# Biopharmaceutical

A **biopharmaceutical**, also known as a **biologic(al) medical product**,[1] or **biologic**, is any pharmaceutical drug product manufactured in, extracted from, or semisynthesized from biological sources. Different from totally synthesized pharmaceuticals, they include vaccines, whole blood, blood components, allergenics, somatic cells, gene therapies, tissues, recombinant therapeutic protein, and living medicines used in cell therapy. Biologics can be composed of sugars, proteins, nucleic acids, or complex combinations of these substances, or may be living cells or tissues. They (or their precursors or components) are isolated from living sources—human, animal, plant, fungal, or microbial. They can be used in both human and animal medicine.[2][3]

Terminology surrounding biopharmaceuticals varies between groups and entities, with different terms referring to different subsets of therapeutics within the general biopharmaceutical category. Some regulatory agencies use the terms **biological medicinal products** or **therapeutic biological product** to refer specifically to engineered macromolecular products like protein- and nucleic acid-based drugs, distinguishing them from products like blood, blood components, or vaccines, which are usually extracted directly from a biological source.[4][5][6] Specialty drugs, a recent classification of pharmaceuticals, are high-cost drugs that are often biologics.[7][8][9] The European Medicines Agency uses the term *advanced therapy medicinal products* (ATMPs) for medicines for human use that are "based on genes, cells, or tissue engineering",[10] including gene therapy medicines, somatic-cell therapy medicines, tissue-engineered medicines, and combinations thereof.[11] Within EMA contexts, the term *advanced therapies* refers specifically to ATMPs, although that term is rather nonspecific outside those contexts.

Gene-based and cellular biologics, for example, often are at the forefront of biomedicine and biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.[12]

In some jurisdictions, biologics are regulated via different pathways from other small molecule drugs and medical devices.[13]

**Biopharmaceutics** is pharmaceutics that works with biopharmaceuticals. **Biopharmacology** is the branch of pharmacology that studies biopharmaceuticals.

## Contents



## Major classes

### Extracted from living systems

Some of the oldest forms of biologics are extracted from the bodies of animals, and other humans especially. Important biologics include:

- Whole blood and other blood components
- Organ transplantation and tissue transplants
- Stem-cell therapy
- Antibodies for passive immunity (e.g., to treat a virus infection)
- Human reproductive cells
- Human breast milk
- Fecal microbiota

Blood plasma is a type of biopharmaceutical directly extracted from living systems.

Some biologics that were previously extracted from animals, such as insulin, are now more commonly produced by recombinant DNA.

### Produced by recombinant DNA

As indicated the term "biologics" can be used to refer to a wide range of biological products in medicine. However, in most cases, the term "biologics" is used more restrictively for a class of therapeutics (either approved or in development) that are produced by means of biological processes involving recombinant DNA technology. These medications are usually one of three types:

1. Substances that are (nearly) identical to the body's own key signalling proteins. Examples are the blood-production stimulating protein erythropoetin, or the growth-stimulating hormone named (simply) "growth hormone" or biosynthetic human insulin and its analogues.
2. Monoclonal antibodies. These are similar to the antibodies that the human immune system uses to fight off bacteria and viruses, but they are "custom-designed" (using hybridoma technology or other methods) and can therefore be made specifically to counteract or block any given substance in the body, or to target any specific cell type; examples of such monoclonal antibodies for use in various diseases are given in the table below.
3. Receptor constructs (fusion proteins), usually based on a naturally occurring receptor linked to the immunoglobulin frame. In this case, the receptor provides the construct with detailed specificity, whereas the immunoglobulin-structure imparts stability and other useful features in terms of pharmacology. Some examples are listed in the table below.

Biologics as a class of medications in this narrower sense have had a profound impact on many medical fields, primarily rheumatology and oncology, but also cardiology, dermatology, gastroenterology, neurology, and others. In most of these disciplines, biologics have added major therapeutic options for the treatment of many diseases, including some for which no effective therapies were available, and others where previously existing therapies were clearly inadequate. However, the advent of biologic therapeutics has also raised complex regulatory issues (see below), and significant pharmacoeconomic concerns, because the cost for biologic therapies has been dramatically higher than for conventional (pharmacological) medications. This factor has been particularly relevant since many biological medications are used for the treatment of chronic diseases, such as rheumatoid arthritis or inflammatory bowel disease, or for the treatment of otherwise untreatable cancer during the remainder of life. The cost of treatment with a typical monoclonal antibody therapy for relatively common indications is generally in the range of €7,000–14,000 per patient per year.

Older patients who receive biologic therapy for diseases such as rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis are at increased risk for life-threatening infection, adverse cardiovascular events, and malignancy.[14]

The first such substance approved for therapeutic use was biosynthetic "human" insulin made via recombinant DNA. Sometimes referred to as rHI, under the trade name Humulin, was developed by Genentech, but licensed to Eli Lilly and Company, who manufactured and marketed it starting in 1982.

Major kinds of biopharmaceuticals include:

- Blood factors (Factor VIII and Factor IX)
- Thrombolytic agents (tissue plasminogen activator)
- Hormones (insulin, glucagon, growth hormone, gonadotrophins)
- Haematopoietic growth factors (Erythropoietin, colony-stimulating factors)
- Interferons (Interferons-α, -β, -γ)
- Interleukin-based products (Interleukin-2)
- Vaccines (Hepatitis B surface antigen)
- Monoclonal antibodies (Various)
- Additional products (tumour necrosis factor, therapeutic enzymes)

Research and development investment in new medicines by the biopharmaceutical industry stood at $65.2 billion in 2008.[15] A few examples of biologics made with recombinant DNA technology include:

| USAN/INN | Trade name | Indication | Technology | Mechanism of action |
|---|---|---|---|---|
| abatacept | Orencia | rheumatoid arthritis | immunoglobin CTLA-4 fusion protein | T-cell deactivation |
| adalimumab | Humira | rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease | monoclonal antibody | TNF antagonist |
| alefacept | Amevive | chronic plaque psoriasis | immunoglobin G1 fusion protein | incompletely characterized |
| erythropoietin | Epogen | anemia arising from cancer chemotherapy, chronic renal failure, etc. | recombinant protein | stimulation of red blood cell production |
| etanercept | Enbrel | rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis | recombinant human TNF-receptor fusion protein | TNF antagonist |
| infliximab | Remicade | rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease | monoclonal antibody | TNF antagonist |
| trastuzumab | Herceptin | breast cancer | humanized monoclonal antibody | HER2/neu (erbB2) antagonist |
| ustekinumab | Stelara | psoriasis | humanized monoclonal antibody | IL-12 and IL-23 antagonist |
| denileukin diftitox | Ontak | cutaneous T-cell lymphoma (CTCL) | Diphtheria toxin engineered protein combining Interleukin-2 and Diphtheria toxin | Interleukin-2 receptor binder |
| golimumab | Simponi | rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis | monoclonal antibody | TNF antagonist |

## Vaccines

Many vaccines are grown in tissue cultures.

## Gene therapy

Viral gene therapy involves artificially manipulating a virus to include a desirable piece of genetic material.

# Biosimilars

With the expiration of numerous patents for blockbuster biologics between 2012 and 2019, the interest in biosimilar production, i.e., follow-on biologics, has increased.[16] Compared to small molecules that consist of chemically identical active ingredients, biologics are vastly more complex and consist of a multitude of subspecies. Due to their heterogeneity and the high process sensitivity, originators and follow-on biosimilars will exhibit variability in specific variants over time, however the safety and clinical performance of both originator and biosimilar biopharmaceuticals must remain equivalent throughout their lifecycle.[17][18] Process variations are monitored by modern analytical tools (e.g., liquid chromatography, immunoassays, mass spectrometry, etc.) and describe a unique design space for each biologic.

Thus, biosimilars require a different regulatory framework compared to small-molecule generics. Legislation in the 21st century has addressed this by recognizing an intermediate ground of testing for biosimilars. The filing pathway requires more testing than for small-molecule generics, but less testing than for registering completely new therapeutics.[19]

In 2003, the European Medicines Agency introduced an adapted pathway for biosimilars, termed *similar biological medicinal products*. This pathway is based on a thorough demonstration of "comparability" of the "similar" product to an existing approved product.[20] Within the United States, the Patient Protection and Affordable Care Act of 2010 created an abbreviated approval pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed reference biological product.[19][21] A major hope linked to the introduction of biosimilars is a reduction of costs to the patients and the healthcare system.[16]

# Commercialization

When a new biopharmaceutical is developed, the company will typically apply for a patent, which is a grant for exclusive manufacturing rights. This is the primary means by which the developer of the drug can recover the investment cost for development of the biopharmaceutical. The patent laws in the United States and Europe differ somewhat on the requirements for a patent, with the European requirements perceived as more difficult to satisfy. The total number of patents granted for biopharmaceuticals has risen significantly since the 1970s. In 1978 the total patents granted was 30. This had climbed to 15,600 in 1995, and by 2001 there were 34,527 patent applications.[22] In 2012 the US had the highest IP (Intellectual Property) generation within the biopharmaceutical industry, generating 37 percent of the total number of granted patents worldwide; however, there is still a large margin for growth and innovation within the industry. Revisions to the current IP system to ensure greater reliability for R&D (research and development) investments is a prominent topic of debate in the US as well.[23] Blood products and other human-derived biologics such as breast milk have highly regulated or very hard-to-access markets; therefore, customers generally face a supply shortage for these products. Institutions housing these biologics, designated as 'banks', often cannot distribute their product to customers effectively.[24] Conversely, banks for reproductive cells are much more widespread and available due to the ease with which spermatozoa and egg cells can be used for fertility treatment.[25]

# Large-scale production

Biopharmaceuticals may be produced from microbial cells (e.g., recombinant *E. coli* or yeast cultures), mammalian cell lines (see Cell culture) and plant cell cultures (see Plant tissue culture) and moss plants in bioreactors of various configurations, including photo-bioreactors.[26] Important issues of concern are cost of production (low-volume, high-purity products are desirable) and microbial contamination (by bacteria, viruses, mycoplasma). Alternative platforms of production which are being tested include whole plants (plant-made pharmaceuticals).

## Transgenics

A potentially controversial method of producing biopharmaceuticals involves transgenic organisms, particularly plants and animals that have been genetically modified to produce drugs. This production is a significant risk for the investor, due to production failure or scrutiny from regulatory bodies based on perceived risks and ethical issues. Biopharmaceutical crops also represent a risk of cross-contamination with non-engineered crops, or crops engineered for non-medical purposes.

One potential approach to this technology is the creation of a transgenic mammal that can produce the biopharmaceutical in its milk, blood, or urine. Once an animal is produced, typically using the pronuclear microinjection method, it becomes efficacious to use cloning technology to create additional offspring that carry the favorable modified genome.[27] The first such drug manufactured from the milk of a genetically modified goat was ATryn, but marketing permission was blocked by the European Medicines Agency in February 2006.[28] This decision was reversed in June 2006 and approval was given August 2006.[29]

# Regulation

## European Union

In the European Union, a **biological medicinal product**[30] is one of the active substance(s) produced from or extracted from a biological (living) system, and requires, in addition to physico-chemical testing, biological testing for full characterisation. The characterisation of a biological medicinal product is a combination of testing the active substance and the final medicinal product together with the production process and its control. For example:

- Production process – it can be derived from biotechnology or from other technologies. It may be prepared using more conventional techniques as is the case for blood or plasma-derived products and a number of vaccines.
- Active substance – consisting of entire microorganisms, mammalian cells, nucleic acids, proteinaceous, or polysaccharide components originating from a microbial, animal, human, or plant source.
- Mode of action – therapeutic and immunological medicinal products, gene transfer materials, or cell therapy materials.

## United States

In the United States, biologics are licensed through the biologics license application (BLA), then submitted to and regulated by the FDA's Center for Biologics Evaluation and Research (CBER) whereas drugs are regulated by the Center for Drug Evaluation and Research. Approval may require several years of clinical trials, including trials with human volunteers. Even after the drug is released, it will still be monitored for performance and

safety risks. The manufacture process must satisfy the FDA's "Good Manufacturing Practices", which are typically manufactured in a cleanroom environment with strict limits on the amount of airborne particles and other microbial contaminants that may alter the efficacy of the drug.[31]

### Canada

In Canada, biologics (and radiopharmaceuticals) are reviewed through the Biologics and Genetic Therapies Directorate within Health Canada.[32]

## See also

- Antibody-drug conjugate
- Genetic engineering
- Host cell protein
- List of pharmaceutical companies
- List of recombinant proteins
- Nanomedicine

## References


1. "Biological" (https://www.lexico.com/en/definition/biological). *Oxford Dictionaries*.
2. Walsh, Gary (2018). "Biopharmaceutical benchmarks 2018" (http://www.nature.com/articles/nbt.4305). *Nature Biotechnology*. **36** (12): 1136–1145. doi:10.1038/nbt.4305 (https://doi.org/10.1038%2Fnbt.4305). ISSN 1087-0156 (https://www.worldcat.org/issn/1087-0156).
3. Ryan, Michael P.; Walsh, Gary (2012). "Veterinary-based biopharmaceuticals" (https://linkinghub.elsevier.com/retrieve/pii/S0167779912001357). *Trends in Biotechnology*. **30** (12): 615–620. doi:10.1016/j.tibtech.2012.08.005 (https://doi.org/10.1016%2Fj.tibtech.2012.08.005).
4. Rader RA (July 2008). "(Re)defining biopharmaceutical" (https://doi.org/10.1038%2Fnbt0708-743). *Nature Biotechnology*. **26** (7): 743–51. doi:10.1038/nbt0708-743 (https://doi.org/10.1038%2Fnbt0708-743). PMID 18612293 (https://pubmed.ncbi.nlm.nih.gov/18612293).
5. "Drugs@FDA Glossary of Terms" (https://www.fda.gov/AboutFDA/Transparency/Basics/ucm194516.htm). Food and Drug Administration. 2 Feb 2012. Retrieved 8 April 2014.
6. Walsh G (2003). *Biopharmaceuticals: Biochemistry and Biotechnology, Second Edition*. John Wiley & Sons Ltd. ISBN 978-0-470-84326-0.
7. Gleason PP, Alexander GC, Starner CI, Ritter ST, Van Houten HK, Gunderson BW, Shah ND (September 2013). "Health plan utilization and costs of specialty drugs within 4 chronic conditions" (https://www.jmcp.org/doi/pdf/10.18553/jmcp.2013.19.7.542). *Journal of Managed Care Pharmacy*. **19** (7): 542–8. doi:10.18553/jmcp.2013.19.7.542 (https://doi.org/10.18553%2Fjmcp.2013.19.7.542). PMID 23964615 (https://pubmed.ncbi.nlm.nih.gov/23964615).
8. Thomas, Kate; Pollack, Andrew (15 July 2015). "Specialty Pharmacies Proliferate, Along With Questions" (https://www.nytimes.com/2015/07/16/business/specialty-pharmacies-proliferate-along-with-questions.html). *New York Times*. Sinking Spring, Pa. Retrieved 5 October 2015.
9. Murphy CO. "Specialty Pharmacy Managed Care Strategies" (https://courses.washington.edu/pharm542/Week4/slidesSpecialty%20Pharmacy%20%20Managed%20Care%20Strategies%200410.pdf) (PDF). Retrieved 24 September 2015.
10. European Medicines Agency, "tooltip definition of advanced therapy medicinal products", *Committee for Advanced Therapies (CAT)* (http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000266.jsp), retrieved 2017-05-15.
11. European Medicines Agency, *Advanced therapy medicinal products: Overview* (https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview), retrieved 2017-05-15.
12. Center for Biologics Evaluation and Research (2010-04-01). "What is a biological product?" (https://www.fda.gov/AboutFDA/Transparency/Basics/ucm194516.htm). U.S. Food and Drug Administration. Retrieved 2014-02-09.
13. United States Food and Drug Administration (August 2008). "Supplemental applications proposing labeling changes for approved drugs, biologics, and medical devices. Final rule" (https://www.govinfo.gov/content/pkg/FR-2008-08-22/pdf/E8-19572.pdf) (PDF). *Federal Register*. **73** (164): 49603–10. PMID 18958946 (https://pubmed.ncbi.nlm.nih.gov/18958946).
14. Kerr LD (2010). "The use of biologic agents in the geriatric population" (https://www.rheumatologynetwork.com/view/use-biologic-agents-geriatric-population). *J Musculoskel Med*. **27**: 175–180.
15. BriskFox Financial. "Biopharmaceutical sector sees rising R&D despite credit crunch, finds analysis" (http://www.briskfox.com/open/years/2009_q1/do_v_c44751.php). Retrieved 2009-03-11.
16. Calo-Fernández B, Martínez-Hurtado JL (December 2012). "Biosimilars: company strategies to capture value from the biologics market" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3816668). *Pharmaceuticals*. **5** (12): 1393–408. doi:10.3390/ph5121393 (https://doi.org/10.3390%2Fph5121393). PMC 3816668 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3816668). PMID 24281342 (https://pubmed.ncbi.nlm.nih.gov/24281342).
17. Schiestl M, Stangler T, Torella C, Cepeljnik T, Toll H, Grau R (April 2011). "Acceptable changes in quality attributes of glycosylated biopharmaceuticals" (https://doi.org/10.1038%2Fnbt.1839). *Nature Biotechnology*. **29** (4): 310–2. doi:10.1038/nbt.1839 (https://doi.org/10.1038%2Fnbt.1839). PMID 21478841 (https://pubmed.ncbi.nlm.nih.gov/21478841).
18. Lamanna WC, Holzmann J, Cohen HP, Guo X, Schweigler M, Stangler T, Seidl A, Schiestl M (April 2018). "Maintaining consistent quality and clinical performance of biopharmaceuticals" (https://doi.org/10.1080%2F14712598.2018.1421169). *Expert Opinion on Biological Therapy*. **18** (4): 369–379. doi:10.1080/14712598.2018.1421169 (https://doi.org/10.1080%2F14712598.2018.1421169). PMID 29285958 (https://pubmed.ncbi.nlm.nih.gov/29285958).
19. Nick C (2012). "The US Biosimilars Act: Challenges Facing Regulatory Approval" (https://www.researchgate.net/publication/297828539_The_US_biosimilars_act_Challenges_facing_regulatory_approval). *Pharm Med*. **26** (3): 145–152. doi:10.1007/bf03262388 (https://doi.org/10.1007%2Fbf03262388). Retrieved 2012-06-13.
20. EMA (2008-10-30). "Questions and answers on biosimilar medicines (similar biological medicinal products)" (http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf) (PDF). European Medicines Agency. Retrieved 2014-10-11.
21. 75 FR 61497 (https://www.federalregister.gov/citation/75-FR-61497); United States Food and Drug Administration (2010-10-05). "Approval Pathway for Biosimilar and Interchangeable Biological Products" (https://www.govinfo.gov/content/pkg/FR-2010-10-05/pdf/2010-24853.pdf) (PDF). *Public Hearing; Request for Comments*.
22. Foster, Luke. "Patenting in the Biopharmaceutical Industry—comparing the US with Europe" (https://web.archive.org/web/20060316164416/http://scientific.thomson.com/free/ipmatters/pii/8180019/). Archived from the original (http://scientific.thomson.com/free/ipmatters/pii/8180019/) on 2006-03-16. Retrieved 2006-06-23.
23. "Growth and Policies Behind Biopharmaceutical Innovation" (https://www.phrma.org/press-release/new-report-reveals-growth-trajectories-and-top-policy-factors-affecting-biopharmaceutical-innovation-and-growth). *phrma.org*. PhRMA. Retrieved 11 April 2018.
24. Carlyle, Erin. "The Guys Who Trade Your Blood For Profit" (https://www.forbes.com/sites/erincarlyle/2012/06/27/blood-money-the-guys-who-trade-your-blood-for-profit/#2ec937e46884). Retrieved 2016-09-29.
25. "Sperm Donors Australia | Donate Sperm" (https://www.spermdonorsaustralia.com.au/). *spermdonorsaustralia.com.au*. Retrieved 2016-09-29.
26. Decker EL, Reski R (January 2008). "Current achievements in the production of complex biopharmaceuticals with moss bioreactors". *Bioprocess and Biosystems Engineering*. **31** (1): 3–9. doi:10.1007/s00449-007-0151-y (https://doi.org/10.1007%2Fs00449-007-0151-y). PMID 17701058 (https://pubmed.ncbi.nlm.nih.gov/17701058).

27. Dove A (October 2000). "Milking the genome for profit". *Nature Biotechnology*. **18** (10): 1045–8. doi:10.1038/80231 (https://doi.org/10.1038%2F80231). PMID 11017040 (https://pubmed.ncbi.nlm.nih.gov/11017040).
28. Phillip B. C. Jones. "European Regulators Curdle Plans for Goat Milk Human Antithrombin" (https://library.wur.nl/WebQuery/file/cogem/cogem_t44fd4747_001.pdf) (PDF). Retrieved 2006-06-23.
29. "Go-ahead for 'pharmed' goat drug" (http://news.bbc.co.uk/2/hi/science/nature/5041298.stm). *BBC News*. 2006-06-02. Retrieved 2006-10-25.
30. The Commission of the European Communities (2003-06-25). "Commission Directive 2003/63/EC amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use" (https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2003_63/dir_2003_63_en.pdf) (PDF). *Official Journal of the European Union*. p. L 159/62.
31. Kingham R, Klasa G, Carver K (2014). *Key Regulatory Guidelines for the Development of Biologics in the United States and Europe* (https://www.cov.com/-/media/files/corporate/publications/2013/10/chapter4_key_regulatory_guidlines_for_the_development_of_biologics_in_the_united_states_and_europe.pdf) (PDF). John Wiley & Sons, Inc. pp. 75–88. Retrieved 11 April 2018.
32. "Biologics and Genetic Therapies Directorate" (https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies/health-products-food-branch/biologics-genetic-therapies-directorate.html). Retrieved 2019-01-20.

## External links

- Biological Products (https://meshb.nlm.nih.gov/record/ui?name=Biological%20Products) at the US National Library of Medicine Medical Subject Headings (MeSH)
- Debbie Strickland (2007). "Guide to Biotechnology" (https://web.archive.org/web/20070927222631/http://bio.org/speeches/pubs/er/BiotechGuide.pdf) (PDF). Biotechnology Industry Organization (BIO). Archived from the original (http://bio.org/speeches/pubs/er/BiotechGuide.pdf) (PDF) on 2007-09-27. Retrieved 2007-12-17.
- Timothy B. Coan; Ron Ellis (2001-06-01). "Report for USA Specialty Pharmaceuticals: Generic Biologics: The Next Frontier" (http://www.cptech.org/ip/health/biotech/genbio062001.pdf) (PDF). Consumer Project on Technology. Retrieved 2007-12-17.
- "About biologics" (https://web.archive.org/web/20060101134831/http://www.psoriasis.org/treatment/psoriasis/biologics/about.php). National Psoriasis Foundation. 2006-11-01. Archived from the original (http://www.psoriasis.org/treatment/psoriasis/biologics/about.php) on 2006-01-01. Retrieved 2007-12-17.