Why Biologics Should Be Called Something Else

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Drugs with selective effects on molecular processes in inflammation and chronic disease should not be called biologics, biologic drugs or other similar terms. Such terms are inaccurate, do not describe the mechanism of action, and obscure the risk of side-effects.

Increased understanding of molecular and immunological processes of disease and modern biotechnological production methods have led to a wide range of new drugs for the treatment of inflammatory diseases and cancer. Best known are different tumour necrosis factor alpha (TNF-α) inhibitors, including infliximab and etanercept. These agents selectively inhibit specific reactions in the inflammatory process in psoriasis, rheumatoid arthritis and Crohn's disease. New drugs targeting other steps in the inflammatory process are being introduced, including different anti-cytokine antibodies. In short, these drugs are monoclonal antibodies and fusion proteins, produced by the use of complicated and time-consuming DNA recombination technology.

These drugs are often referred to as "biological" drugs, so-called biological drugs (or agents), biologicals or biologics. These terms are used by leading medical journals, national drug authorities, and medical nomenclature agencies, in both the USA and the World Health Organization. There are, however, many definitions of the term biologics. A Google search (using the term "define: Biologics", on 21 July 2010) revealed conflicting definitions of biologics (Table I). Most definitions include a requirement that the agents are derived from biological material, as opposed to synthetically produced drugs. Some definitions include a statement that "biological" in this context also includes drugs produced by modern biotechnology, while other definitions include only those agents manufactured by biotechnology methods. Other definitions emphasize that the agents have specific biological effects, such as immune modulation. In short, the various definitions are based on the agents' origin, production method and/or mechanism of action.

Table I. *Selected definitions of the term biologics from a Google search (using the term "define: Biologics", 21 July 2010)*

- Biologics include a wide range of medicinal products, such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins created by biological processes (as distinguished from chemistry).
- An extremely complex drug, vaccine or antitoxin that is made from a living organism, or from products of a living organism; of or pertaining to biology; pertaining to a living or a once-living organism.
- A classification of products derived from living sources, such as humans, animals, bacteria and viruses. Vaccines, immune globulin, and anti-toxins are biologics.
- A biological product used in medicine.
- A new class of medications that specifically targets parts of the immune system.
- A new class of systemic therapies that contain proteins derived from living cells, as opposed to traditional pharmaceutical drugs that are made up of non-living chemicals.
- All viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, live microorganisms, killed microorganisms, and the antigenic or immunizing components of microorganisms intended for use in the diagnosis, treatment, or prevention of diseases.
- Protein- or peptide-based therapeutic (e.g. vaccines, monoclonal antibodies).
- A drug made from a living organism that is used in the diagnosis or treatment of disease.
- A virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other similar product used to prevent, treat or cure disease or injury.
- A therapeutic agent derived from living things.
- Agents of biological origin that are used to diagnose or treat disease.
- Encompass most drugs whose manufacture involves purification from biological sources such as human or animal tissue or body fluids, or micro-organisms, including those derived using biotechnology.

Biological products

Legally, there has long been a distinction between biological products and drugs (1, 2). In 1902, the US Congress passed a law on biological products, known as the *Biologics Control Act*, which included, among others, virus, serum, toxin, anti-toxins, vaccines, blood, blood components, allergenic products, and arsenic used in medicine. This is the original meaning of the term biologics. The law put particular emphasis on the production process. Four years later a law on drugs

was passed, referred to as the *Pure Food and Drug Act*, which focused more on product specification, testing and labelling. This distinction between biological products and drugs had several medical criteria. Biological products consisted of large molecules that were difficult to characterize structurally, and which could easily transfer infection and induce anaphylactic reactions.

With major scientific advances after World War II, however, the distinction between biological products and (synthetic) drugs became increasingly unclear (1–3). Using modern biotechnology, scientists were able to produce large molecules that were identical, or almost identical, to biologically-occurring molecules with specific biological effects. New concepts, such as biopharmaceuticals and biologic response modifiers, were introduced. Soon afterwards, the terms biological drugs, biologic drugs and biologics appeared in the scientific literature. Thus, the meaning of the term biologics was expanded and partially changed. From 1996, biological drugs were considered equivalent to conventional medicines in a regulatory context by US law (4).

For pharmaceutical companies, it was clear that the terms biological drugs, biologic drugs, biologicals and biologics would be more helpful than more complicated terms in marketing the drugs. For doctors (and authors of scientific articles), who need to express themselves concisely, it was convenient to have a short term. To underline the inadequacy of the terms, many enclosed them in quotation marks, which were subsequently omitted to make the terms easier to write.

With the great attention these agents have received in clinical medicine, most doctors would probably consider the term biologics to mean modern biotechnology-derived pharmaceutical agents. Some definitions of biologics include *only* such agents. The meaning of the term biologics has thus changed from the original definition.

Problematic terminology

The terms biologics and biologic drugs (and their variations) are problematic as they imply that the drugs are "mild" and "natural" and have few side-effects. However, the opposite is true. Drugs with selective immunomodulatory effects on inflammatory diseases should, in our opinion, be referred to as *selective immunomodulating drugs*. This term is more accurate, more precise and more understandable, at least for physicians. This term has been used in many scientific publications. In addition, patients and their families must be given medical information in an understandable, comprehensive and objective way and not be given a false impression of the drugs' origin, nature or risk of adverse events.

In Norway, Eli Nordal, a dermatologist, has suggested using the term *biologikum/biologika* in Norwegian, i.e. a direct translation of biologics and a parallel to *antibiotika* (antibiotics) and other types of pharmaceuticals (5). However, if it is considered important to emphasize the overall effects of drugs, as in antibiotics, antifungal agents and chemotherapy, the drugs should rather be called antibiologics, as they do not promote, but *suppress* biological processes.

We are not the only ones to address this problem of pharmacological nomenclature. In 2006 Kenneth Katz, an American dermatologist, wrote a critical editorial in the *British Journal of Dermatology* (1). In 2007 Edward Korwek, an American lawyer, published a comprehensive analysis of the concept of biologics in a legal journal (2). In 2008, in a long commentary in *Nature Biotechnology*, Ronald Rader pointed out that the confusion surrounding biopharmaceuticals (and similar terms) is far more than just semantics (3). However, these articles are rarely cited in scientific papers. By 2010, they had been cited six, five and three times, respectively.

There are many possible reasons for this lack of interest. Most doctors are more concerned about the therapeutic effects of the drugs than about semantics and details. Some doctors may be reluctant to criticize the producers of the drugs they prescribe. Many doctors are involved in testing and marketing pharmaceuticals and receive support for congress travel and research. It could also be the case that they disagree with, or are indifferent to or dismissive of, criticism of the term biologics.

Conclusion

The terms biologics, biologicals, biologic drugs, and biological drugs should be avoided. Instead, doctors and authors of scientific articles should rather say and write more explicitly what type of drug or drug they refer to, for example, infliximab, etanercept, TNF-α inhibitors, and monoclonal antibodies, sometimes by specifying the target. When a more comprehensive generic term is needed, we propose the term *selective immunomodulating drugs*.

Acknowledgements

The authors thank Erlend Hem for helpful comments.

This article is a translated version of an article in Norwegian published in *Tidsskrift for Den Norske Legeforening* (*Journal of the Norwegian Medical Association*) (6).

Conflicts of interest. Petter Gjersvik has received financial support for attending scientific congresses from pharmaceutical companies that manufacture and market selective immunomodulating drugs.

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