Chapter 1

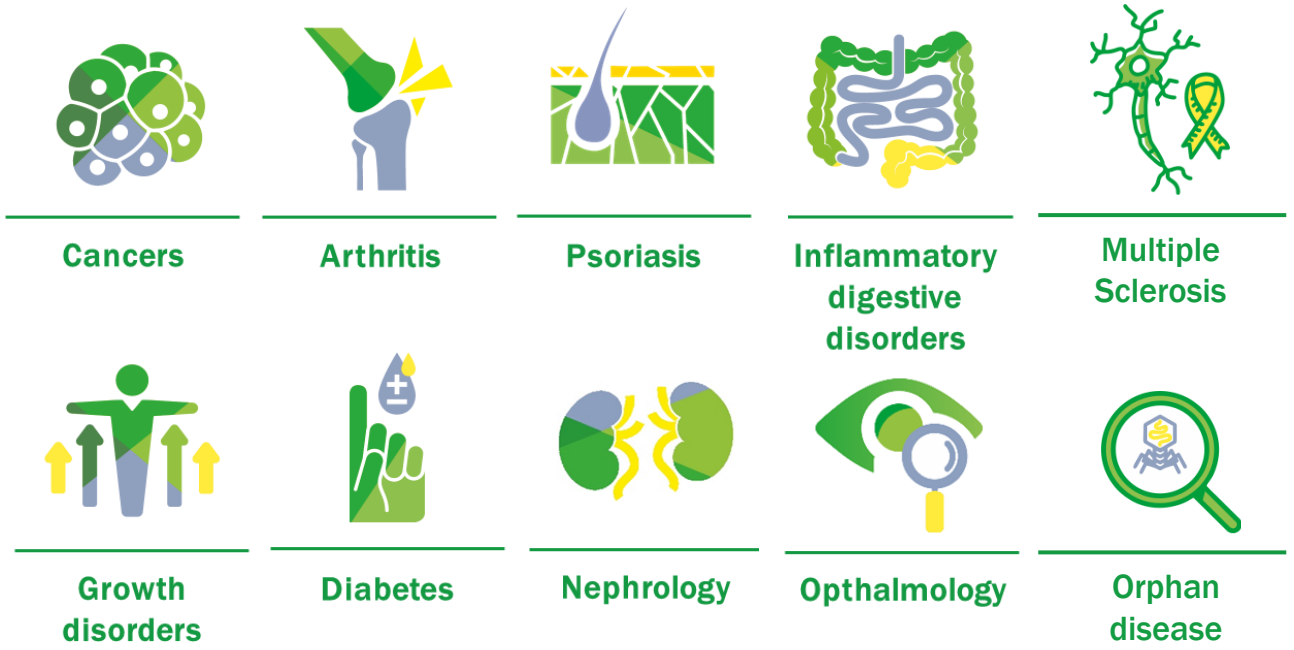
# The era of biological medicines

> Since their first use in the 1980s, biological medicines (including biosimilar medicines) have grown to become an indispensable tool in modern medicine. Worldwide, millions of patients have already benefited from approved biological medicines, but what exactly are they, and how are they produced?[1,2]

**References: 1.** Kinch MS. *Drug Discov Today* 2015;20:393–8; **2.** European Commission. Consensus Information Paper. Accessed February 2020.

# Biological medicines[1] have revolutionized the treatment of many disabling and life-threatening diseasesd

- Biological medicines:
  - include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapies, tissues, and recombinant therapeutic proteins
  - are highly specific and targeted medicines
  - help to treat or prevent many rare and severe diseases, including:




**Biological medicines are developed based on a deep understanding of the disease biology**

**References: 1.** FDA. Vaccines, Blood & Biologics. Accessed February 2020.

# Since the 1980s, biological medicines have become an indispensable tool in modern medicine[2]

- Biological medicines contain one or more active substances made by or derived from a biological source[1]

**Monoclonal antibody** receives first FDA approval[3]

**Europe** approves **first** biosimilar medicine[5]

**Europe** approves **first** biosimilar medicine for **breast cancer treatment**[7]

**Europe** and **the U.S** accept **first** biosimilar medicine application for **multiple sclerosis**[9] and

1980s | 1986 | 1998 | 2006 | 2014 | 2017 | 2021 | 2022 | 2023

The first biological medicinal products produced by **DNA recombinant techniques** were approved[2]

First biological medicine for **rheumatoid arthritis** is introduced[4]

By 2014, **over 245 biological medicines** had been approved in the EU and US, representing 166 different active substances[6]

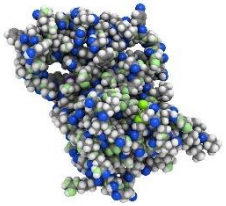
**Europe and the U.S** approve **first** biosimilar medicine in **ophthalmology**[8]

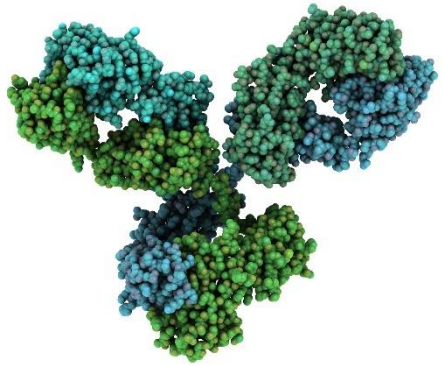
**Europe** authorises the first biosimilar in an **orphan** indication[10]

**Biological medicines are an integral and indispensable part of modern medicine[6]**

**References: 1.** EMA. Biosimilar medicines. Accessed March 2020; **2.** Kinch MS. *Drug Discov Today* 2015;20:393–8; **3.** Liu JKH. *Ann Med Surg (Lond)* 2014;3:113–6; **4.** De Keyser F. *Curr Rheumatol Rev* 2011;7:77–87; **5.** Medicines for Europe. Factsheet on Biosimilar Medicines 2016. Accessed February 2020; **6.** Walsh, G. *Nat Biotechnol* 2014;32: 992–1000; **7.** EMA rituximab biosimilar EPAR Truxima | European Medicines Agency (europa.eu); **8.** Byooviz (ranibizumab): EU approval - Byooviz (ranibizumab-nuna) FDA approval. Accessed October 2021; 9. https://www.biopharma-reporter.com/Article/2022/07/20/EMA-accepts-application-for-Polpharma-Biologics-MS-biosimilar-natalizumab. Accessed July 2022; 10. https://www.ema.europa.eu/en/medicines/human/EPAR/epysqli Accessed Sept 2023

# Biological medicines are predominantly larger and more complex than chemically synthesized medicines





| | Chemically synthesized medicine | Growth hormone | Antibody |
|---|---|---|---|
| Type of molecule | Small molecule | Protein (without sugars) | Glycoprotein (variable sugars) |
| Synthesis | Chemical | Bacterial | Mammalian |
| Uniformity | Single substance | Single main substance | Mixture of variants |
| Size | 21 atoms (aspirin) | 3000 atoms (HGH) | >20,000 atoms (mAb) |

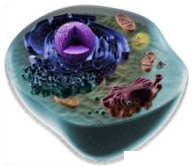
**The complexity of biological medicines is such that they cannot usually be synthesized by conventional methods**

**Abbreviations:** HGH, human growth hormone; mAb, monoclonal antibody.

**References:** International Alliance of Patients' Organizations. Briefing paper on Biological and Biosimilar Medicines 2013. Accessed February 2020.

# Producing biological medicines tends to be more complex than producing chemically derived medicines[1,2]

**1. Cell culture**
Clone DNA into host cells



Select cell clone that produces the highest quality protein

**2. Fermentation**
Grow a large batch of cells

**3. Harvesting**

Release protein from cells

Separate cells from liquid medium

**4. Purification**
Multistep process targets the final protein

**5. Formulation**
Protein formulated into stable, therapeutic product

Product filled into devices for administration

**Finished medicinal product**

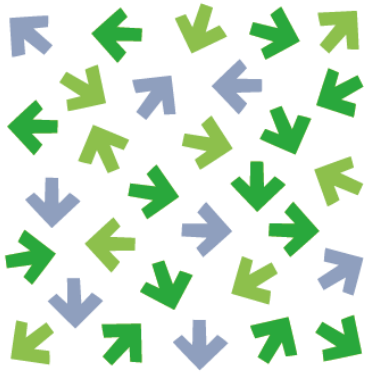
Figure adapted from Apobiologix[3]

**The inherent variability of living organisms and the manufacturing process result in the biological medicine displaying a certain degree of variability ('microheterogeneity')[1]**

**References: 1.** WHO. Annex 3: Guidelines for assuring quality of pharmaceutical and biological products prepared by recombinant DNA technology. 1991. Accessed March 2020; **2.** EC/EMA. Biosimilars in the EU – Information guide for Healthcare Professionals 2017. Accessed March 2020; **3.** Apobiologix. Manufacturing. Accessed March 2020.

# A biological medicine is a mixture of closely related variants of the same protein[1]

- The living organisms used to make biological medicines are **naturally variable**[2]
- An inherent degree of minor variability (‘**microheterogeneity**’) is thus normally present in biological medicines[2]
- Microheterogeneity is also present **within and/or between batches** of the same biological medicine[2]
- The degree of variability **must fall within a range** agreed upon by the health authority to ensure consistent safety and efficacy[2]
- **Strict controls** are always in place during manufacturing to ensure batch-to-batch consistency, and that the differences do not affect safety or efficacy[1]



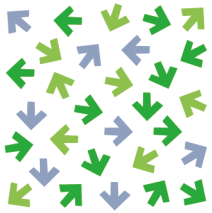
**Strict controls ensure safe and efficacious biological medicines[1]**

**References: 1.** EC/EMA. Biosimilars in the EU – Information guide for Healthcare Professionals 2017. Accessed March 2020; **2.** Woodcock J, *et al. Nat Rev Drug Discov* 2007;6:437–442.

# Summary: The era of biological medicines

Biological medicines contain one or more active substances **made by or derived from a biological** source[1]

The complexity of biological medicines is such that they **cannot usually be synthesized** by conventional methods[2]



The **variability** of living organisms contributes to **microheterogeneity**[3]

Microheterogeneity is normal, and seen **within or between different batches** of the same biological product[4]

**Strict controls** during manufacturing consistently **ensures safe and effective** biological medicines[4]

Biological medicines have grown to become an **indispensable therapeutic tool** in modern medicine[5]

**References: 1**. EMA**.** Biosimilar medicines. Accessed March 2020; **2.** International Alliance of Patients' Organizations. Briefing paper on Biological and Biosimilar Medicines 2013. Accessed March 2020; **3.** Gudat U. *Pharma Horizon* 2016;1:35–38; **4.** EC/EMA. Biosimilars in the EU – Information guide for Healthcare Professionals 2017. Accessed March 2020; **5.** Kinch MS. *Drug Discov Today* 2015;20:393–8.