

Commentary

Biopharmaceuticals and biotechnology medicines: an issue of nomenclature

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Abstract

Over the past two decades terms such as ‘biopharmaceuticals’ and ‘biotechnology medicines’ have crept into the pharmaceutical vocabulary. Such terms often have different meanings for different people and it is perhaps time that they were more formally defined. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

The term ‘biopharmaceutical’ is one which is now in common use, but what exactly does it refer to? Pharmaceutical dictionaries contain no entry for the term, and various books published on the subject (Lubinieccki and Vargo, 1994; Zito, 1997; Walsh, 1998; Grindley and Ogden, 1999) also lack concise or clear descriptions/definitions. The 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. In essence this equated the term ‘biopharmaceutical’ with therapeutic proteins synthesized in engineered biological systems. In contrast therapeutic proteins obtained by direct extraction from a naturally producing source are not considered biopharmaceuticals. Examples of the latter include insulin extracted from pancreatic tissue of slaughterhouse animals and clotting factors extracted directly from blood.

The above description has been largely satisfactory until relatively recently. Of the 84 ‘biopharmaceutical’ products approved for medical use by mid-2000 (Walsh, 2000), 74 entirely fit this description. The remaining ten products fit less completely and of these nine antibody based products are used for in vivo diagnostic as opposed to therapeutic purposes: OncoScint and ProstaScint (Cytogen), CEA-scan and Leuko-scan (Immunomedics), Indimacis 125 (Cis bio),

MyoScint (Centocor), Tecnemab K1 (Sorin), Verluma (Boehringer) and Humaspect (Organon Teknika). More significantly, nucleic acid based therapeutic agents used for antisense technology and gene therapy are now also usually referred to as ‘biopharmaceuticals’. Vitravene (ISIS Pharmaceuticals), for example, is an antisense oligonucleotide first approved for medical use in the USA in 1998. The Pharmaceutical Research and Manufacturers of America (PhRMA) report that their member companies have nine antisense and 25 gene therapy based products in clinical trials (PhRMA, 2001). In addition to the obvious fact that these are nucleic acid as opposed to protein based therapeutic products, antisense oligonucleotides are invariably manufactured not in/by a biological system, but by direct chemical synthesis.

2. Biopharmaceuticals, a definition

Given what is now considered in practice to be a biopharmaceutical, constructing a definition for this term on the basis of a single criterion (e.g. source, method of manufacture, use or structure) becomes an apparently impossible task. A combination of criteria must be employed, and the following formula of words is now proposed: “A biopharmaceutical is 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” (Table 1). By defining the method of manufacture in negative terms (i.e. “... produced by means other than direct extraction from

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Table 1
Summary of proposed definitions

Biopharmaceutical	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
Biotechnology medicine/product of pharmaceutical biotechnology	Any pharmaceutical product used for therapeutic or in vivo diagnostic purposes, which is produced in full or in part by either traditional or modern biotechnological means

native biological sources”), methods such as direct chemical synthesis of e.g. oligonucleotides as well as recombinant protein production and hybridoma based antibody production are all accommodated, while direct extraction from a native source material is obviously excluded.

3. Biotechnology medicines

‘Biotechnology products’, ‘biotechnology medicines’ and ‘products of pharmaceutical biotechnology’ are terms also now sometimes used (interchangeably) within the pharmaceutical sector. They are frequently used by, for example, PhRMA in relevant reports (PhRMA, 2001). Again, in the absence of a precise definition, the range of substances encompassed by these terms, and their relationship to the term ‘biopharmaceutical’, remains to be fully explored.

As used by PhRMA these terms encompass “only those products that involve recombinant DNA, monoclonal antibody/hybridoma, continuous cell lines, cellular therapy and gene therapy” (PhRMA, 2001). The current understanding/usage of the terms ‘biotechnology medicines/products’ or ‘products of pharmaceutical biotechnology’ thus appears to incorporate recombinant proteins, monoclonal antibodies, gene therapy, antisense products and cell/tissue therapy. Although overlapping with the term ‘biopharmaceutical’, these terms are somewhat broader, including not only information rich macromolecules (proteins and nucleic acids), but also whole cells/tissues. Several cell/tissue based products have gained regulatory approval over the last few years. These include ‘Apligraf’ from Novartis (graft skin approved in 1998 for treatment of venous leg ulcers) and ‘Carticel’ from Genzyme tissue repair (autologous cultured chondrocytes approved in 1997 for repair of cartilaginous defects).

Again it seems timely to explore if the terms ‘biotechnology medicines/products’ or ‘products of pharmaceutical biotechnology’ are appropriate to the profile of medicinal products currently included by default under these headings. Unlike the term ‘biopharmaceutical’, which was coined 15–20 years ago with a specific subset

of pharmaceutical products in mind, the term ‘biotechnology’ has a much longer and established history, as well as a far broader meaning. The European Federation of Biotechnology has defined the term as “the integration of natural sciences and engineering sciences in order to achieve the application of organisms, cells parts thereof and molecular analogues for products and services” (Oxford Dictionary, 1997). Additional definitions/explanations of biotechnology are to be found in a wide range of dictionaries and books but, while the exact wording may differ, all essentially refer to biotechnology as the use of biological systems (e.g. cells or tissues) or biological molecules (e.g. enzymes or antibodies) for/in the manufacture of products which are of applied/commercial significance. The term ‘biotechnology’ therefore refers equally to long established processes such as brewing and cheese making, as well as to modern processes such as recombinant DNA technology and hybridoma technology. It follows that terms such as ‘biotechnology medicines’ or ‘products of pharmaceutical biotechnology’ should refer to any pharmaceutical product produced (exclusively or in part) by biotechnological means. With the exception of antisense oligonucleotides synthesized chemically, the products currently included under these headings, in practice, fit (oligonucleotides synthesized enzymatically would also be included). However, these terms should equally apply to pharmaceutical products produced by more traditional biotechnological routes. Such products include non-recombinant therapeutic proteins, antibiotics extracted directly from a natural producer source or produced by semi-synthesis, and plant derived drugs, be they extracted directly from the plant, from cell cultures of the same plant, or from cell cultures exhibiting enhanced secondary metabolite metabolism due to either breeding or genetic engineering (Tables 1 and 2). Such products of ‘traditional’ biotechnology are currently in practice excluded from this definition.

It is proposed in this article that terms such as ‘biotechnology medicines’ or ‘products of pharmaceutical biotechnology’ should be used to describe all products produced in part or in full by biotechnological means, either traditional or modern (Tables 1 and 2).

4. Current regulatory terminology

The relationship between the terms and definitions proposed and formal regulatory terminology is of obvious importance. In this context ‘biologic(s)’ as well as ‘biological response modifier(s)’ are the relevant FDA terms while, in the European Union, the EMEA employs the term ‘biological medicinal product(s)’.

The FDA definition of a biologic (biological product) is: “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product

Table 2

The categorization of pharmaceutically significant biomolecules using the definitions provided in Table 1

Pharmaceutical product	Biopharmaceutical?	Biotechnology medicine?
Recombinant protein	Yes	Yes
Monoclonal antibody	Yes	Yes
Proteins obtained by direct extraction from native source (e.g. blood derived clotting factors and polyclonal antibodies)	No	Yes
Gene therapy products	Yes	Yes
Antisense oligonucleotides manufactured by direct chemical synthesis	Yes	No
Antisense oligonucleotides produced by enzymatic synthesis	Yes	Yes
Peptides manufactured by direct chemical synthesis	No	No
Peptides, if obtained by direct extraction from native producer source	No	Yes
Antibiotics obtained by direct extraction from native producer, or by semi-synthesis	No	Yes
Plant based products obtained by direct extraction from a native producer, or by semi-synthesis (e.g. taxol)	No	Yes
Cell/tissue based therapeutic agents	No	Yes

or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment or cure of a disease or condition of human beings” (FDA, 2001). The definition clearly does not encompass all medicines obtained from biological sources. Biologics traditionally encompassed products such as vaccines, various toxoids, skin test antigens, allergenic extracts, blood and blood products and certain in vitro test kits intended for testing biological products. This definition can also accommodate many recombinant products (e.g. recombinant blood products, vaccines, cytokines and monoclonal antibodies). If strictly applied however, it would appear to preclude some modern products of biotechnology such as manipulated, cultured or expanded human cells, tissue based therapeutics and most gene therapy based products (an exception presumably being gene therapy based vaccines). Such products are none the less regulated by the FDA’s Center for Biologics Evaluation and Research (CBER). Furthermore, while the majority of therapeutic proteins produced by recombinant means fall within the ambit of CBER, some do not. Recombinant hormones such as insulin, glucagon and human growth hormone are classified as drugs (as opposed

to biologics) and their regulation falls within the remit of the FDA’s Center for Drug Evaluation and Research (CDER). The protein product OP-1 (composed of a mixture of recombinant human osteogenic protein-1 and bovine collagen, which is implanted into bone fractures and promotes new bone formation), on the other hand is classified by the FDA as a medical device.

An additional pertinent term used in US regulatory circles is ‘biological response modifier’. A search of the FDA website failed to provide an exact definition for this term, although it was described on the site as “a generic term for hormones, neuroactive compounds and immunoreactive compounds that act at the cellular level; many are possible candidates for biotechnological production”. This is a somewhat loose description, making straightforward delineation of compounds fitting this category virtually impossible for non-regulatory experts. To add to the confusion, some industry sources do not seem to distinguish between the terms ‘biologic’ and ‘biological response modifier’. The US biotechnology industry association (BIO) for example appears to consider both terms to be synonymous, describing them as “substances that alter the growth or functioning of a cell. Includes

hormones and compounds that effect the nervous and immune systems” (BIO, 2001).

Within the European Union the regulatory authorities employ the term ‘biological medicinal product(s)’. The UK definition for a biological medicinal product originated in 1921 and “broadly refers to those products the potency or purity of which cannot be adequately tested by chemical or physical means, thus a biological test is necessary” (Ayling, 1984). In practice these products are usually derived from a biological source and include antibiotics, hormones and enzymes, blood products, vaccines, monoclonal antibodies and genetically engineered products (Ayling, 1984). A review of EU pharmaceutical directives (EU, 2001, Vol. 1) failed to unearth a precise definition of a biological medicinal product, with directives using (partially) descriptive language (e.g. “biological medicinal products such as vaccines, serums, toxins, allergen products and medicinal products derived from human blood or plasma”, directive 75/318/EEC). In practice the term ‘biological medicinal product’ within EU regulatory circles is taken to encompass genetically engineered and monoclonal antibody based products (EU, 2001, Vol. 4).

5. Conclusion

It becomes obvious from the above discussion that straightforward classification of many modern biotechnological based pharmaceutical products using traditional industry and/or regulatory terminology is a difficult task. The lack of precise definitions for broadly accepted categorizations of such pharmaceutical products merely reflects the speed at which the biotechnological-related pharmaceutical sector has grown over the last two decades. However, given that almost 100 such products have now gained regulatory approval, and approximately an additional 500 products are in clinical trials, the introduction of clear definitions has become desirable. As with any attempted classification system these definitions may not meet with universal acceptance. Some may argue that method of manufacture does not constitute a wholly appropriate basis of product classification. However, in the case of ‘biopharmaceuticals’ and ‘biotechnology medicines’, method of manufacture has become a de facto

instrument of industry based classification (e.g. insulin extracted directly from pancreatic tissue is not considered a biopharmaceutical whereas recombinant insulin is; monoclonal/engineered antibodies are considered biopharmaceuticals whereas polyclonal antibody preparations are not). Also, certainly in EU regulatory circles, method of manufacture is regarded as critical in shaping appropriate regulatory control (EU, 2001, Vol. 4).

The definitions proposed herein specifically attempt to reconcile the product profiles which have accumulated almost by default under the headings ‘biopharmaceutical’ and ‘biotechnology medicines’, with a more stringent and logical basis of categorization. On a broader issue, the discussion presented highlights the need for a more generalized debate on pharmaceutical nomenclature issues, particularly with regard to the exact meaning of the formal regulatory terms ‘biologic’ and ‘biological medicinal product’ in the context of the age of pharmaceutical biotechnology.

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