economics* (Milken Institute, Santa Monica, CA, USA, 2004). <http://www.milkeninstitute.org/pdf/biopharma_report.pdf>
14. <http://www.burrillandco.com/burrill/pr_11713 02475/>
15. Ernst & Young. *Convergence: Ernst & Young's Biotechnology Industry Report*, Millennium Edition (Ernst & Young, New York, 2000).
16. PhRMA. *Introduction, 2005 Industry Profile* (PhRMA, Washington, DC, 2006). <http://members.phrma.org/publications/publications//2005-03-17.1144.pdf>
17. PhRMA. *Annual Report 2006–2007: Biopharmaceutical Inspiration*, (PhRMA, Washington, DC, 2007). <http://www.phrma.org/files/Annual_Report_2006_2007.pdf>
18. Myshko, D. *PharmaVOICE*, October, 40–44 (2006).
19. Frantz, S. *Nat. Rev. Drug Discov.* **5**, 977–979 (2006).
20. Simons, J. *Fortune*, 28 February 2006. <http://money.cnn.com/2006/02/27/news/companies/pluggedin_fortune/index.htm/>
21. Anonymous. *Seeking Alpha*. 9 January 2007. <http://seekingalpha.com/article/23696-the-biotech-industry-30-years-of-failure-starting-with-genentech/>
22. Chase, M. *The Wall Street Journal*, p. B1 (June 5, 2007). <http://online.wsj.com/public/article/SB118100806142024548-PFa4u2AiKfDHi25uT1jvHmdJZKA_20070612.html?mod=blogs>
23. Schoemaker, P. & Tomczyk, M.S. *BioProcess Intl.* **4**, 64 (2006).
24. Rader, R.A. *US BIOPHARMACOPEIA Registry of Biopharmaceutical Products* (Biotechnology Information Institute, Rockville, MD, USA, 2007). <http://www.biopharmacopeia.com/>
25. German Association of Research-Based Pharmaceutical Companies (VFA). *Biological/Biotechnological Generics Cannot Exist* (VFA, Berlin, Germany, July 25, 2006). <http://www.vfa.de/vfa-bio_en/vb_press/vb_positionen_en/biosimilars.html>
26. Miller, H.I. *Trends Biotechnol.* **5**, 56–59 (2007).
27. Rader, R.A. *BioProcess Intl.* **5**, 28–39 (March 2007). <http://www.biopharma.com/whatsabiogeneric_pt1.pdf>
28. Rader, R.A. *BioProcess Intl.* **5**, 20–27 (May 2007). <http://www.biopharma.com/whatsabiogeneric_pt2.pdf>
29. Katz, K.A. *Br. J. Dermatol.* **154**, 809–812 (2006).
30. <http://www.fda.gov/cber/faq.htm#3/>