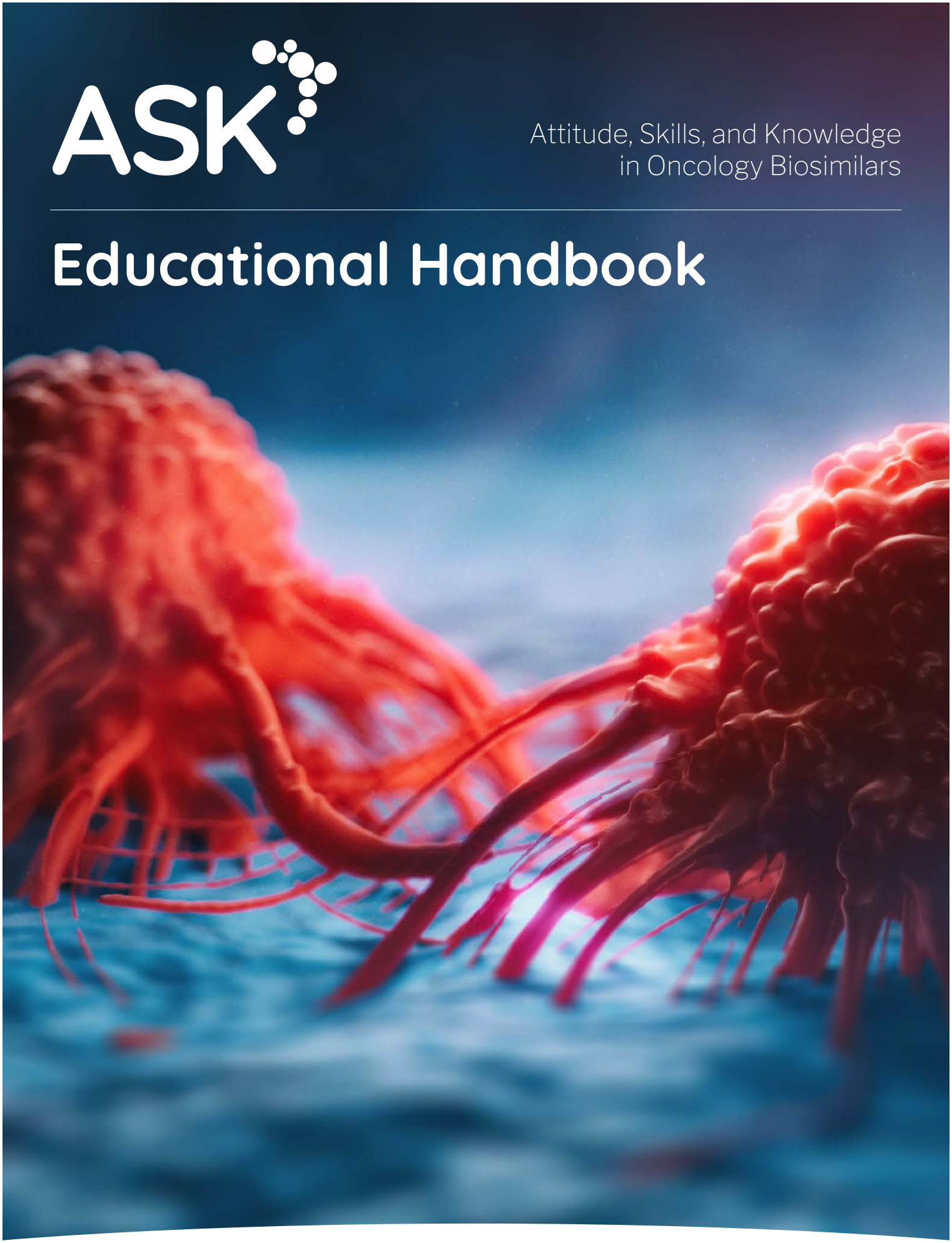
ASK

Attitude, Skills, and Knowledge in Oncology Biosimilars

Educational Handbook



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Biologics are a vital part of the care pathway for numerous major chronic conditions, notably cancer and autoimmune diseases, and represent around 30% share of total pharmaceutical sales in several countries.[1] In 2020, the biologics market was valued at approximately $302.63 billion, and is continually expanding, with projections of $509.23 billion by 2026.[2] The expiry of patents and exclusivity periods for biologics has permitted the development of biosimilars, of which there are over 25 licensed in the US and more than 50 in the EU.[3] The introduction of biosimilars has provided patients with improved access to important, life-changing therapeutics.

Over time, confidence in the use of biosimilars has increased; however, they remain a relatively novel class of treatment, and are associated with complex production and regulation processes that may not be well-understood. This handbook aims to increase prescriber confidence in biosimilars for the treatment of solid tumours via education on the foundations of protein synthesis, specifics of biosimilar manufacture, stringency of regulatory requirements and the application of biosimilars in clinical practice.

Biologics, and therefore biosimilars, used for the treatment of cancer are replicas of naturally occurring proteins, which are made *in vitro*. To understand how biologics and their biosimilars are manufactured, it is important to understand the fundamentals of cellular protein synthesis and how laboratory manufacturing procedures mimic natural processes (Chapters 1 and 2). As an organic product, biosimilar molecules are inherently unstable, which can be further impacted by environmental conditions and so different approaches are employed to stabilise the biosimilar molecules during manufacture (Chapters 3–5).

The reproduction of existing pharmaceuticals is not a new concept; the development of generics for products whose patents have expired is common and results in a product that is identical to the originator, contains the same active ingredient and works in the exact same way. The replication of biologics as biosimilars differs since they are generally large, complex compounds that are made using living cells. The replication process is influenced by various factors including culture duration, nutrient concentration, pH, temperature, etc., which will introduce a degree of variability in the final product. That is why these molecules are termed 'biosimilars' instead of 'generics'. As a result, regulatory requirements for biosimilars are stringent but do vary slightly across regions. In general, to be approved, products must demonstrate high similarity to the reference biologic in manufacturing quality, biologic activity, safety, efficacy and rate of risk of immune reactions. Specific clinical studies are required to demonstrate this similarity (Chapter 6).

Post-approval, as with any pharmacological treatment, it is important to understand and be aware of the potential for adverse reactions. As biologics are naturally occurring entities, the potential for immunogenicity, which can be influenced by certain patient characteristics, must be recognised and monitored. Immunogenicity can be defined as the propensity of a therapeutic biologic to generate an immune response to itself and to related proteins, or to induce immunologically related non-clinical effects or adverse events. As an emerging therapeutic class, compliance with immunogenicity guidelines and pharmacovigilance procedures remains paramount for biosimilars (Chapters 7 and 8).

As with all new therapies, regulatory approval isn't the final hurdle to prescribing biosimilars. Regional reimbursement advice and formulary inclusion both influence access to treatment. Pharmacists play a key role in the development of such advice and of localised pathways, including guidance for switching from originator biologics to biosimilars (Chapter 9).

Any decision to prescribe must be made in collaboration with the patient. Further, considering that biosimilars are still a relatively new concept, it is likely that patient awareness of this class of treatments will be low. Therefore, it is essential that consistent and effective communication between pharmacists and patients takes places and covers what a biosimilar is and what they can expect from their treatment. It is also important to identify any specific needs of the individual in order to provide tailored information with the aim of ensuring patient satisfaction, improving treatment compliance and achieving optimal outcomes (Chapter 10).

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Chapter 1: Protein biology and biologics

Learning objectives

After completing this chapter, the reader will be able to:

- recall the principles of protein or biologic production in a cell
- explain the significance of protein structure (primary, secondary, tertiary and quaternary) in determining biological activity and how this relates to biologic and biosimilar medicines
- describe the principles of post-translational modification and how these impact biologic and biosimilar medicines

Introduction

Though **biologics** have been in common use for decades, **biosimilars** are relatively novel molecules. Biologics are therapeutics, derived via naturally occurring processes, many of which are produced as **recombinant** proteins.

Before delving into the complexities and idiosyncrasies of biosimilar manufacturing and regulation (discussed in subsequent chapters), this chapter summarises the fundamentals of **protein synthesis:** a natural cellular process that is mimicked *in vitro* to produce some of the most used biologics and their biosimilars.

Protein synthesis

Proteins are large, complex molecules that have many critical roles in the body. They are the foundation of the structure, function and regulation of any organism. The main types of protein and their function can be found in Table [1].

Protein synthesis is a complex process and is tightly controlled within cells. The genetic code for all proteins is found in an organism's DNA, which is held inside a cell's nucleus. Within the nucleus, the DNA code for a particular protein is processed into a shorter string of messenger RNA (mRNA) via a process called **transcription**. The mRNA is transported out of the nucleus to the **ribosome**, via the cell cytoplasm. At the ribosome, the mRNA code undergoes **translation**; the mRNA is read to determine which amino acids the transfer RNA molecules need to transport to the ribosome. The amino acids are joined by peptide bonds (forming a polypeptide chain) at the ribosome to assemble the protein. Together, the processes of transcription and translation are known as **gene expression** (Figure 1). A process called gene regulation is responsible for turning **gene expression** on or off within a cell.[3]

Table 1. Main types of protein and their function (table adapted from U.S. National Library of Medicine)[1]

Protein type	Function	Examples
Antibody	Protective proteins that bind to specific foreign particles (called antigens), e.g. viruses and bacteria, to mark them for destruction and elimination	Immunoglobulin G
Enzyme	Catalyse chemical reactions, including the formation of new proteins	Phenylalanine hydroxylase
Messenger	Transmit signals that coordinate biological processes between different cells, tissues and organs (e.g. cytokines and hormones)	Erythropoietin, TNF, VEGF
Receptor[2]	Receive and transduce signals through a variety of mediators	EpoR, VEGFR1
Structural components	The building blocks for cells and structures in an organism	Actin
Transport/storage	Bind and carry atoms and small molecules within and between cells	BCRP, Ferritin, P-gp

BCRP, breast cancer resistance protein; EpoR, erythropoietin receptor; P-gp, permeability glycoprotein; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor; VEGFR1, vascular endothelial growth factor receptor 1.

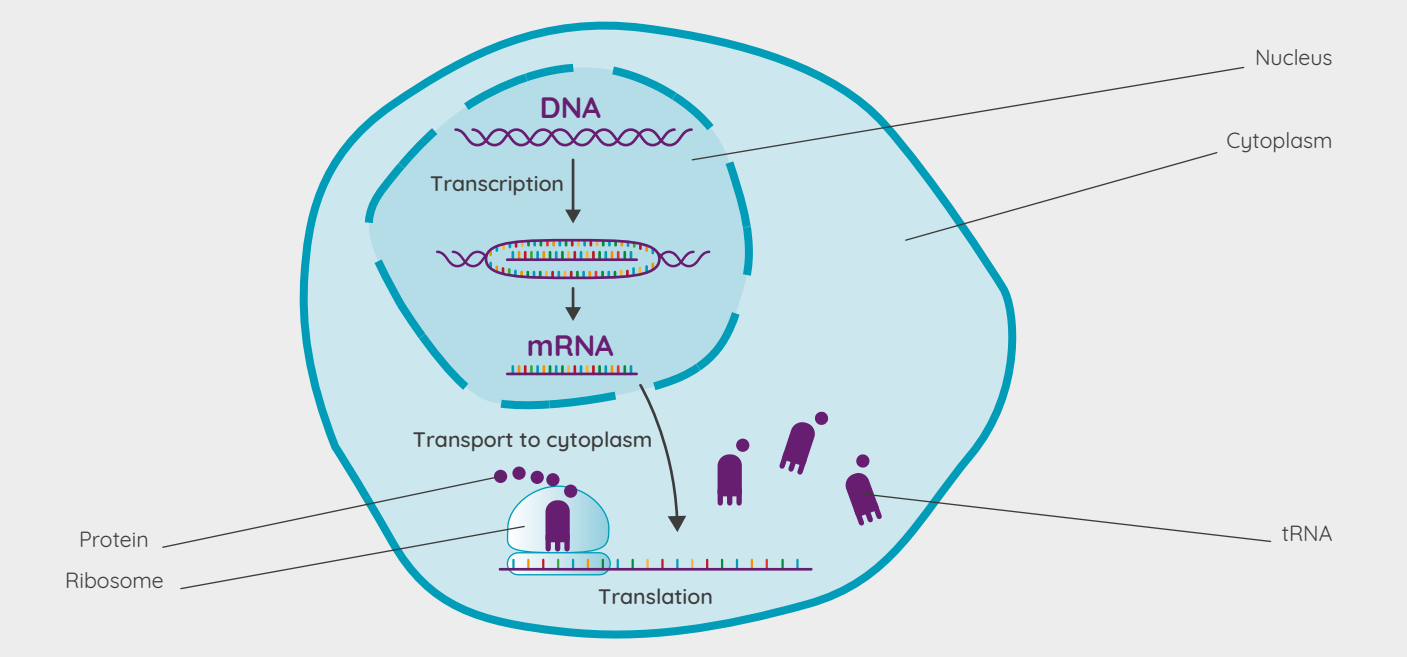


Figure 1. Simplified illustration of protein production via gene expression (mRNA, messenger RNA; tRNA, transport RNA; adapted from US National Library of Medicine 2021).[3]

Modification of gene expression

The human genome contains about 21,000 genes, but the human proteome comprises between 1 million and 2 million proteins.[4] Therefore, the DNA sequence can be transcribed and translated differently to create a range of protein products. Modifications alter specific parts of the mRNA transcript or protein, which diversifies protein structure and function. The types of modification vary by organism. The gene expression process can be altered at several stages to create a derivative protein, as demonstrated in Figure 2.

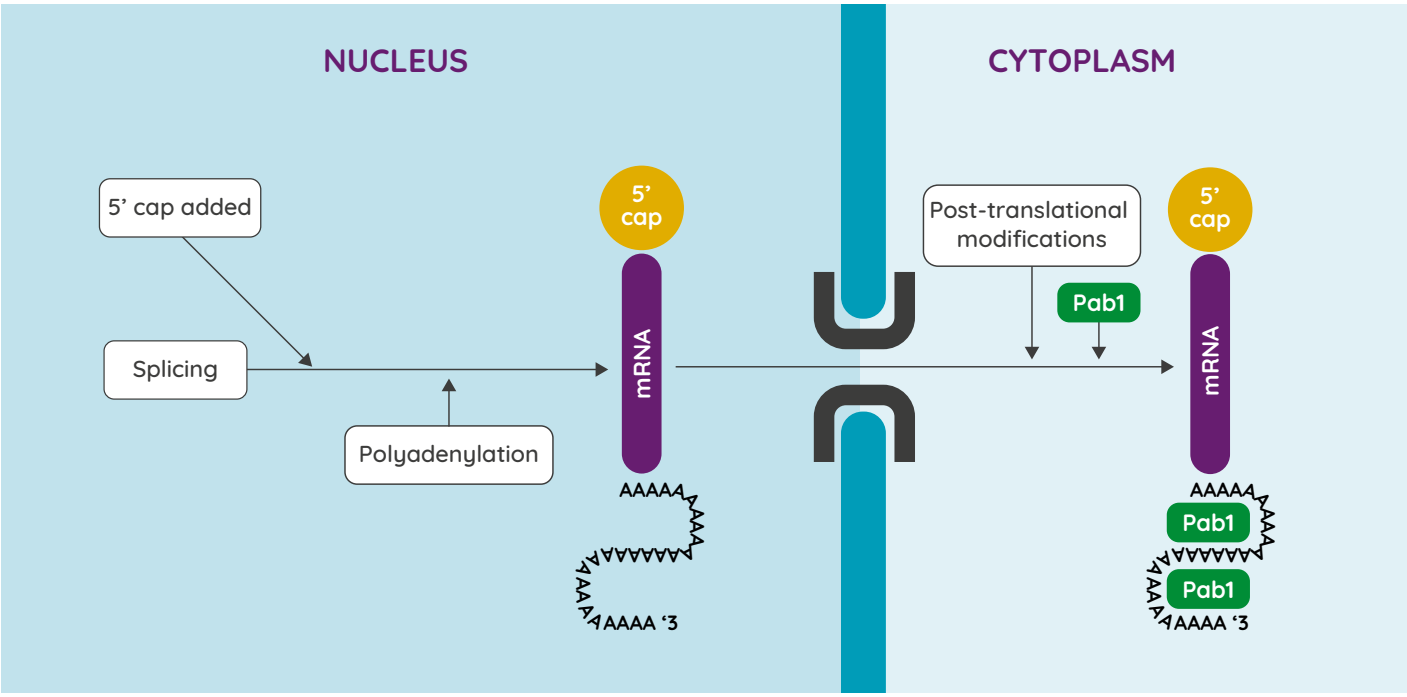


Figure 2. Gene expression modification processes and locations (mRNA, messenger RNA; adapted from Stewart 2019).[5]

Post-transcriptional (or co-transcriptional) modifications to an mRNA transcript occur prior to translation. Two essential post-transcriptional modifications occur: the addition of a 'cap' to one end of the mRNA transcript, which is important for binding the ribosome,[6] and 'polyadenylation' of the opposite end, forming a 'poly-A tail'. The tail is critical for the stability and nuclear export of mRNA transcripts.[5]

Distinct from these essential modifications, the mRNA transcript also undergoes 'splicing', where the mRNA is 'cut' in different ways to produce 'splice variants' that code distinct proteins. Most genes produce several splice variants simultaneously, although one isoform is usually predominant.[7] Splicing is important for increasing the diversity of the proteome but is frequently deregulated during cancer development and progression.[7]

In cancer cells, splicing alterations that affect the efficacy of cancer treatments have been identified. The effects of these alterations on cancer treatments are elimination of domains or enzymatic activities, gain of functions that circumvent certain modes of action and disruption of targeted signalling pathways.[7]

Modification can also occur during translation or post-translation. **Co-translational** modifications are structural changes that occur during translation as the polypeptide chain is extruded from the ribosome tunnel.[4,8] **Post-translational** modifications are a common form of structural change and occur after translation has completed.[8,9] Post translational modifications can take place in various organelles, including the rough endoplasmic reticulum, Golgi apparatus, endosomes, lysosomes and secretory vesicles.[8] Nearly all known proteins undergo some form of post translational modification,[9] but not all organisms carry out all post-translational modifications, e.g. glycosylation is rare in bacteria.[10] In addition to functional differences, post-translational modifications can introduce pathological changes that may evoke an immune response and be implicated in autoimmune diseases; e.g. citrullination (deimination), carbamylation and oxidation are linked to rheumatoid arthritis.[11] There are many types of post-translational modification, some examples of which can be found in Table 2.

Modifications of the mRNA transcript, polypeptide chain or resulting protein can also occur following interaction with foreign substances (i.e. infections) or environmental damage (e.g. UV exposure or chemical pollutants).[11]

Table 2. Summary of gene expression modifications and features.

Modification	Features
Acetylation[12,13]	• Reversible • Common • Regulates many diverse functions, including DNA recognition, protein–protein interaction and protein stability
Carbamylation[11,14]	• Non-enzymatic • Irreversible • Responsible for altering structural and functional properties of proteins, which participate in their molecular aging
Citrullination/ deimination[11,15]	• Enzymatic • Converts the amino acid arginine into the non-standard amino acid citrulline post-translation • Implicated in a growing number of physiological processes (innate and adaptive immunity, gene regulation, embryonic development, etc.) and several human diseases (cancer, rheumatoid arthritis, neurodegenerative diseases, female infertility, etc.)
Glycosylation[11,12]	• Abundant covalent modification • Reversible • Plays a key role in immune regulation (e.g. in the development, survival and reactivity of T cells) • Role in cell–cell interaction and regulation of proteins
Methylation[12,13]	• Common • Role in gene regulation and protein stability
Nitration[11-13]	• A result of oxidative damage during inflammation • Disrupts collagen structures
Oxidation[11,12]	• Caused by reactive oxidative species • Damages cell membranes, lipids, nucleic acids, proteins and constituents of the extracellular matrix such as proteoglycans and collagens • Cysteine oxidation (including disulphide formation and glutathionylation) is reversible
Phosphorylation[12,13]	• Reversible • Role in regulation of protein activity and signalling
Ubiquitination[12,13]	• Reversible • Common • Signalling, degradation

Protein structure

Proteins generally contain between 50 and 1,000 amino acid residues per polypeptide chain and may comprise one or more polypeptide chains.[16] Complexes that contain two or three identical polypeptides are called homodimers and homotrimers, respectively; conversely, complexes that contain different polypeptides are called heterodimers, heterotrimers, etc.

The flexible nature of polypeptide chains allows them to fold into distinct 3-dimensional structures, which they must do to become functional proteins. The 3-dimensional formations are determined by the sequence of amino acids within the polypeptide chain(s)[3] and have unique properties and binding capabilities.[17]

The structure of a protein is described according to four domains (see Figure 3).[17]

- Primary structure: the amino acid sequence in a polypeptide chain.
- Secondary structure: the folding of a segment of a polypeptide chain. While there are numerous possible secondary structures, the β-pleated sheet, α-helix and turn configurations are the most common.
- Tertiary structure: a view of the entire 3-dimensional structure, e.g. globular or fibrous, including spatial arrangements of different segments.
- Quaternary structure: proteins with just one polypeptide chain have primary, secondary and tertiary structures, while those with two or more polypeptide chains also have quaternary structures, e.g. haemoglobin. The quaternary structure refers to the way the chains are arranged with respect to each other.

Though weak, these interactions are sufficient to stabilise a protein's structure, yet can be easily broken so the protein can assume the different conformations necessary for their biological function.[17]

Secondary, tertiary and quaternary structures are held in place by weak, non-covalent interactions between regions.[17]

- Hydrogen bonds: interaction between an electronegative atom and a hydrogen atom attached to a second electronegative atom.
- Ionic bonds: attraction between positively and negatively charged ionic groups.
- Hydrophobic interactions: folding patterns are strongly influenced by interactions between hydrophobic side chains on different parts of the polypeptide.
- Van der Waals interactions: weak electrostatic interactions (and repulsions) between polarised/non-polarised groups.

The biological activity of a protein is related to its 3-dimensional structure, formed according to the specific gene modifications it has undergone, as well as the environment in which it is placed. Any change in these factors will likely affect the biological activity of the protein.

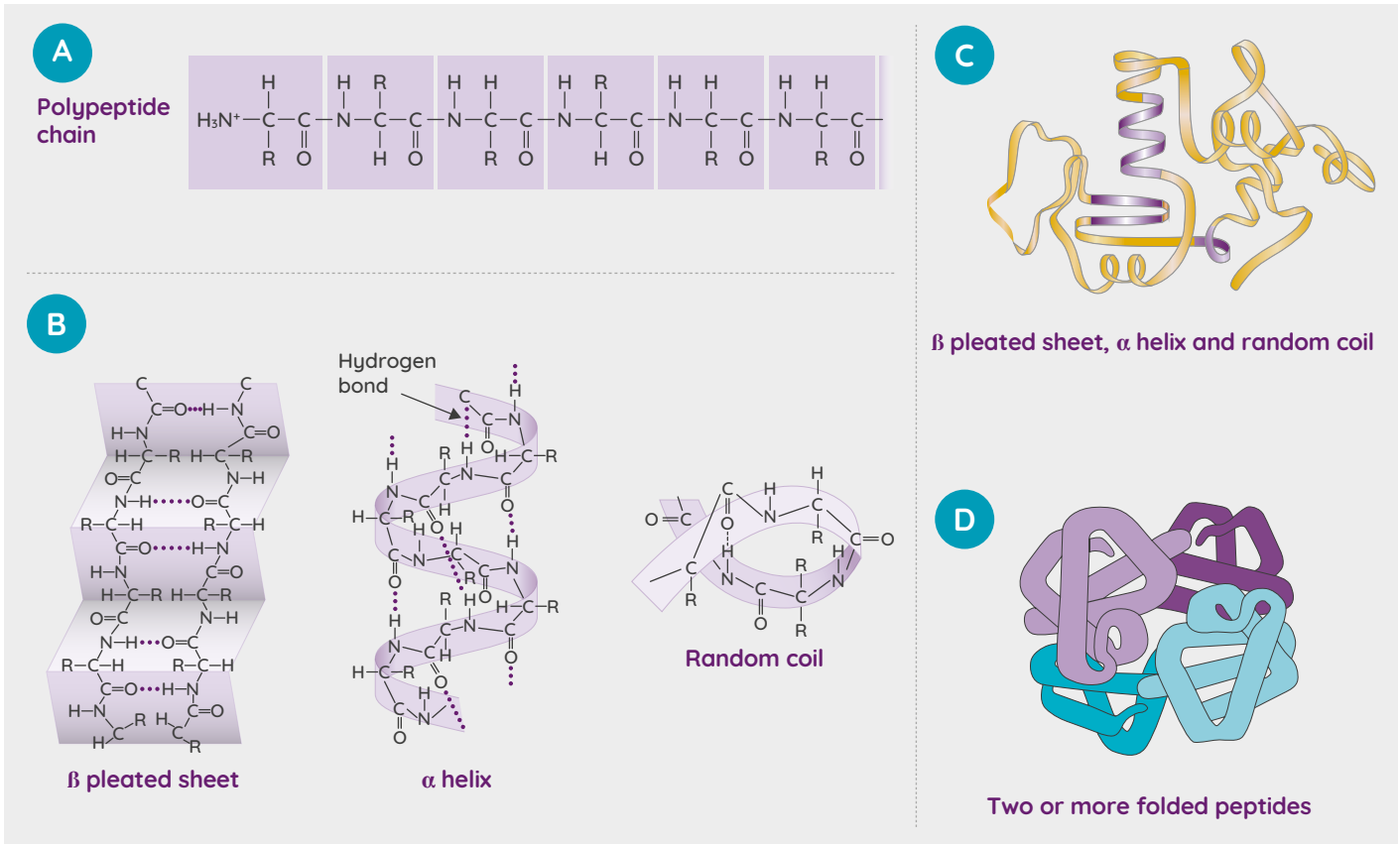


Figure 3. The four domains of protein structure: a) primary; b) secondary; c) tertiary; d) quaternary (adapted from Tropp 2012).[17]

Proteins as medicines: 'biologics'

Considering the wide-ranging function of proteins (e.g. in cell signalling and immune response activation) it stands to reason that their activity could be exploited for therapeutic purposes. Investigation of proteins as treatments dates back to the 1800s, culminating in von Behring receiving the Nobel Prize in Medicine in 1901 for his role in the discovery and development of a serum therapy for diphtheria.[18] Shortly after, in 1922, insulin was purified from animal pancreases and administered to patients with diabetes mellitus.[18] Advances in technology led to the next breakthrough in the 1970s, which allowed the production of 'human' proteins, the first of which being insulin, and those that mimic the natural immune response (monoclonal antibodies; mAbs) via recombinant DNA technology.[18]

These important technological advances led to substantial investment in the production of therapeutic proteins manufactured in, extracted from or semi-synthesised from biological sources, frequently termed 'biologics'. Biologics have offered changes in the treatment of many conditions, notably immune disorders and cancer. More than 100 biologics are approved for clinical use in the European Union and the USA.[18]

Table 3. Examples of available biologics

Biologic	Type	Mechanism of action	Conditions
Abatacept[19]	Recombinant **fusion protein**	T-cell deactivation	Arthritis
Bevacizumab[20]	Recombinant humanised mAb	Inhibition of VEGF and tumour growth	Metastatic carcinoma of colon or rectum
Epoetin alpha[21]	Recombinant protein	Stimulation of red blood cell production	Anaemia
Filgrastim[22]	Recombinant protein	Stimulates white blood cell production	Neutropenia (including chemotherapy-induced febrile neutropenia)
Pegfilgrastim[23]	PEGylated recombinant protein		
Rituximab[24]	Chimeric mAb	Binding to CD20 antigen on pre-B and mature B lymphocytes to effect B-cell lysis	Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis
Trastuzumab[25]	Humanised mAb	Inhibition of HER2 signalling and proliferation of tumour cells	Breast cancer, gastric cancer

HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; VEGF, vascular endothelial growth factor.

Owing to the complexity of proteins, the manufacturing process for each biologic is highly specialised. Since the functionality of proteins relies on their structure, manufacturing of biologics must ensure that all four structural domains are replicated (discussed in detail in Chapter 2).

Some examples of approved biologics, including their mechanism of action and conditions they treat, can be found in Table 3.

Though effective and the mainstay of treatment in certain indications, biologic products have historically been associated with high costs, which has limited access to these medicines for some patients. However, the expiration of patents or data exclusivity for '**originator**' biologic products has permitted the development of 'biosimilars'.[26]

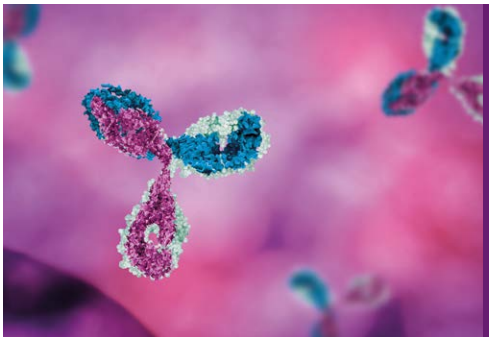
Biosimilars are defined by the European Medicines Agency as a biological medicine highly similar to another already approved biological medicine (the 'reference medicine' or originator). Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines. An approved biosimilar is deemed highly similar based on comparison of the pharmacokinetic, pharmacodynamic, safety and efficacy data, according to specific guidelines (i.e. there are no clinically meaningful differences from the reference biologic).[26] Both biosimilar and reference medicine must have the same posology and route of administration, but differences in the formulation, presentation and administration device are permitted if they have no effect on efficacy and safety of the product.[27]

The first biosimilar was approved by the EU in 2006 (the growth hormone somatropin); since then, many biosimilars of originator products have been approved globally.[27] For example, there are currently six different biosimilars of trastuzumab (originator Herceptin®) licensed in the European Union,[28] four in Canada[29] and three in Japan.[30]

It is important to note that biosimilars are not considered generics of the originator biologic, as though they must be highly similar in terms of structure and function, natural variability and *in vitro* manufacturing processes do not allow an exact replication.[26] The main differences between a biosimilar and a generic medicine can be found in Table 4.

Table 4. Comparison of the features of biologic and generic medicines[27]

Biosimilar	Generic
Obtained from a biological source	Usually produced by chemical synthesis
Possible to reproduce the molecule to a high degree of similarity	Generally possible to reproduce the same molecule
Generally larger, structurally more complex molecules, which require multiple technologies for their characterisation	Mostly smaller molecules, easy to characterise
Full data requirements on pharmaceutical quality, plus additional quality studies comparing the structure and biological activity of the biosimilar with the reference medicine	Full data requirements on pharmaceutical quality
Development based on demonstration of biosimilarity using comparability studies (comprehensive head-to-head comparison of the biosimilar with the reference medicine to show high similarity in chemical structure, biological function, efficacy, safety and immunogenicity)	Development based on demonstration of bioequivalence (i.e. that the generic and the reference medicine release the active substance into the body at the same rate and to the same extent under similar conditions)
In addition to comparative pharmacokinetic and pharmacodynamic studies, safety and efficacy data may be required, particularly for more complex biological medicines	Clinical data requirements are mainly pharmacokinetic bioequivalence studies
Efficacy and safety must be justified in each indication. However, confirmatory clinical trials with the biosimilar are usually not needed in every indication that has been approved for the reference medicine. After demonstration of biosimilarity, extrapolation of data to other indications is possible if the available scientific evidence addresses all specific aspects of these indications	All indications approved for the reference medicine can be granted based on demonstrated bioequivalence, without the need for further clinical data



Conclusion

Advances in biotechnology over the past few decades have led to the ability to replicate naturally occurring processes and artificially synthesise organic molecules for therapeutic purposes, termed ‘biologics’. Biologics have revolutionised care for certain conditions, notably cancer and immune disorders, but have historically been associated with high costs. The expiration of patents on originator biologics has permitted the production of ‘highly similar’ products, termed ‘biosimilars’. Biosimilars are associated with complex manufacturing and regulatory processes, which are discussed in subsequent chapters.

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Chapter 2: Biologic and biosimilar manufacture

Learning objectives

After completing this chapter, the reader will be able to:

- Recall the stages of the manufacturing process for biologic and biosimilar medications
- List the sources of variation between batches of biologics, and the extent of heterogeneity between biosimilars and the reference biologic
- Explain the quality management principles applied during the manufacture of biologics and biosimilars

Introduction

Biologics are distinct from small peptides/oligonucleotides and other synthetic pharmacological treatments. Their production entails the precise replication of complex, naturally occurring processes within a living cell to produce large, highly specific molecules. This has contributed to both the high cost attributed to this class of treatment and the stringent approval requirements placed on **biosimilars** (covered in Chapter 6).[1]

The cellular processes that are replicated in the production of biologics and biosimilars must be carried out in an appropriate cell type under specific conditions. The result is a molecule that is functionally identical to the naturally occurring protein; however, since *in vitro* protein synthesis is difficult to precisely control and replicate, and is influenced by external factors, small differences between molecules may be introduced. Quality control of the manufacturing process and final product is strict and assessed according to a variety of factors throughout **manufacture**.

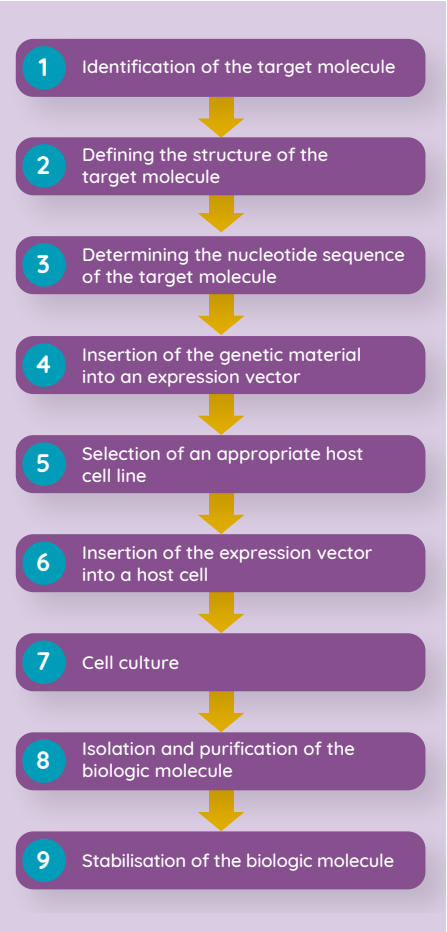


Figure 1. Key steps in the development and manufacture of biologics and biosimilars.[2-6]

Developing and manufacturing biologics or biosimilars

There are several steps involved in the development and manufacture of biologics and biosimilars (Figure 1).

1. Identification of the target molecule

The first stage of developing a biologic is the identification of a **target protein** whose function can be exploited for therapeutic benefit. An example of this is an antibody that targets an antigen known to be overexpressed on certain cancer cells and halts their proliferation or marks them for destruction.[7] For biosimilars, the target molecule is the reference biologic.[8]

2. Defining the structure of the target molecule

Once a target molecule has been chosen, its 3-dimensional structure must be characterised. Since this is responsible for its functionality, it must be replicated as closely as possible in the developed biosimilar. Databases of protein structures exist, which may be utilised for this purpose.

3. Determining the nucleotide sequence of the target molecule

The folded shape of the protein depends directly on its linear amino acid sequence.[2] Determining the amino acid sequence allows the characterisation and replication of the genetic material needed to reproduce the protein. Information on amino acid sequences is also usually available, but should be confirmed as it may be misleading or incomplete.[8]

4. Insertion of the genetic material into an expression vector

The genetic material is then spliced into an **expression vector**, which is a small DNA molecule taken from an organism such as a bacterium or virus and contains the necessary genetic coding to initiate protein synthesis in a **host cell**.

5. Selection of an appropriate host cell line

A host cell line is selected based predominantly on its cell growth and protein expression characteristics. Gene expression is possible in a variety of cell systems including bacteria, yeast and animals, as well as in transgenic animals and plants.[9]

Bacterial cells (e.g. *Escherichia coli*) are commonly used to manufacture non-glycosylated biopharmaceuticals,[10] owing to their rapid growth rate, high product yield, cost effectiveness and ease of process scale-up. Glycosylation is essential to the functioning of many proteins, and mammalian cells are preferred to produce biologics and biosimilars.[10]

Hybridoma technology is a well-established method of developing mammalian host cell lines that are a fusion of B-cells and myeloma cells, e.g. murine melanoma cells. Hybridoma cell lines produce high-quality monoclonal antibodies and are used for the manufacture of several approved biologics; however, some glycoproteins have shown potential for immunogenicity, which has likely limited their use for therapeutic antibody production.[3]

Almost all recombinant monoclonal antibodies, including trastuzumab,[7] bevacizumab[4] and rituximab,[5] are produced using Chinese hamster ovary (CHO) cells. CHO cells are the preferred host as they are capable of high productivity,[9] are suitable for large-scale culturing, exhibit consistently good growth phenotypes, can be easily adapted to culture media and are less susceptible to infections by human viruses.[6] Importantly, CHO cells are able to carry out glycosylation in a way that is similar to human cells,[6,9,11] producing glycoforms that are not generally immunogenic.

6. Insertion of the expression vector into a host cell

Following selection of a host cell line, the expression vector is inserted into the host cell – this is known as transfection.

7. Cell culture

The transfected cells are expanded in a culture medium that provides key nutrients for cell growth. Cells that demonstrate a stable, high-level expression of the desired protein are selected and cloned to ensure genetic uniformity. Cloned cells form the basis of the master cell bank: a cryopreserved store of cells that contain the gene that encodes the desired protein, and the source of all cells used to manufacture the medicinal product. For commercial reasons, master cell banks are created for each biologic and biosimilar and will therefore differ between products.

When required, vials of cells from the master cell bank are expanded in bioreactors to form the working cell bank.[9] Temperature, pH, oxygen supply and agitation should be well-controlled to optimise cell growth.[12,13] Any waste products that may negatively impact on the culture performance are removed.[12,13]

8. Isolation and purification of the biologic molecule

After culture of the cells in optimal conditions for a defined period, the target protein must be isolated from the media.[13] This is done via filtration, sedimentation, floatation and/or centrifugation.[13] The product must then be purified to remove impurities introduced by the cells (e.g. other proteins and nucleic acids), the process (e.g. buffers and ligands) and the product (e.g. aggregates and fragments).[13] This purification is done via precipitation and/or chromatography.[13] Chromatography is generally the preferred purification technique as, despite high cost implications, it is very effective and has a wide range of applications.[13] Chromatographic methods can be grouped into five classes: (i) affinity, (ii) ion exchange, (iii) hydrophobic interactions, (iv) size exclusion and (v) mixed-mode chromatography.[13]

9. Stabilisation of the biologic molecule

As they are replicas of a naturally occurring product, biologics and biosimilars are vulnerable to degradation; therefore, it is necessary to prolong their shelf-life as long as possible and ensure they remain stable until use. Optimising storage conditions is essential to ensure stability of the product, but other techniques are also employed, such as the addition of excipients that are specifically selected to protect, but not interfere with, the functioning of the protein. This is covered in more detail in Chapters 3–5.

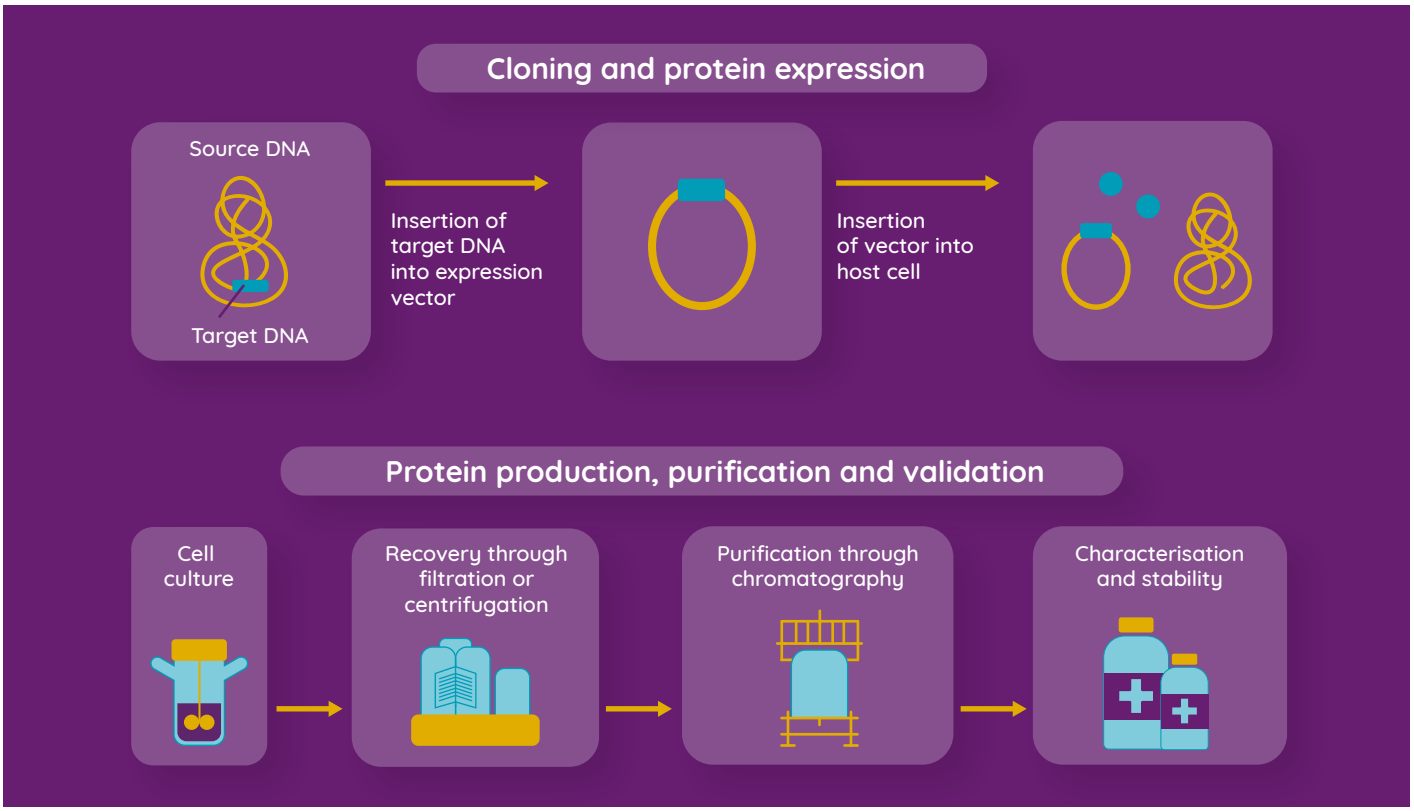


Figure 2. Manufacturing process for biologics and biosimilars (adapted from Raffals LE, *et al.* 2018).[14]

Critical Quality Attributes

A **Critical Quality Attribute** (CQA) is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired quality of a biosimilar.[15] The CQAs will guide initial development of the candidate biosimilar molecule. As such, maintaining stability of these properties can be a challenge (see Chapter 3). When developing a new drug, manufacturers must list the CQAs of the drug substance and the rationale for designating these properties or characteristics as CQAs.[15] Determination of CQAs that might impact upon the safety and efficacy of a product is, of course, important for evaluation of biosimilars and accepting an extrapolation of indications.[16] Publishing biosimilarity assessments of CQAs in scientific literature is one of many strategies to improve learning and understanding in biosimilar development.[17]

Inherent variability

According to international guidance, a well-defined manufacturing process assures that the product is produced on a consistent basis.[18] This is a challenge for manufacturers of biologics and biosimilars since they are produced using living systems. In contrast to chemically synthesised products, biologics and biosimilars have a certain degree of natural variability, introduced by processes such as post-translational modification (see Chapter 1); as such, there is an inevitable amount of batch-to-batch variation,[9] both within the manufacture of the reference biologics and within the manufacture of each of their biosimilars. Glycosylation is the main cause of heterogeneity among therapeutic proteins.[10]

Product heterogeneity is influenced by any variations in the manufacturing process. For example, culture duration, nutrient concentration, cellular growth state, pH, temperature and levels of dissolved gases can all influence glycosylation.[9] Characteristics of the products also may vary slightly over time (known as product drift[19]) as manufacturers attempt to optimise production methods.[10] However, the manufacturer should confirm that any modifications provide at least similar or more effective control of the product quality, compared to those of the original process.[18]

This is further complicated when considering the manufacture of biosimilars, since information regarding the manufacturing process for the **reference product** is not generally available, and a proprietary manufacturing process must be developed. This is expected to lead to minor differences between the biosimilar and the biologic; however, stringent requirements are in place for approval of the biosimilar, including proof that the biosimilar is highly similar to the reference product (see Chapter 6). Sensitive bioassays are used to ensure that the biological properties are comparable between products.

Quality management

Biosimilars and reference biologics are approved according to different regulatory frameworks across countries (see Chapter 6), but have to meet the same quality standards.[20] Quality management is extensive and ensures patients receive a "safe, pure, potent and stable product".[9]

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use was established to generate and harmonise regulatory guidelines for pharmaceutical development and manufacturing between the European Union, the US and Japan,[21] and has provided extensive guidance specific to the manufacture and quality assessment of biotechnological products.[22] The World Health Organization has also provided guidelines for national authorities on quality assurance for biological products to ensure standards are upheld globally.[23]

Quality management of biologics involves assessing an array of attributes across the entire manufacturing process and of the resulting product.[9,10] According to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Q6B, these fall into three broad categories:[24]

- Characterisation of the biological product:
  - physiochemical properties
  - biological activity
  - immunochemical properties
  - purity, impurities and contaminants
  - quantity.
- Analytical considerations:
  - reference standards and reference materials
  - validation of analytical procedures.
- Process controls:
  - process-related considerations
  - in-process acceptance criteria and action limits
  - raw materials and excipient specifications (see Chapter 5).

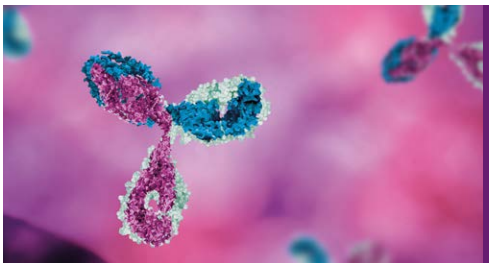
Cell culture conditions and isolation/purification methods influence the protein produced; therefore, there is heavy reliance on in-process sampling and testing.[9] High-resolution mass spectrometry, for example, is used to detect functionally relevant glycans, minor structural variation (e.g. sequence variants, truncations and incorrect disulphide bridges) and impurities (e.g. host cell proteins).[20] As all oncology products are provided as injectable solutions, and are administered parenterally, careful attention must be paid to the maintenance of sterility of the final product.[9]

Any variation in the manufacturing process will affect the end product. It is vital that any variability introduced is minimal, and manufacturers must demonstrate that any changes to a process do not adversely impact quality of the product.[18]

Biosimilars are subject to the same quality standards as the reference biologic, but additional studies must be conducted to demonstrate that the product is highly similar to the reference biologic (see Chapter 6).

Future developments

The next generation of biopharmaceuticals is expected to advance biologics from recombinant versions of natural products to more complex genetically engineered or adapted protein constructs that offer improved drug delivery, enhanced catalytic activity and stability, better tolerability and lower immunogenicity. For example, techniques such as site-directed mutagenesis can insert new sites for post-translational modification (e.g. glycosylation), resulting in altered properties of the protein.[13] The research and development processes for these next-generation treatments will likely mean higher costs.[13]



Conclusion

Manufacturing biologics and biosimilars is an expensive and convoluted process. Due to the increased potential for variation between biologics and biosimilars, these processes must be tightly controlled to ensure the efficacy, stability and quality of the product. Advances in biotechnology will mean improvements in the discovery, modification, production and purification of biopharmaceuticals.

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Chapter 3: Biologic product stability – background theory

Learning objectives

After completing this chapter, the reader will be able to:

- explain the factors that affect stability and degradation of biologics and biosimilars
- outline the types of studies that are used to measure the stability of biologics and biosimilars

Introduction

The activity of biologics and biosimilars depends on maintenance of their structure; however, as molecules whose structures are held in place by relatively weak bonds, they are vulnerable to degradation and thus loss of function (see Chapter 1). In addition to impacting their biological activity, structural changes can also introduce immunogenicity (see Chapter 7).[1]

Various methods are used to stabilise biologics and biosimilars (see Chapter 5), and regulators mandate stability studies to generate evidence that the product remains stable over its **shelf-life**. Beyond regulatory requirements, the stability of the product over time and under certain conditions (e.g. once reconstituted) is an important consideration when making formulary and prescribing decisions.

Factors affecting the stability of biologics and biosimilars

Every biologic or biosimilar has its own properties and it is essential that its critical quality attributes (CQAs; see Chapter 2) are maintained over time to ensure efficacy and safety. The US Food and Drug Administration criteria on stability of pharmaceutical forms state that no more than 10% of the active ingredient should deteriorate over 2 years,[2] and this is a widely accepted standard across the globe. The stability of biologics and biosimilars can be compromised by changes in environmental conditions, such as temperature, composition of the medium (e.g. pH, salt concentration), light, agitation or mechanical stress and shearing forces (Figure 1).[3]

Interactions with excipients can also promote degradation (see Chapter 5), and extractables or leachables that the product may come into contact with (e.g. stirrers used in the manufacturing process[4]) may exert a toxic effect or impact stability.[5] Post-production, it is important to ensure the formulation, container, delivery method and storage are appropriate for the biologic or biosimilar.[6]

Healthcare professionals need to be aware of the potential for alterations to biologic and biosimilar products over time (**product drift**, see Chapter 2), and with changes to environmental conditions (e.g. temperature excursions during transport or storage errors), and how these may impact the product. Alterations in the protein structure can result in the production of neutralising or blocking antibodies, which diminish clinical effect and necessitate switching to another drug with a different mechanism of action.[2] In rare cases, alterations in the protein structure can also induce severe harmful immune reactions, including incidents of hypersensitivity, and induction of anaphylaxis or cytokine storms (the rapid release of proinflammatory cytokines).[2]

Types of instability

Instabilities can be largely grouped into **chemical instabilities**, which involve processes that make or break covalent bonds, generating new chemical entities (see Chapter 1), and **physical instabilities**, whereby there are no changes to the chemical composition, but the physical state of the protein is altered (summarised in Table 1).[7]

Demonstrating stability

In order to gain approval, regulators require manufacturers to conduct stability studies that demonstrate the product's efficacy and safety over time. More country-specific information can be found in relevant national regulatory agency guideline documents.

According to Good Manufacturing Practice (GMP) guidelines from the International Council for Harmonisation of Technical

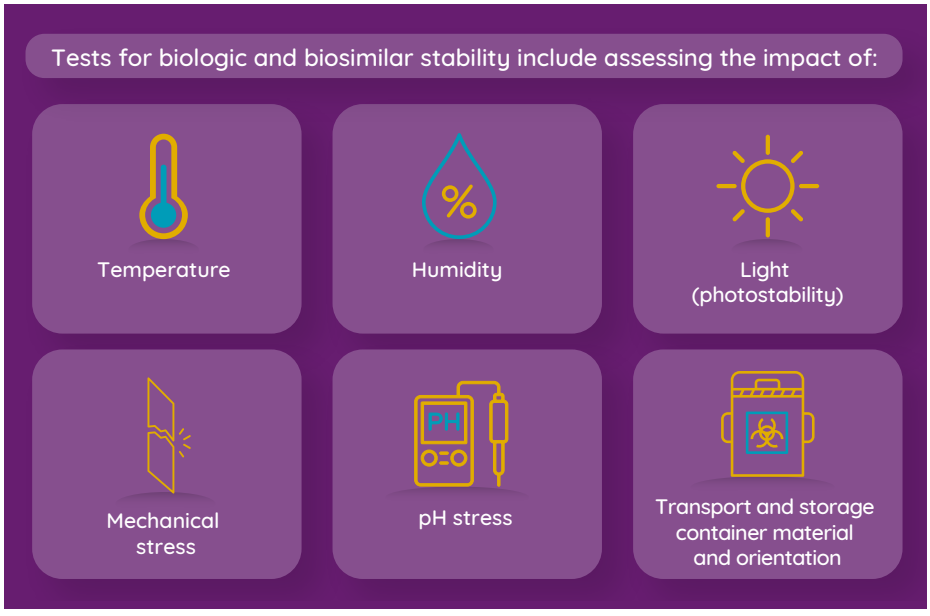


Figure 1. Key factors with potential to affect the stability of biologics and biosimilars[3]

Requirements for Pharmaceuticals for Human Use (ICH) on stability testing of biotechnological/biological products (Q5C):[3]

- the manufacturer should identify product intermediates and generate in-house data and process limits that assure their stability within the bounds of the developed process
- where bulk material is to be stored after manufacture but prior to formulation and final manufacturing, stability data should be provided on at least three batches
- a minimum of 6 months of stability data (at the time of submission) should be submitted in cases where storage periods greater than 6 months are requested
- the first three manufacturing-scale batches submitted for approval purposes should be placed into a long-term stability program after approval.

ICH Q5C also specifies that the substance studied for stability must be representative of the final product and be made and stored under the same conditions.[3]

Stability studies might be able to detect subtle differences that are not readily detectable by protein characterisation studies alone.[8] For example, the presence of trace amounts of a protease or ions leached from a container closure system might only be detected by performing stability tests over an extended period.[8]

Table 1. Summary of common types of chemical and physical instability in biopharmaceutical products[7]

Chemical instabilities	
Deamidation	• Responsible for much of the heterogeneity observed in mAbs • Most common chemical degradation pathway for peptides and proteins • Generates process-related impurities and degradation products • May contribute to increased immunogenicity
Glycation	• Can affect function • Occurs when a protein is incubated in the presence of a reducing sugar (e.g. glucose, lactose, fructose, maltose) • One of the primary reasons that manufacturers tend to avoid using reducing sugars in formulations
Oxidation	• Major degradation process • Can occur during any stage of production, purification, formulation and storage • Rate of occurrence affected by extrinsic factors (e.g. pH and buffer type)
Physical instabilities	
Denaturation	• Loss of 3-dimensional structure • Commonly caused by elevated temperature • Often irreversible
Aggregation	• Adversely impacts biological function of the molecule and increases likelihood of immunogenic effects during therapy • Can occur during purification, formulation, filtration, vial and syringe filling, pumping, transportation and storage • Can be suppressed by addition of stabilising agents (see Chapter 5)
Surface adsorption	• Changes physical state of the protein • Known to occur when proteins are in aqueous solution – myriad surfaces are encountered by biologics and biosimilars during manufacture and in final dosage form • After initial adsorption, surface tension forces can drive aggregation • Surfactants used to limit adsorption

mAb, monoclonal antibody.

Any changes to the manufacturing process during the clinical development of a biologic or biosimilar may necessitate the repetition of stability studies to demonstrate that the changes did not adversely impact the safety or efficacy of the product (see Chapter 2).[8]

Stability studies

Stability studies take several years to complete, and no single assay or parameter can adequately indicate the stability of a biologic or biosimilar. Manufacturers must design a range of studies that will provide assurance of the stability of the individual product, which should encompass:[3]

1. potency
2. purity and molecular characterisation
3. other product characteristics
4. storage conditions

1. Potency

Potency is the specific ability or capacity of a product to achieve its intended effect.[3] For some biological products, potency is dependent upon the conjugation of the active ingredient(s) to a second moiety.[3] Dissociation of the active ingredient(s) from the conjugate should be examined in real-time/real-temperature studies (including conditions encountered during shipment).[3]

2. Purity and molecular characterisation

Owing to the effect of glycosylation, deamidation or other post-translational modifications, the absolute purity of a biological product is extremely difficult to determine and thus should be assessed by more than one method.[3] Stability tests for purity should focus on determination of degradation products.[3] Accelerated and stress stability studies are often useful tools to establish degradation profiles.[3] Acceptable limits should be determined, taking into account the levels observed in material used for preclinical and clinical studies.[3,8]

Analytical techniques used should permit a comprehensive characterisation of the product (e.g. molecular size, charge, hydrophobicity) and the accurate detection of degradation changes that may result from deamidation, oxidation, sulfoxidation, aggregation, **hydrolysis**,[9] **deglycosylation**,[9] **Maillard reaction**[9] or fragmentation during storage.[3]

Analytical methods that may contribute to molecular characterisation include:

- electrophoresis (e.g. SDS-PAGE, immunoelectrophoresis, isoelectrofocusing)
- high-resolution chromatography (e.g. reversed-phase chromatography, gel filtration, ion exchange, affinity chromatography)
- peptide mapping[3]

3. Other product characteristics

The following characteristics should be monitored and reported:[3]

- visual appearance of the product (colour and opacity for solutions/suspensions, and colour, texture and dissolution time for powders)
- visible particulates in solutions, or after the reconstitution of powders or lyophilised cakes
- pH
- moisture level of powders and lyophilised products
- sterility (e.g. container/closure integrity testing) at a minimum initially and at the end of the proposed shelf-life
- occurrence and effect of additive (e.g. stabilisers, preservatives) or excipient degradation (see Chapter 5)

4. Storage conditions

Appropriate studies should be considered to confirm that suitable storage conditions are selected, encompassing:[3]

- temperature
- humidity
- light
- container/closure

It is recommended that the product be tested under accelerated and stress conditions reflective of plausible variations in the above.[3] This is useful in determining whether accidental exposure to conditions other than those proposed (e.g. during transport) are deleterious to the product.[3] These studies also reveal degradation patterns and can inform the design of long-term stability studies.[3,8]

Unexpected problems related to leachables from the product container have been observed even after product launch; therefore, manufacturers need to perform extractable and leachable studies in retrospect to satisfy regulatory bodies.

From shelf-life to ready-to-administer solution

The shelf-life of a product provides assurance of stability to those making decisions regarding which product to use. Shelf lives are designated based on the stability of the product (i) in an unopened container and (ii) once the product has been reconstituted for use, both are important to bear in mind when considering use of one product over another in practice (see Chapter 9).

Shelf-lives of biopharmaceutical products can vary from days to years.[3] ICH Q5C states that the product should retain its specifications within established limits for safety, purity and potency throughout its proposed shelf-life.[3] The shelf-life and expiration dating of the product are based upon the stability data submitted to the regulatory body.[3]

While chemical and physical stability are important considerations,[7] common practices in the preparation of ready-to-administer solutions, such as reconstituting, diluting and storing, have the potential to result in instabilities, such as microbiological instability (covered in Chapter 4).[10]

Appropriate storage according to prescribing information is essential to all aspects of the stability (and therefore function) of the product. Most currently commercially available pharmaceutical forms that contain monoclonal antibodies must be kept between 2°C and 8°C, including during transit. In cases where a product is accidentally exposed to elevated temperatures, the manufacturer should be consulted to obtain the necessary stability data to determine whether the drug should be discarded.

Ideally, the reconstitution, dilution and preparation of hazardous or complex intravenous biological products should be carried out by a pharmacy technician or an aseptically trained pharmacy assistant under the supervision of a registered pharmacist. Where this is not possible for all preparations, low-risk preparations may be prepared by other trained members of the multidisciplinary team (e.g. by nurses on the treatment ward); a risk assessment of the preparation method and location should be undertaken.

It is crucial that all staff, including non-skilled staff, who will be involved in handling of the product, such as porters, volunteers and delivery drivers, are aware of any sensitivities or factors that will affect the stability of the preparation. For example, if a preparation is sensitive to agitation, should it need to be transported from the preparation area to a ward, the porters should be aware of the need to minimise agitation of the transport trolley and the impact that agitation could have on the efficacy of the medicine (see Box 1).

The primary concerns associated with incorrect storage, reconstitution and handling of biologic drugs are:[2]

- potential loss of clinical efficacy of the product
- delay to patient treatment;
- potential wastage incurring substantial cost (see Chapter 9)
- hypersensitivity reactions in patients.[2]

Box 1: alglucosidase alfa – gentle handling to ensure stability[11]

The biologic drug alglucosidase alfa is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Pompe disease. This drug is an example of a biologic that requires very sensitive handling from pharmacy to bedside, emphasising the need for the entire multidisciplinary team to be aware of stability concerns for biologic drugs.

Very careful handling of the drug is required, with specific directions from the manufacturer given to avoid inversion, swirling or shaking the vial during reconstitution and to avoid shaking and excess agitation during dilution. It is critical that all team members involved in the delivery of the preparation to the patient understand that mishandling leads to decreased efficacy of the drug, which impacts the patient's treatment and has cost implications.

Stability of biosimilars

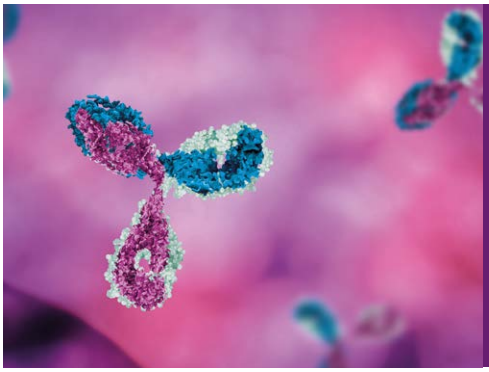
The stability of a biosimilar versus the reference biologic must be demonstrated under various stress conditions, such as light and accelerated temperature.[12] Regulatory bodies allow for advancements in formulation science for biosimilars, i.e. the

Table 2. Comparison of the shelf-lives of biosimilars and their reference products

Reference product		Biosimilar name EU/UK/Canada [approved name in Japan]	
Herceptin®[13]	Unopened vial: 4 years After aseptic reconstitution: • with sterile water – chemical and physical stability of reconstituted solution for 48 hours at 2°C–8°C. After aseptic dilution: • in polyvinylchloride, polyethylene or polypropylene bags containing 9 mg/ml (0.9%) NaCl – chemical and physical stability for up to 30 days at 2°C–8°C, and 24 hours at temperatures ≤30°C.	**Herzuma®[14]**	Unopened vial: 6 years After aseptic reconstitution: • with sterile water – chemical and physical stability for 7 days at 2°C–8°C. After aseptic dilution: • in polyvinylchloride, polyethylene or polypropylene bags containing 9 mg/ml (0.9%) NaCl – chemical and physical stability for up to 30 days at 2°C–8°C, and 24 hours at temperatures ≤30°C.
		Trazimera[15] [trastuzumab biosimilar 3]	Unopened vial: 4 years After aseptic reconstitution: • with sterile water – chemical and physical stability for 48 hours at 2°C–8°C. After aseptic dilution: • in polyvinylchloride, polyethylene, polypropylene or ethylene vinyl bags, or glass intravenous bottles containing 9 mg/ml (0.9%) NaCl – stability for up to 30 days at 2°C–8°C, and 24 hours at temperatures ≤30°C.
Avastin®[16]	Unopened vial: 2 years Diluted medicinal product: chemical and physical in-use stability for 30 days at 2°C–8°C plus additional 48 hours at 2°C–30°C in 9 mg/ml (0.9%) NaCl.	**Truxima®[20]**	Unopened vial: 3 years Diluted medicinal product: chemical and physical in use stability for up to 35 days at 2°C–8°C after dilution and up to 48 hours at temperatures ≤30°C in 9 mg/ml (0.9%) NaCl.
			Unopened vial: 30 months Diluted medicinal product: chemical and physical in-use stability for 30 days at 2°C–8°C plus an additional 48 hours at temperatures ≤30°C in 9 mg/ml (0.9%) NaCl.
MabThera®[19]	Unopened vial: 36 months After aseptic dilution in NaCl solution: physically and chemically stable in 0.9% NaCl for 30 days at 2°C–8°C plus additional 24 hours at ≤30°C. After aseptic dilution in D-glucose solution: physically and chemically stable in 5% D-glucose for 24 hours at 2°C–8°C plus additional 12 hours at room temperature.	**Rixathon®[21]** [rituximab biosimilar 1]	Unopened vial: 4 years Diluted product: physically and chemically stable in 0.9% NaCl for 30 days at 2°C–8°C plus additional 24 hours at room temperature (≤30°C). Physically and chemically stable in 5% glucose solution for 24 hours at 2°C–8°C plus additional 12 hours at room temperature (≤30°C).
			Unopened vial: 3 years After aseptic dilution in NaCl solution: chemical and physical stability in 0.9% NaCl for 30 days at 2°C–8°C plus additional 24 hours at room temperature (≤25°C). After aseptic dilution in glucose solution: chemical and physical stability in 5% glucose solution for 24 hours at 2°C–8°C plus additional 12 hours at room temperature (≤25°C).

All information correct at the time of writing (August 2021).

excipients in the formulation may differ from those of the reference product, providing tests are undertaken to assess any relevant effects of the revised formulation on the stability, physiochemical and functional characteristics of biosimilars.[12] For this reason (and depending on stability studies conducted and submitted by the manufacturer), biosimilars do not necessarily have the same shelf-life and expiration dating as the reference product (see Table 2) and **extended stability data** may be available for some products and not others (see Chapter 4). This is important to remember when considering whether to switch products in formularies.



Conclusion

Stability studies are heavily regulated to ensure compliance with ICH guidelines and take several years to complete; however, the ultimate aim of assessing the stability of a product is to ensure its safety and efficacy over its shelf-life. From the perspective of the prescriber, nursing and pharmacy colleagues, and all colleagues involved in the treatment chain, understanding the factors influencing the stability of a biologic or biosimilar is crucial to optimising treatment outcomes, organising administration for patients, preventing the occurrence of serious adverse events and minimising expenditure. However, stability studies may be numerous and complex, and interpretation of data requires careful consideration (see Chapter 4).

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Chapter 4: Interpretation of stability data

Learning objectives

After completing this chapter, the reader will be able to:

- Describe the factors to consider when interpreting stability data for biologic and biosimilar medications
- Identify the data relating to stability presented in the regulatory documentation
- List some of the considerations and benefits of using manufacturers' stability data vs. extended study stability data.

Introduction

Data on the stability of biologics and biosimilars are generated during the development of a new product or formulation (see Chapter 3). Stability refers to how long the product remains functionally active and safe, and under what conditions; therefore, it is an important consideration when making formulary and prescribing decisions. Owing to the relative instability of biologics and biosimilars vs. other types of therapeutic molecule, it is crucial to bear stability in mind when transporting and preparing the product for use (Figure 1). Data regarding the product's storage and preparation are generally briefly described in regulatory documentation; however, more comprehensive sources of stability data are available. It is important to be able to interpret data on stability for each individual biologic or biosimilar.

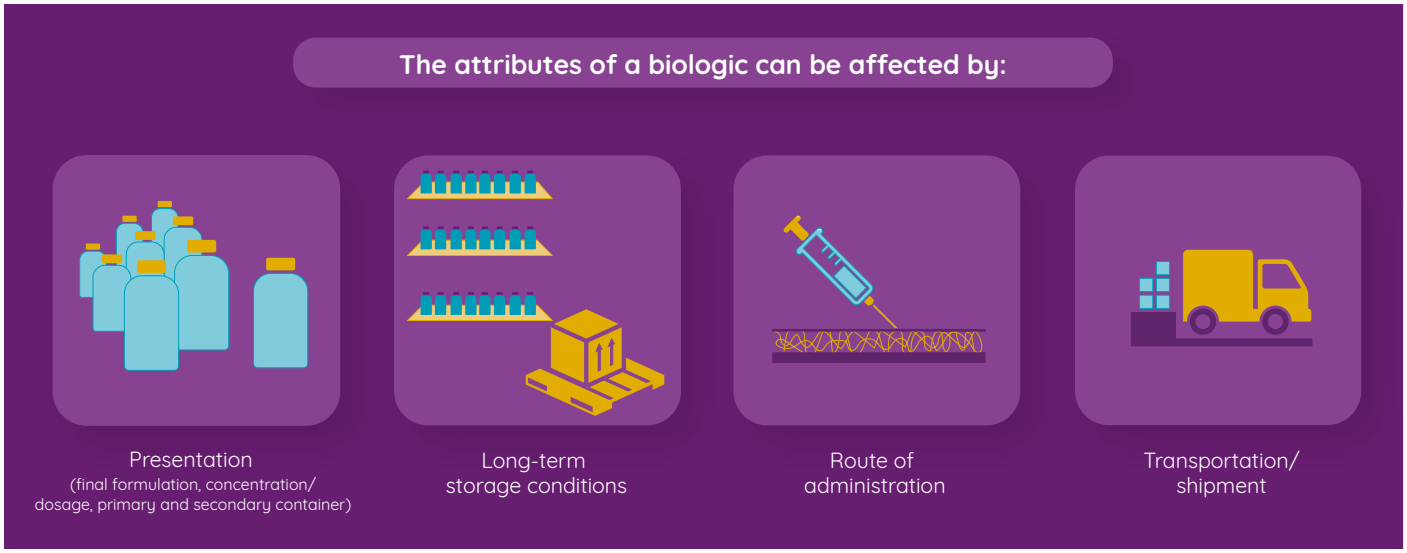


Figure 1. The common manufacturing processes that affect the attributes of biologics[1]

The applicability and quality of stability data

There are a variety of real-time and accelerated methods to test the stability of biologics, encompassing physical, chemical, conformational, thermal and photostability aspects (see Chapter 3).[2] The choice of test depends on the molecular characteristics, required purity and potency, as well as the type of expected degradants.[2]

Forced degradation tests are generally performed prior to stability studies to provide information on the nature of drug degradation and its degradants.[2] Subsequently, the attributes that are most susceptible to change during storage should be tested. Acceptance criteria are a lot more difficult to define for biologics and biosimilars than for small molecules,[3] but must be clinically relevant and defined for each individual product.[4]

Stability data should include, as appropriate, results from the physical, chemical, biological and microbiological tests, including those related to particular attributes of the formulation.[5] Testing is recommended to encompass a minimum of three complementary **separating methods**[4] (e.g. SDS-PAGE or chromatography).[5] While guidelines on stability studies have been published,[6] it is not necessary to provide a

full validation report; although a tabulated summary should be submitted.[7]

Certain quantitative attributes (e.g. assay, degradants) of a product are assumed to follow **zero-order kinetics** (i.e. a constant amount is eliminated per unit time) during long-term storage, and are therefore amenable to statistical analysis, including linear regression and **poolability testing** (determining if regression lines from different batches have a common slope and a common time zero intercept, i.e. that pooling data from multiple batches is possible).[5] Although the kinetics of other quantitative attributes (e.g. pH, dissolution) are generally unknown, the same statistical analysis can be applied, where appropriate.[5] However, qualitative and microbiological attributes are not amenable to this kind of statistical analysis.[5]

The nature of biologic molecules and the use of proprietary manufacturing techniques (including excipients and containers) introduce a level of heterogeneity between products (see Chapter 2); therefore, it is not appropriate to extrapolate the stability data of a reference biologic to the biosimilar, and users should refer to data specific to the product.[3]

Stability information per regulatory documentation

The regulatory documentation for a product can provide brief information regarding the stability of a product, which reflects the data supplied to the regulatory body for approval purposes. This may not be the latest or most comprehensive source of stability data but should be referred to as it details the authorised use of the product.

Information on stability provided in regulatory documentation varies by organisation, but will generally capture storage requirements, any incompatibilities with materials the product is likely to come into contact with, shelf life (unopened and once reconstituted) and details of the container. Excipients used to stabilise the product may also be listed (see Chapter 5). Figure 2 provides examples of the stability information found in regulatory documentation for the reference biologic rituximab (marketed as MabThera® and Rituxan®).

Product stability is ensured by adherence to appropriate storage and handling conditions, maintenance of the '**cold chain**' and good distribution practices. It is important to follow the storage and preparation advice provided by regulatory documentation, particularly with respect to temperature, to ensure that the product remains efficacious and safe. In general, oncology biologics and biosimilars need to be kept at 2–8°C,[11] and maintenance of the cold chain between transit and storage is paramount to ensure the product does not undergo denaturation or degradation (see Chapter 3). This necessitates costly refrigeration infrastructure;[11] it is essential that refrigeration in a treatment centre or pharmacy is reliable and of sufficient capacity for the quantity of product to be stored. Cold chain breaches not only introduce safety concerns but can also have a considerable impact on cost through wastage, regardless of whether the product has been damaged as most liquid preparations, if accidentally frozen, should not be used after thawing.[11]

Stability can be affected by different handling procedures as well as factors such as choice of final container, amount of air present and amount of silicone oil in syringes.[2] Handling and preparation per regulatory documentation provides assurance that the product is being used in an efficacious and safe way. The default diluent is generally 0.9% w/v sodium chloride or 5% w/v glucose.[2] Reconstitution and preparation of anticancer drugs usually takes

place in centralised compounding units in a controlled and validated environment with expert staff.[4] Compounding units are used to control dose accuracy, assure sterility, manage occupational exposure and control stability.[4] Closed-system transfer devices or robots may be used to prevent microbial contamination and exposure to cytotoxics, which can occur during compounding.[12,13]

Stability data beyond regulatory documentation

Though it is important to follow the advice provided in the product label to ensure it is being used correctly, this often does not reflect the totality of evidence available and is considered to provide a conservative indication of stability. Manufacturers are responsible for submitting data to regulatory bodies which demonstrate the stability of a product over the proposed shelf life according to accepted methods of testing, but they and others (e.g. companies that specialise in external compounding) may also have accumulated extended data, some of which may be available in the public domain.

Extrapolation to the retest period or shelf life beyond the period covered by long-term data is commonplace; however, post-dilution or reconstitution stability data are frequently limited to 24 hours for bacteriological reasons, regardless of the true stability, which is longer in many cases.[4] This can result in wastage of expensive medicines and does not allow a great deal of advanced preparation. In practice, oncology treatments may require infusions to be prepared several days ahead of use to allow, for example, the filling of ambulatory devices for continuous infusions or batch preparations for dose banding.[5] Advanced preparation reduces patient waiting times and allows more cost-effective preparation.[3,14] Preparation is carried out according to Good Manufacturing Practice and Good Preparation Practice in pharmacies, and the pharmacist is responsible for the quality, safety and efficacy of the preparation of medicinal products.[15]

To evaluate the stability of a drug, it is essential to consider critical requirements (dose accuracy, sterility assurance, contamination safety and stability under practical clinical conditions), which make it possible to determine the period of validity of the preparation. It is fundamental to have well-documented data on the stability of drugs after opening of the primary package,

A

6.2 Incompatibilities
No incompatibilities between MabThera and polyvinyl chloride or polyethylene bags or infusion sets have been observed.

6.3 Shelf life
Unopened vial
36 months

Diluted medicinal product

After aseptic dilution in sodium chloride solution

The prepared infusion solution of MabThera in 0.9% sodium chloride solution is physically and chemically stable for 30 days at 2˚C–8 ˚C plus an addillonal 24 hours at ≤ 30 ˚C

- After aseptic dilution in D-glucose solution

The prepared infusion solution of MabThera in 5% D-glucose solution Is physically and chemically stable for 24 hours at 2 ˚C–8 ˚C plus an additional 12 hours al room temperature.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 ˚C–8 ˚C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Store in a refrigerator (2 ˚C–8 ˚C). Keep the container in the outer carton in order to protect from light. For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container
MabThera 100 mg concentrate for solution for infusion
Clear Type I glass vials with butyl rubber slopper containing 100 mg of rituximab in 10 mL. Pack of 2 vials.
MabThera 500 mg concentrate for solution for infusion
Clear Type I glass vials with butyl rubber stopper containing 500 mg of rituximab in 50 mL. Pack of 1 vial.

B

16. HOW SUPPLIED/STORAGE AND HANDLING
Rituxan vials [100 mg/10 mL single-use vials (NDC 50242-051-21) and 500 mg/50 mL single-use vials (NDC 50242-053-06)] are stable at 2°C–8°C (36°F–46°F). Do not use beyond expiration date stamped on carton. Rituxan vials should be protected from direct sunlight. Do not freeze or shake.

Rituxan solutions for infusion may be stored at 2°C-8°C (36°F-46°F) for 24 hours. Rituxan solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since Rituxan solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between Rituxan and polyvinylchloride or polyethylene bags have been observed.

C

STORAGE AND STABILITY

Unopened vial
RITUXAN (rituximab) vials are stable at 2–8°C. Do not use beyond expiration date stamped on carton. Keep the vial in the outer carton to protect it from light.

Diluted medicinal product
- 0.9% Sodium Chloride solution

Aseptically prepared infusion solution of RITIJXAN in 0.9% sodium chloride solution is physically and chemically stable for 30 days at 2–8°C plus an additional 24 hours at ≤ 30°C.

- 5% Dextrose solution

Aseptically prepared infusion solution of RITUXAN in 5% dextrose solution is physically and chemically stable for 24 hours at 2–8°C plus an additional 12 hours at room temperature.

As RITUXAN for infusion does not contain any antimicrobial preservative, it is essential to ensure that prepared solutions for infusion are not microbiologically compromised. The diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. Administration should take place as per standard practices after the aseptic preparation of intravenous admixtures.

Incompatibilities
No incompatibilities between RITUXAN and polyvinylchloride or polyethylene bags have been observed.

Figure 2. Stability information for rituximab (MabThera®/Rituxan®) according to regulatory documentation: a) Summary of Product Characteristics; b) US Food and Drug Administration label; c) Health Canada product monograph.8–10

defined by the European Medicines Agency as in-use stability.[16] Extended stability studies for hospital needs and compounding pharmacy units may therefore be helpful in informing prescribing decisions, allowing more efficient preparation and conserving costs. However, caution is advised when adopting approaches not captured within regulatory documentation, which are regarded as off-label use.[17] The view on responsibility and liability related to use of the product changes when use is off-label, and robust justification should be provided for this approach.[17]

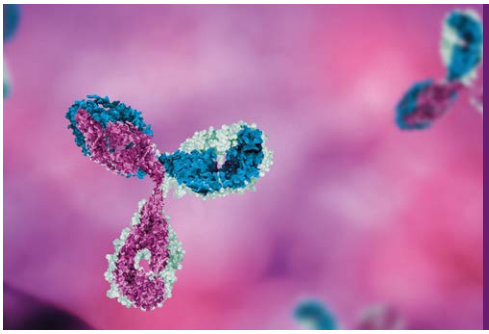
Changes in manufacturing processes may impact the validity of existing shelf life data; therefore, extended shelf life data should be routinely reviewed.[3]

Accessing extended stability data

Searching the published literature, e.g. via PubMed,[i] can help to ascertain whether extended stability data exist for a particular biologic or biosimilar. Studies published without appropriate peer review should not be used to determine shelf life; however, studies published in robust peer-reviewed journals can be used to inform on the wider stability picture for the product.[3] Alternatively, there are databases that can be used as informative sources on compatibility and stability of injectable drugs. The most relevant source is the Trissel's™ 2 Clinical Pharmaceutics Database;[ii] this database requires a subscription but provides high-quality content and a dedicated team to ensure rigour during the editorial process.

In Europe, the most popular database is the Stabilis database,[iii] which is a freely accessible, high-quality resource that holds stability monographs for injectable and non-injectable drugs, including a measure of the quality of evidence. The Stabilis database provides stability information with pictograms and is translated into many different languages.

i. https://pubmed.ncbi.nlm.nih.gov/
ii. https://www.wolterskluwer.com/en/solutions/lexicomp/resources/lexicomp-user-academy/trissels-iv-compatibility-databases
iii. https://www.stabilis.org/



Conclusion

Owing to the complex nature of biologics and biosimilars, assessment of their stability is similarly complex and requires specialist input to design robust trials and interpret data from multiple specialised techniques. To ensure a product is not subject to conditions that are deleterious with respect to its efficacy and safety, regulatory documentation should be referred to for approved storage, handling and preparation instructions. However, stability information in regulatory documentation is often limited and not sufficient for routine practice; thus, the published literature and Stabilis database should be consulted for extended stability data.

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Chapter 5: Excipients

Learning objectives

After completing this chapter, the reader will be able to:

- classify the reasons for using excipients in the manufacturing and final formulations of biologics or biosimilars
- explain the classification of excipients used in biologics and biosimilars
- describe how excipients help to maintain the stability and integrity of biologics or biosimilars
- recall that excipients may alter the immunogenicity of a biologic or biosimilar

Introduction

The molecular structure of **biologic** drugs, which determines their function (see Chapter 1), is held in place by relatively weak bonds; as such, maintaining stability of biologics is a key aim during the development process (see Chapter 3). The addition of **excipients** is often used to improve stability and ensure functionality of biologic or **biosimilar** drugs, as well as for other purposes such as **bulking** to allow accurate measurement.[1] Excipients are common in the final formulations of most biologics, biosimilars and small molecule drugs.[1,2]

An excipient is a substance other than an active drug or pro-drug that is employed during manufacture or contained in the final pharmaceutical formulation.[1,2] The function performed by excipients varies depending on the nature of the drug and can include stabilisation during transport or bulking to allow accurate measurement.

The excipients used in a biosimilar do not have to match the excipients used in the originator product, which can result in differences in immunogenicity (see Chapter 7) and stability (see Chapter 3) between biosimilars and their reference biologic. As the use of biosimilars continues to increase, understanding potential differences in the formulation of biologics and biosimilars, including use of excipients, is vital.

Classification of excipients

Excipients are classified according to the function they perform within a formulation (e.g. buffering agents, tonicity modifiers or preservatives).[1,3] Table 1 lists common examples of excipient classifications.[3]

The excipients used in biosimilars will not necessarily be identical to the originator biologic product. For example, the active ingredient of both Trazimera® (approved in the EU) and Herceptin® is the monoclonal antibody trastuzumab, and both drugs carry the same indication; however, the bulking agent used in Trazimera®, sucrose, is not identical to that used for Herceptin®, α, α-trehalose dihydrate.[4,5]

Table 3. Examples of excipients and their classifications (adapted from Ionova and Wilson. 2020 © licenced under CC BY 4.0)[3]

Functional category	Excipient class	Types
pH modifier (acidifying/ alkalising/buffering agent)	Buffering agents	Acetate, citrate, tartrate, histidine, glutamate, phosphate, tris, glycine, bicarbonate, succinate, sulphate, nitrate
Tonicity agent	Tonicity modifiers	Mannitol, sorbitol, lactose, dextrose, trehalose, sodium chloride, potassium chloride, glycerol, glycerin
Bulking agent	Sugars and polyols	Sucrose, trehalose, glucose, lactose, sorbitol, mannitol, glycerol
	Amino acids	Arginine, aspartic acid, glutamic acid, lysine, proline, glycine, histidine, methionine, alanine
	Polymers and proteins	Gelatin, PVP, PLGA, PEG, dextran, cyclodextrin and derivatives, starch derivatives, HSA, BSA
Antioxidant	Antioxidant preservatives	Histamine, methionine, ascorbic acid, glutathione, vitamin E, poly(ethylenimine)
Antimicrobial preservative	Antimicrobial preservatives	Benzyl alcohol, metacresol, phenol, 2 phenoxyethanol
Chelating and/or complexing agents	Chelator preservatives	Edetate disodium, DTPA, citric acid, hexaphosphate, thioglycolic acid, zinc
Reduction of aggregation[6]	Surfactants	Urea, dextrans, albumin, PEG, polysorbate-80, polysorbate-20

BSA, bovine serum albumin; DTPA, diethylene triamine pentaacetic acid; HSA, human serum albumin; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); PVP, poly(vinylpyrrolidone).

Excipient function

The function performed by excipients can vary depending on the nature of the drug and can include stabilisation during transport or adding bulk. Biologic drugs are, at time of writing (2021), all administered via ophthalmic injection, injection (subcutaneous or intramuscular) or intravenous infusion owing to gastrointestinal degradation of biologics or biosimilars. Therefore, certain functions carried out by excipients in, for example, oral formulations, such as enhancing bioavailability,[1,2] are not relevant to biologic and biosimilar drugs at present. Many companies are attempting to develop oral biologic or biosimilar drug products;[7] should they be successful, these excipient functions may become relevant to certain biologic and biosimilar products.

Excipients have a variety of functions. The most common functions of excipients when used with biologic and biosimilar drugs are to ensure stability, prevent degradation, provide bulk, improve acceptability and reduce loss of product.[1,2] Many excipients have more than one use, which can be an advantage since it reduces the number of excipients needed and minimises the risk of interactions between them.

Excipients can be used to enhance stability by facilitating compressibility or lyophilisation when packaged in a vial (see Box 1 for an example).[8–11] In addition, excipients are used to prevent physical or chemical degradation of biologic and biosimilar drugs, thus maintaining the structure and function of the products. Excipients are also used to provide bulk to potent drugs, allowing easier measurement of small amounts and accurate dosing when preparing batches of drug for patients.[1] As well as adding bulk, excipients can be used to reduce aggregation and loss of product (e.g. at the seal or on the surface of the container).

Excipients can also be used to improve tolerability;[8–10] for example, by minimising localised irritation on injection.[10] Several factors, including volume of injection, pH of the formulation and viscosity of the preparation, can influence injection site pain following subcutaneous injection.[12] Altering the excipients employed as preservatives or as buffering agents can impact on the overall sensation of pain.[12] For example, adalimumab, a monoclonal antibody used in the treatment of several immune-related inflammatory diseases, was reformulated to remove the citrate buffering excipient as it was found to contribute to injection site pain.[13] A retrospective cohort study showed that adherence to and persistence with the treatment regimen were significantly improved with a citrate-free formulation of adalimumab compared with the citrate containing formulation.[13]

Box 1: lyophilisation of biologics and biosimilars – excipients in action

Lyophilisation (freeze-drying) is a widely used method that stabilises and allows fast reconstitution of biologic and biosimilar drug products. The lyophilisation process uses excipients to protect the activity of the biologic or biosimilar drug from the potentially denaturing steps involved.

Lyophilisation involves freezing, primary drying and secondary drying. Residual water is removed to ensure stability and prevent loss of activity of the biologic or biosimilar drug. These processes expose the biologic or biosimilar drug to freezing and drying stresses and so excipients, such as sucrose and trehalose, can be used to protect the drug from such stresses.[11]

In addition to protection from temperature and drying stresses, the avoidance of the Maillard reaction during lyophilisation is an important consideration for producing stable biologic or biosimilar drugs, and appropriate excipient selection (e.g. use of non-reducing sugars) must be made.[11]

In most cases following lyophilisation, the finished product is reconstituted in water for injection, so a short reconstitution time is preferable to allow quick administration to the patient.[11]

Side effects and interactions of excipients

Excipients are often presumed to be pharmacologically inert but increasing evidence shows that certain excipients can alter the properties of the active pharmaceutical.[10,14,15] However, adverse reactions associated with excipients in biosimilars and other biopharmaceutical products are rare.[3]

A 2020 literature review of 230 biologic or biosimilar formulations identified 1,024 separate excipients. From these formulations, the review identified just 17 case reports of excipient-related adverse events, including injection site reactions, anaphylaxis, hyperglycaemia and acute renal failure.[3] While excipient-induced adverse events are rare, maintaining an awareness of the potential of excipients to elicit a reaction is prudent.

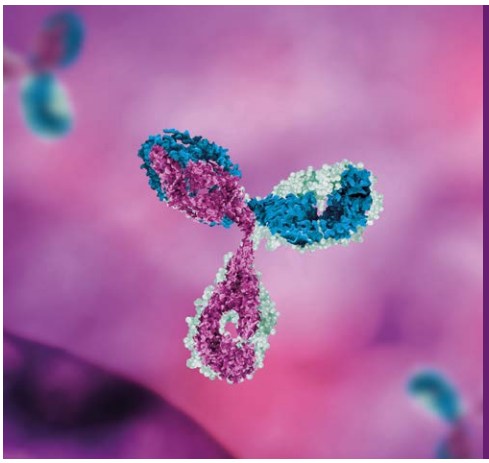
Excipients may also impact on the immunogenicity of biologic and biosimilar products,[3] resulting in rare complications, such as pure red cell aplasia (PRCA; see Box 2).[16,17]

Box 2: case example of excipient-induced immunogenicity: epoetin and PRCA

Epoetin has been used to treat symptomatic anaemia since the late 1980s. A rare immunogenic side effect of epoetin treatment is PRCA. Between 1988 and 1997, three patients developed neutralising antibodies to erythropoietin after treatment with epoetin, leading to PRCA.[18] However, between 1998 and 2004, a total of 191 patients with epoetin-associated PRCA were identified, predominantly in France, Canada, the United Kingdom, Spain, Australia, Germany, Italy, and the United States, with a smaller number of cases in other countries in Asia, Africa, South America and Europe.[16,18]

Although cases were described with all formulations, 92% of cases were in patients who received Eprex®, a particular formulation of epoetin alfa.[16,17] The incidence rate rose drastically between 1998 and 2002 after a change to the formulation which replaced human serum albumin with polysorbate-80 as a stabilising agent.[17] Other factors, including subcutaneous administration and uncoated rubber stoppers, were also indicated in the development of immunogenicity to the epoetin product.[16,18]

By 2004, regulatory authorities mandated Eprex® be administered via the intravenous route and manufacturers added Teflon® coating to prefilled syringes of Eprex®. Subsequently, PRCA cases decreased dramatically, with only six cases reported between 2004 and 2008.[18]



Conclusion

Excipients are used in biologic and biosimilar drug product formulations to enhance stability, maintain biological function and provide bulk, among other functions. They are classified according to the function they perform within the formulation (e.g. citrate is used in some formulations as a buffering agent).

Excipients can be used to facilitate processes such as lyophilisation, which enhances stability by dehydrating and cooling the product, preventing degradation and loss of activity.

Although low, there is a risk that differences in, or changes to, excipients can impact on the safety profile of biologic and biosimilar drug products, as seen in the cases of epoetin and adalimumab.

Sourcing information on excipients

Despite the importance of knowing the concentrations of inactive ingredients in biologic and biosimilar drugs to determine any potential role in adverse reactions, reporting of such information by manufacturers is not compulsory.[3] When searching for information on excipient concentrations, pharmacists should consider:

- checking the approved product monograph
- consulting the **Martindale monographs**
- reviewing **Material Safety Data sheets**
- contacting the product manufacturer for more details.

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Chapter 6: Approving a biosimilar

Learning objectives

After completing this chapter, the reader will be able to:

- Summarise the regulatory principles underlying approval of biosimilars
- Describe how regulatory approval of a biosimilar differs from that of the reference biologic and small molecule generics
- Discuss the best strategy to adopt for the study and trial design to obtain regulatory approval
- Explain that extrapolation is a scientific rationale based on evaluation of the totality of evidence from the entire development programme

Introduction

As discussed in Chapter 2, except for small peptides and short oligonucleotides which can be synthesised chemically, most **biopharmaceuticals** are made by, or extracted from, **living cells.** Differences in manufacturing between the **biosimilar** and reference biopharmaceutical can influence potentially clinically significant characteristics (see Chapter 1).[1] For example, manufacturing differences leading to **glycosylation** and deamidation variants could alter the stability, functioning and safety profiles of the **biologic** and its biosimilar.[2–4]

Biologic manufacturing is closely monitored so molecular changes to the product do not result in negative patient outcomes over its lifecycle.4 For example, following a manufacturing change (e.g. production step up or facility transfer), a biosimilar is required to demonstrate **biosimilarity** to the original.[3] Thus, the focus of the biosimilar approval pathway is to provide assurance that slight differences in production do not impact on clinical performance compared with the originator biologic.[3] Failure to demonstrate comparability to the originator is the most common reason for denying approval of a biosimilar marketing application.[5]

Some principles of regulatory demands for novel candidate biosimilars in various regions around the world (i.e. EU, Canada, Japan) are summarised in this chapter. Because the biopharmaceutical landscape is a rapidly developing and innovative scientific, medical and legislative scenario responsive to ever-changing societal needs, the reader is urged to keep abreast of updates to local regulations for biosimilar approvals.

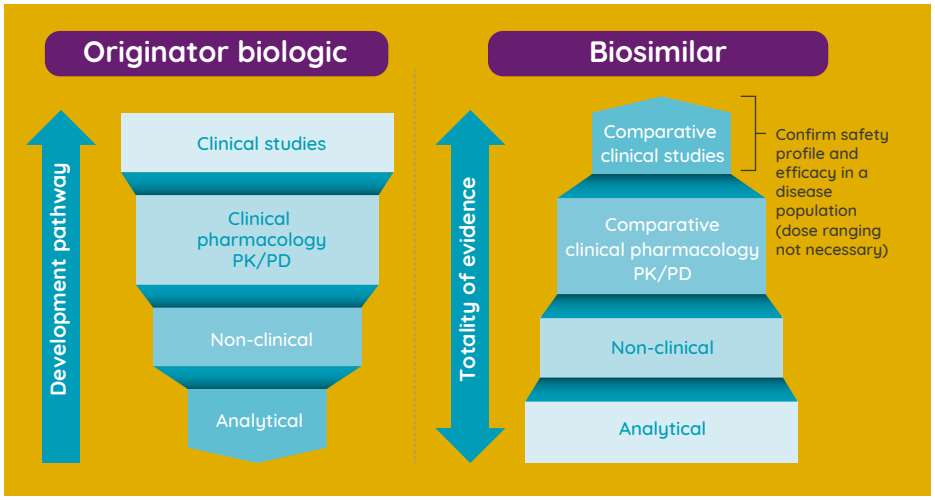


Figure 1. Development pathways for reference biopharmaceuticals and biosimilars (adapted from Verrill *et al.* 2019)[6]

PD, pharmacodynamic; PK, pharmacokinetic.

Biosimilar regulatory approval based on 'totality of evidence'

The regulatory approval process for biosimilars differs from that for reference biopharmaceuticals in several important ways (see Figure 1). Whereas biologic approval follows a stepwise development programme based on pre-clinical studies followed by large-scale clinical testing, biosimilars are evaluated on a 'totality of evidence' approach focused on their ability to demonstrate comparative similarity to the reference product without any clinically meaningful differences.[4] This largely analytically based assessment paradigm is designed to remove the necessity of repeating lengthy and expensive clinical trials for biosimilars.

Regulatory history

The European Medicines Agency (EMA) was the first regulatory body to develop guidelines for biosimilar development, in 2003.[7] With the exception of minor differences, the approval pathways for a biosimilar published by major regulatory bodies such as the EMA, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), and Health Canada are broadly similar and based on establishing biosimilarity with the reference biopharmaceutical.[7–10] Table 1 summarises requirements for biosimilar approvals in the EU, Japan and Canada.

In Japan, guidelines for safety, efficacy and quality of biosimilars (called 'follow-on biologics') roughly follow those published by the EMA, with some notable differences.[11] The

Table 1. Requirements for approval of a biosimilar by the EMA, PMDA and Health Canada (adapted from Nixon NA, *et al.* 2018 & Ministry of Health, Labour and Welfare)[7,12]

Characteristic	EMA (EU)	PMDA (Japan)	Health Canada
Pre-clinical data			
In vitro	Concentration–activity levels, PK, PD data	*In vitro* bioactivities closely related to clinical efficacy compared to originator biologic	Receptor binding studies should be conducted, when appropriate
In vivo	Based on the need for further confirmation after *in vitro* studies; focus (one or more of PK, PD or safety) depends on the need for additional information	In some cases, a bioassay to compare *in vivo* activities vs. originator may be necessary, as may animal studies of immunogenicity	PD and PK studies; at least one repeat-dose toxicity study including toxicokinetic parameters
Clinical data			
Purpose	PK, PD and immunogenicity assessment; PD study might be sensitive enough on its own Must also demonstrate safety and efficacy	PK, PD and immunogenicity assessment using crossover or parallel group design Comparative clinical studies may be necessary	PK, PD, clinical efficacy and safety assessment
Population	Sensitive to demonstrate equivalence	Appropriate population	Population in whom product is indicated unless otherwise justified
Endpoint	For an anticancer mAb, disease-free survival, progression-free survival and overall survival are preferred	Clinically established or appropriate surrogate endpoints	Endpoint sensitive to detect clinically meaningful differences
Interchangeability	Substitution policies are within the remit of the EU member states	Follow-on biologic should not be substituted or used alternately with original biologic	Not recommended
Extrapolation of indications	Possible, based on the overall evidence of comparability provided from the comparability exercise and with adequate justification; if different mechanisms of action are relevant (or uncertainty exists), applicants should supply relevant data	Possible for approved indications of reference product where mechanism of action is the same	Possible; should be justified based on mechanism of action, pathophysiologic mechanism, safety profile in the respective conditions or populations (or both), and clinical experience with reference drug
Post-marketing surveillance or pharmacovigilance	Applicant should present risk-management plan in accordance with EU legislation and pharmacovigilance guidelines	Method and design of post-marketing surveillance study and risk-management plan as discussed with, and approved by, regulatory authorities	Adverse drug reaction reports and periodic safety update reports required The authority to suspend an authorisation is outlined in the Food and Drug Regulations Products must be labelled to indicate that the product is a 'subsequent entry biologic' There should be no claims that the biosimilar is better
Labelling	Summary of product characteristics must be derived from those of the reference product	Non-proprietary names for biosimilars include the word 'biosimilar'; biologics must be ordered by their exact name[13]	Statement indicating that the product is a biosimilar and that similarity between the drugs has been established Comparative data generated by the biosimilar for which the decision for market authorisation was made summarised in tabular format Relevant safety and efficacy information from the biologic drug authorised in Canada to which a reference is made There should be no claims for bioequivalence or clinical equivalence

mAb, monoclonal antibody; PD, pharmacodynamic; PK, pharmacokinetic.

Japanese guideline for follow-on biologics has, until recently, excluded polyglycans such as low-molecular-weight heparin, which is marketed in Japan as a **generic** (not a biosimilar); interchangeability of follow-on biologics is generally permitted and automatic substitution strongly discouraged.[11]

The approval pathway for biosimilars in the USA has some differences to that in operation in the EU, Japan and Canada. In the USA, analytical studies are required to demonstrate that the product is highly similar in structure and function to its originator, and animal studies must be performed to assess toxicity. Clinical evaluation of candidate biosimilars in the USA closely follows the legislative requirements in the EU and these studies are performed in a 'highly sensitive population'.

Pharmacovigilance practices should take into account any safety or efficacy concerns. For example, naming of biosimilars in the USA includes a four-letter identification suffix known as a 'biologic modifier', and product labels require a 'biosimilarity statement' describing the biosimilar's relationship to its reference product.[7]

'**Interchangeability**' is a concept that differs across regulatory agencies. Essentially, whether pharmacists are allowed to substitute a prescribed biologic with a biosimilar may be guided by national guidelines or professional organisation guidelines (e.g. European Society for Medical Oncology position statement vs. European Association of Hospital Pharmacists position statement) and 'automatic substitution' can be interpreted in different ways. Regarding nomenclature rules, the US Food and Drug Administration (FDA) has stipulated that non-proprietary names for biosimilars be given a suffix to differentiate these drugs from originator biologics. For example, biosimilars of infliximab (marketed as Remicade® in the USA) are each assigned a 'devoid of meaning' suffix (infliximab-dyyb, infliximab-abda, infliximab-qbtx) that distinguishes them from the reference biologic and other licensed biosimilar products.[4] EU rules state that biosimilars must have an invented (proprietary) name and an international non-proprietary name (INN) signifying the active substance and both of these should be used for all prescriptions and traceability.

As experience with biosimilars has accumulated, some regulatory requirements have become less stringent: in the EU, which accounts for 90% of biosimilar sales worldwide, guidelines and risk tolerance are considered more lenient than in the USA.[9] For example, some EMA-approved biosimilars were rejected by the FDA, and the FDA has proved stricter in approving extrapolation of accepted biosimilars to other indications.[9] In the case of a trastuzumab biosimilar that exceeded the predefined non-inferiority margins in a pivotal phase III clinical trial, the EMA granted approval based on the sponsor's explanations whereas the FDA asked that the trial be repeated before authorising the biosimilar. Also, whereas in the EU, rituximab biosimilars are approved for all indications for which the originator biologic is authorised, in the USA, the FDA withheld **extrapolation**. Importantly, the EMA has shown significant success in maintaining the balance between due diligence of upholding quality standards and fostering the goal of approving more biosimilars to improve accessibility of treatments in the future.[5]

Non-clinical assays

To demonstrate biosimilarity of a novel proposed product, regulatory agencies require robust comparative physicochemical and functional studies to be conducted to evaluate the biosimilar vs. its reference biologic.[14] Planning for these analytical studies includes selection of an appropriate **expression system** encoding the product's amino acid sequence, design of a high-quality manufacturing process and scientifically sound choice of analytical methodologies to assess the product's physicochemical properties. Finally, multiple functional assays are required to demonstrate the product's biological activity in terms of its posited mechanism of action (MOA), for example, its enzymatic, receptor-mediated and target-binding capabilities.

Regulatory principles

In addition to the above non-clinical tests, extensive head-to-head comparator studies are required to demonstrate biosimilarity of a proposed product and its reference biopharmaceutical.[8] Approval of a biosimilar places more emphasis on physicochemical and biological characterisation and comparative analytical testing, and somewhat less emphasis on data from clinical trials than required for the originator.[8] Importantly, clinical data cannot justify marked differences in analytical outcomes.[15] However, although the clinical data requirement is reduced, the approval process is no less comprehensive.

In general, analytical studies are performed to demonstrate structural and functional similarity to the originator, supplemented by toxicity analyses *in vitro*, and clinical studies are also required to gauge efficacy, **immunogenicity** and **pharmacokinetics/pharmacodynamics** (PK/PD).[16,17]

One of the foundational elements of the EU and USA biosimilar approval processes is the 'stepwise approach' (Figure 2), in which each successive approval step is focused on unanswered regulatory questions from prior steps, supporting more targeted investigations as the process continues.[4,18] Another element particularly pertinent to approvals in the USA is the 'totality of the evidence', with each approval step viewed on aggregate to give a full perspective on the biosimilar.[4]

Clinical trial design

The abbreviated approval pathway for biosimilars, which focuses greatly on analytical testing, nonetheless requires these drugs be tried in well-designed, randomised, controlled clinical studies,[19,20] especially for extrapolation of indications, in either originator biologic-naïve patients or those who have previously received the originator biologic but with a sufficiently long interim wash-out period.[21]

The aim of clinical studies of biosimilars is, broadly speaking, to evaluate PK/PD, efficacy, safety and immunogenicity.[6] During clinical development, new biosimilars are always compared to their originator biologic.[6] Trial design elements must account for: therapeutic indications, target population, background therapy, blinding, stratification, transition design (switch from originator to biosimilar product), primary dependent variable, choice of equivalence vs. non-inferiority design and selection of equivalence margin.[22]

Although biosimilars are generally required to undergo at least one phase III clinical trial in the target patient population, confirmatory PK/PD studies may be sufficient to demonstrate clinical biosimilarity in some cases.[8] PK studies enrol healthy volunteers, who are considered a homogeneous population in whom detectable differences between the biosimilar and the reference biopharmaceutical are likely due to the products themselves and not other factors, such as disease.[8] PD studies can also be used to establish clinical biosimilarity, provided the manufacturer can show a clear dose–response relationship and there is an

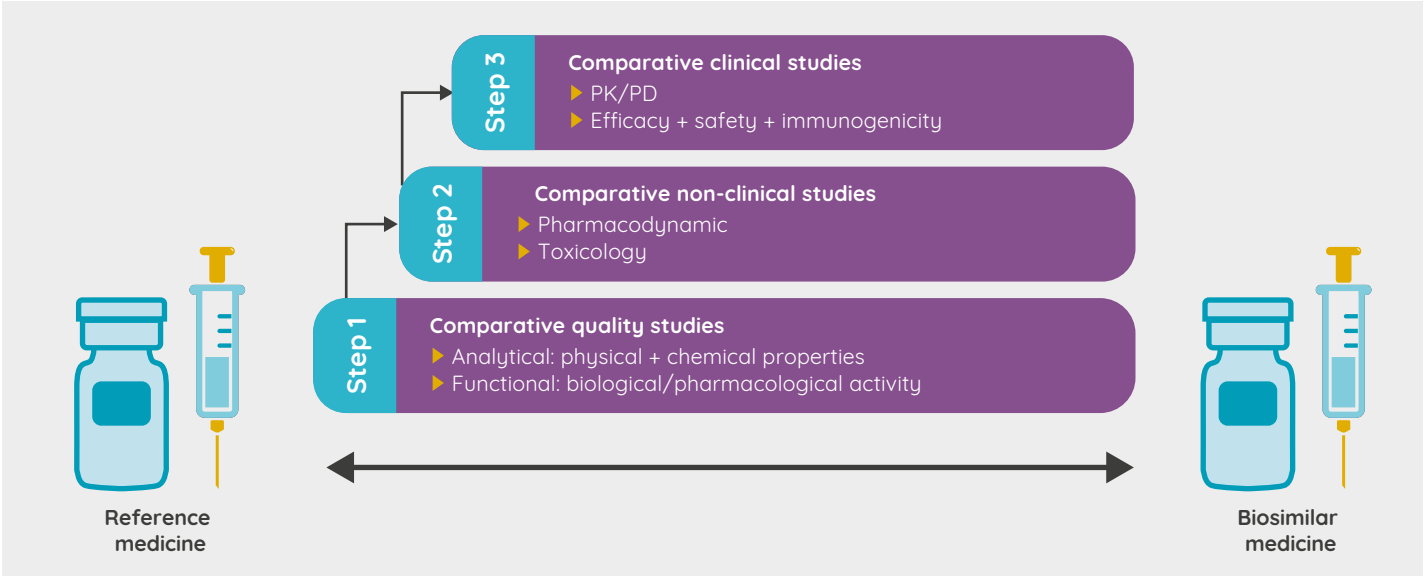


Figure 2. Stepwise approach to biosimilar development (adapted from European Medicines Agency)[18]
PD, pharmacodynamic; PK, pharmacokinetic.

accepted surrogate marker indicative of patient response.[8,15]

More typically, approval of a biosimilar includes a phase I study and at least one phase III study for one of the reference biopharmaceutical's approved indications.[8] Recruitment to phase III equivalence studies should enrol the most sensitive patient population to reduce the effects of potential confounders (e.g. differences in disease burden, previous lines of treatment, comorbidities, locations of metastases).[7,8] As such, a homogeneous patient population increases the confidence that any differences in outcome are attributable to test product rather than individual patient or disease characteristics.[8]

A highly sensitive population can be defined as the set of patients in whom the impact of adding the reference biologic onto standard of care treatment demonstrated the largest impact. For example, the monoclonal antibody bevacizumab was shown to exert greatest impact in patients with non-small cell lung cancer treated with carboplatin + paclitaxel. So, this population was targeted in the phase III clinical trials of bevacizumab biosimilars because it would most likely reveal any differences in clinical efficacy between the biosimilar and the reference biologic. Indeed, in the case of the trastuzumab biosimilar developed by Amgen, clinical trials in the most sensitive populations (defined as early breast cancer[8]) demonstrated reduced quality vs. originator and, as a result, this biosimilar was held up and only approved after a second submission to the USA regulators.

Conventional clinical endpoints in phase III studies of anticancer drugs, such as progression-free survival and overall survival, may not be feasible in biosimilar trials due to the long follow-up needed to capture these outcomes and a lack of sensitivity to show comparability (e.g. due to tumour burden, performance status and other lines of treatment).[8] Rather, phase III studies of biosimilars typically investigate the drug's effects on a sensitive marker of shorter-term activity, such as overall response rate or pathologic complete response.[8,10] Moreover, phase III studies are designed to assess safety in terms of adverse events (AEs), particularly AEs of special interest associated with the reference biopharmaceutical, as well as immunogenicity profiles (see Chapter 7).[8]

Because many commonly used cancer treatments (e.g. radiation therapy and chemotherapy) are myelosuppressive, previous lines of treatment could influence a biosimilar's immunogenicity profile.[7] People with previously treated cancer may, therefore, be a less homogeneous and sensitive population than those with early malignancies for immunogenicity assessments.[7]

Extrapolation of indications

A biosimilar can be approved for all indications for which the reference product is licensed, without being individually tested in each disease scenario (a process called extrapolation), which further avoids conducting unnecessary clinical studies.[8] For biosimilars, the reference product is always the originator biologic, not another biosimilar.[6] Regulatory authorities approve extrapolation of indications based on the overall evidence of comparability, including safety, efficacy and immunogenicity, in an indication that is considered most suitable to detect clinically meaningful differences.[8] However, extrapolation raises various challenges. For example, originator trastuzumab is approved for the treatment of metastatic breast cancer, early breast cancer and gastric cancer;[7] therefore, if a biosimilar version demonstrated comparable efficacy to originator product in the setting of metastatic cancer, can clinicians really be confident that similar efficacy will be achieved in patients with early breast cancer and gastric cancer?

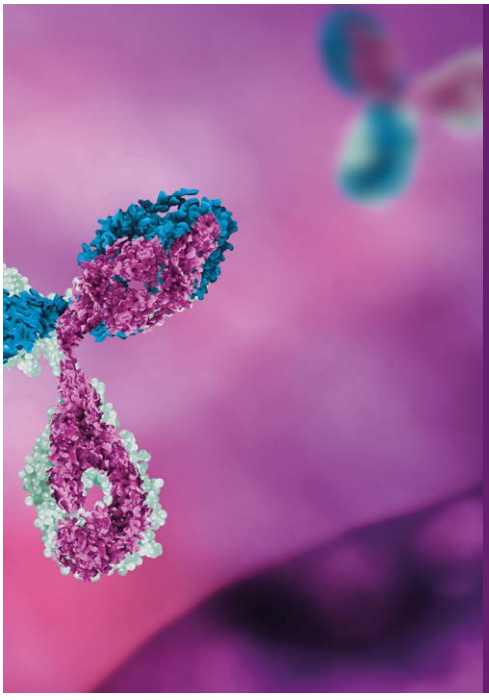
Regulatory authorities consider the scientific justification for the extrapolation of indications, which depends on detailed knowledge of the MOA and the molecular targets, PK profile, immunogenicity and AEs.[8] Regulatory authorities may require additional data if the biosimilar's MOA in different indications is complex.[8] For instance, several MOAs possibly contribute to trastuzumab's effectiveness including degradation of HER2, antibody-dependent cellular cytotoxicity and interference in downstream signalling.[7] Each MOA's relative contribution in different cancers or patient populations is unknown and may be disproportionately affected by

minor differences among biosimilars and the reference biopharmaceutical.[7]

Extrapolation of indications can be even more challenging if the reference biopharmaceutical is used across different therapeutic areas (e.g. autoimmune disease and oncology), as well as in different lines of therapy[8] or in combination with other drugs. Extrapolation of indications also applies when a new formulation of a licensed product is developed,[8] or following significant changes to a licensed product's manufacturing process that could induce clinically meaningful changes to its performance.[23]

After approval

Pharmacovigilance (Chapter 8) is the process of verifying that efficacy and safety evidence leading to approval of any drug, including biologics and biosimilars, is continually confirmed post-approval in real-world clinical practice, when a much larger number of patients receives the treatment for longer.[15] As part of pharmacovigilance, each biosimilar must be prescribed using its brand name to facilitate tracking of its safety profile.[1,24] Health Canada recommends that the unique brand name and the non-proprietary name, as well as other product-specific identifiers such as the Drug Identification Number and lot number, be used throughout the prescription process.[25] To maximise safety and efficacy of biosimilars, education of healthcare providers and patients is critical (Chapter 10).[26] Patients should be monitored closely for AEs associated with the reference biologic as well as any side effects unique to the biosimilar. Patient questions about biosimilars may be addressed by describing the stepwise testing and robust evidence of biosimilarity required for these products.



Conclusion

Differences in manufacturing processes between biosimilars and their reference biopharmaceutical can influence potentially clinically significant characteristics concerning stability, function and safety. Hence, the focus of a biosimilar approval is to provide assurance that considering the 'totality of evidence' slight differences in production do not impact on clinical performance compared with the originator. In contrast, approval of originator biologics follows a stepwise development program based on pre-clinical studies followed by clinical testing. Approval pathways for a biosimilar from the EMA, Japanese PMDA, Health Canada, Australian Therapeutic Goods Administration and US FDA are broadly similar, albeit with some differences regarding, for example, interchangeability and nomenclature rules.

All regulatory bodies require that biosimilarity be demonstrated by robust comparative physicochemical and functional studies covering each aspect of its manufacture and testing, culminating in clinical comparison in a highly sensitive population vs. its reference biopharmaceutical. However, approval of a biosimilar places more emphasis on analytical data than clinical evaluation since patient safety and efficacy have been previously demonstrated for the originator. Biosimilars are evaluated on their totality of evidence, including considerations for extrapolation of its usefulness in the originator product's other indications. Finally, approval of a biosimilar is conditional on the creation of an extensive and long-term post-marketing pharmacovigilance program.

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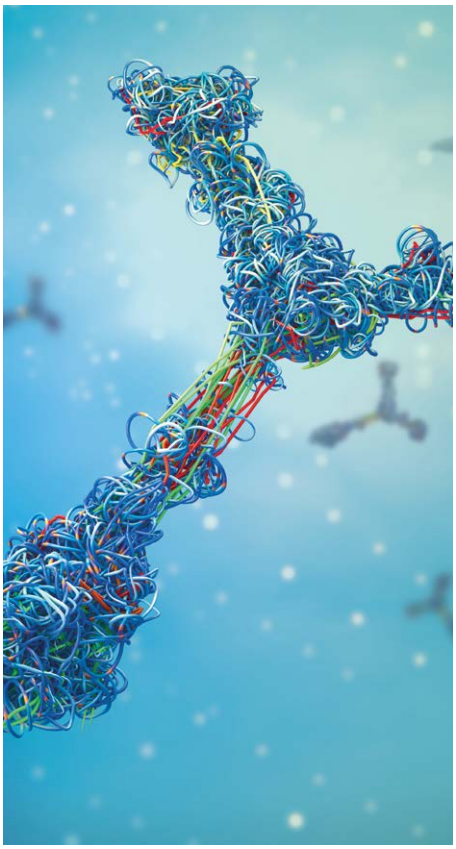
Chapter 7: Immunogenicity

Learning objectives

After completing this chapter, the reader will be able to:

- evaluate the impact of immunogenicity on use of biopharmaceutical drugs
- describe the influence of minor changes to the manufacturing process (or formulation) on the immunogenicity and resultant safety and efficacy of a biopharmaceutical
- recall and discuss the immune-, patient- and product-related factors associated with immunogenicity to a biopharmaceutical and the need for pharmacovigilance



Introduction

Therapeutic proteins (**biologics** and **biosimilars**) may be recognised by the human immune system as antigens and could provoke an immune response, a process known as **immunogenicity**.[1] Protein–drug immunogenicity can lead to safety issues and impact drug efficacy and potency.[2] Immunogenicity is defined as the propensity of antigenic motifs within a therapeutic biologic to stimulate an immune response to itself and to related proteins, or to induce immunologically related non-clinical effects or adverse events.

An immunogenic response to a **biopharmaceutical** is not necessarily undesirable (e.g. following vaccination);[3] however, immunogenicity may lead to lack of efficacy and other unwanted effects in some cases.[4] In this chapter, immunogenicity will refer to an adverse immune response to biologic drugs.

There are several guidelines available to help assess the risk of a biopharmaceutical product inducing an unwanted immune response and analyse the clinical significance of immunogenicity (e.g. EMA recommendations[1]). The immunogenic potential of biologics may be complex to ascertain, and finitely conducted clinical trials of a therapeutic protein may not be adequate to reveal rare adverse reactions or slowly evolving immune responses.[1] Thus evaluation of immunogenicity should be based on integrated analyses of immunological, **pharmacokinetic** (PK), **pharmacodynamic** (PD), clinical efficacy and safety data, and supplemented by a detailed **risk management plan** for **pharmacovigilance** in the post-marketing phase.[1]

Molecular and cellular basis of immunogenicity

Immunogenicity is primarily mediated by **CD4⁺ T-cells** recognising **major histocompatibility complex** (MHC; also known as human leukocyte antigen) class II **epitopes** (short peptide fragments) as a necessary step in the production of **immunoglobulin** (Ig)G antibodies, including **anti-drug antibodies** (ADAs).[2]

Antigen processing and presentation are critical steps in immunogenicity (Figure 1). **Antigen-presenting cells** (APCs) capture foreign (or self) antigens by cellular internalisation and degrade them into antigenic peptides, which bind to MHC class II molecules. The resulting peptide–MHC II complexes are transferred to the APC cellular membrane surface.[5] There, they are recognised by **T-cell receptors**, thus activating the T-cells.[5,6] **T helper cells** interact with B-cells and stimulate their proliferation into plasma cells that secrete antibodies.[7] Alternatively, independent of T-cells, antigenic epitopes can directly crosslink B-cell receptors and stimulate B-cells to differentiate and produce antibodies.[7] The released antibodies seek out and neutralise the foreign material that stimulated their production; in the case of antigenic drugs, these antibodies are termed ADAs.

In susceptible individuals, activated T- and B-cells (and ADAs) can also cross-react with self-peptides that share homology (i.e. have similar epitopes) with foreign antigens, including biopharmaceuticals.[8] This "molecular mimicry" could potentially lead to autoimmunity.[8] However, the balance between self-tolerance and autoimmunity is highly complex and involves inherent (i.e. host genetics) and environmental factors,[8] as evidenced by the relative rarity of biopharmaceutical related immunogenic events. Autoimmunity arising as a consequence of molecular mimicry is reviewed in detail elsewhere.[8]

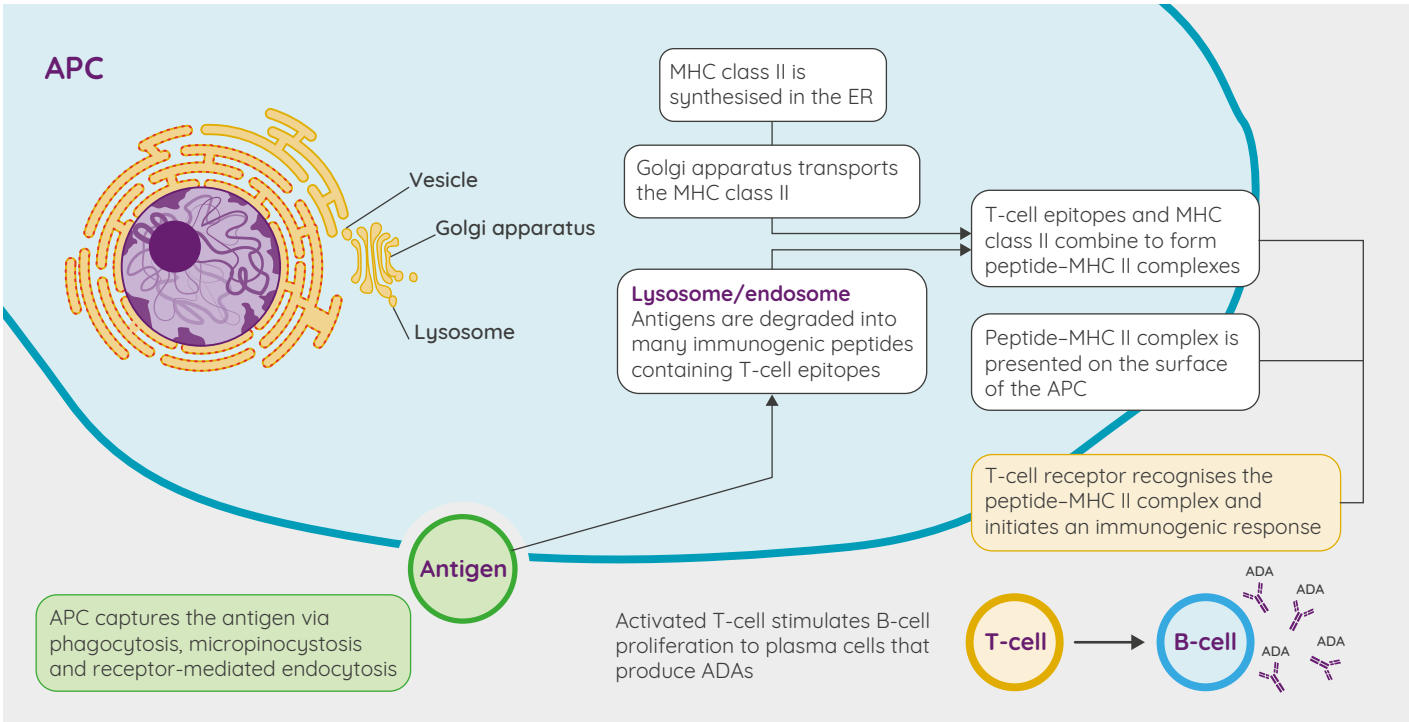


Figure 1. Antigen processing by APCs, and T- and B-cell activation leading to ADA release
ADA, anti-drug antibody; APC, antigen-presenting cell; ER, endoplasmic reticulum; MHC, major histocompatibility complex.

Immune responses

Immune responses are launched against "foreign" (or "self" in autoimmunity) substances such as proteins expressed on invading pathogens and pathogen-derived antigens used in vaccines.[4] Biopharmaceuticals (biologics and biosimilars), which are typically proteins (antibodies, hormones or **cytokines**), may also be antigenic and can sometimes induce a host immune response leading to production of ADAs.[3]

Whether an ADA affects a biopharmaceutical's PK, PD or tolerability profile depends on numerous factors including the **ADA titre** (level of antibody production), duration and neutralising activity.[3] So-called neutralising antibodies bind to active protein domains and reduce the biopharmaceutical's activity,[3] whereas non-neutralising antibodies, although not binding the active domain, bind to other sites on the biopharmaceutical and thereby influence drug clearance, altering its PK and PD profile and compromising tissue targeting.[1,3,9] Moreover, ADAs can cross-react with endogenous proteins or elicit anaphylactic (allergic) reactions, which may be life-threatening.[3]

ADAs can cross-react with endogenous protein homologs (i.e. if the biologic is a replacement therapy), causing the immune system to attack the body's natural counterpart proteins,[9] as has happened in the case of recombinant erythropoietin (leading to pure red cell aplasia [PRCA], a form of severe anaemia; see below),[3,10] growth hormone (leading to growth failure in children) and coagulation factor VII[3] (leading to bleeding).

Self-tolerance is regulated by circulating **regulatory T-cells**. Biopharmaceuticals can 'breach self tolerance' similar to an immune response evoked by autoantigens in autoimmune diseases.[4] For example, antigenic epitopes on the tumour necrosis factor inhibitors adalimumab and infliximab elicit dissimilar immune responses *in vivo*; adalimumab has fewer T-cell epitopes and a higher number of epitopes recognised by regulatory T-cells and consequently is less immunogenic in clinical practice than infliximab.[4] Indeed, early work that led to the development of infliximab recognised that **monoclonal antibodies** engineered from non-human sources (in this case, mice) could be rendered less immunogenic by replacing the murine portion of the gene sequence with human components – that is, by creating a humanised (or chimeric) antibody.[11]

Immunogenicity to a biopharmaceutical characterised by IgE-isotype ADAs can cause **type 1 hypersensitivity** reactions mediated by basophils and mast cells, triggering infusion reactions or in severe cases, **anaphylaxis**.[4] Large therapeutic protein–ADA complexes that are not cleared metabolically can precipitate in tissues, potentially causing tissue damage and organ failure.[4]

Whether the production of biopharmaceutical ADAs can lead to autoimmune diseases per se is uncertain.[12] In the case of vaccine-induced autoimmunity, for example, information is mostly based on anecdotal reports and uncontrolled observational studies.[12] Autoantibody positivity is transient and not followed by any clinical consequences, and autoantibody production rarely develops into autoimmune disease.[12] As more knowledge of the use of biopharmaceuticals accrues, further clarification of their possible association with risk of developing autoimmune diseases will transpire.

Factors affecting immunogenicity of therapeutic proteins

Numerous patient-, disease- and product-related factors potentially influence the risk of immunogenicity; some examples are shown in Table 1.

The presence of immunodeficiency disorders, chronic infections, allergies and

Table 1. Factors affecting or influencing immunogenicity of therapeutic proteins (adapted from European Medicines ageny[1], Jawa *et al.* 2020[4] and Heo *et al.* 2009[10]

Factor	Potential effect(s)
Genetic background	• Patient's immune defect may indicate a lack of natural immune tolerance • Inter-patient variability in response to biopharmaceutical treatment[1] • Genetically determined variation in MHC molecules and TCRs may modify immune recognition of biopharmaceutical components[1] • Differentially expressed cytokines and receptors may influence intensity and evolution of immune response[1,4] • HLA haplotype and B and T lymphocyte repertoire contribute to immune response to a given biopharmaceutical[4]
Type of disease	Antibody production may be increased by infectious diseases or reduced by immunosuppression
Type of protein	• Non-human molecules are usually more immunogenic • **Glycosylation** components and **protein modifications**[1] • Non-purified fragments of cell or organism used to make the biopharmaceutical[1] • Excipients (see Chapter 5)[1] • Biophysical and biochemical factors[1] • Degradants[1] • Aggregates[1,4] • Contaminants[1,13] • Impurities[1,4,13]
Conjugates	Could create new antigenic determinants
Fragments	Could expose new antigenic epitopes
Route of administration	• IM or SC route generally most immunogenic, with IV the least immunogenic[13,14] • SC may be more immunogenic than IV formulations due to differences in antigen processing by dendritic cells and other APCs14
Dose frequency	Immunogenicity increases with more frequent dosing
Duration of treatment	Short-term generally less immunogenic than long-term
Manufacturing process	May introduce impurities or alter 3-dimensional structure (e.g. via oxidation or aggregation)
Handling and storage	May alter 3-dimensional structure (e.g. via oxidation or aggregation)

APC, antigen-presenting cell; HLA, human leukocyte antigen; IM, intramuscular; IV, intravenous; MHC, major histocompatibility complex; SC, subcutaneous; TCR, T-cell receptor.

concomitant immunosuppressant drugs may influence (positively or negatively) a biopharmaceutical's immunogenicity.[1,4]

It is known that immune function and systemic metabolism are closely linked.[15] Whole organism nutritional status can influence immune function by altering circulating cytokines and affecting immune cell populations: undernutrition is associated with immune suppression whereas overnutrition can induce chronic low-grade inflammation that disrupts protective immunity and promotes autoreactivity.[15]

Patients with genetic disorders leading to deficient natural protein expression may not tolerate replacement therapeutic forms

of the protein if the substitution product appears as a neoantigen and is recognised as non-self.[1]

Patient age may also influence the immune response to a biopharmaceutical; young patients with different levels of immune system maturation may show a discrepant response whereas older individuals may potentially exhibit age related immunosenescence.[1]

Drug–drug interactions can alter a medicine's PK profile (disposition) when co administration is with medicines with common metabolic pathways, such as cytochrome P450 enzymes or cell membrane drug transporters.[16] Since monoclonal antibodies are not metabolised and eliminated via these mechanisms, they are thought to be unlikely to compete with chemically synthesised small molecule medicines and therefore present a low risk of drug–drug interactions. On the other hand, immunomodulation due to biopharmaceutical therapy could hypothetically lead to alterations of drug clearance. So far, however, interactions between biopharmaceuticals and small molecule drugs have not shown any significant alterations in systemic exposure.[16]

Biopharmaceuticals are generally classified as two types: natural protein replacements (e.g. insulin, blood coagulation factors, erythropoietin) and therapeutic antibodies or cytokines that target other signalling molecules, cells and receptors implicated in disease pathogenesis. Protein replacement-type biologics (e.g. **hormones** or **enzymes/zymogens**) tend to be smaller in size and have less structural complexity than monoclonal antibodies and are less immunogenic. Factors that determine the immunogenicity of hormone type biologics include the sequence variation from endogenous protein, notably the degree of "humanisation" (i.e. using recombinant technology) vs. animal derived replacement products (e.g. early forms of exogenous insulin derived from cows and pigs).

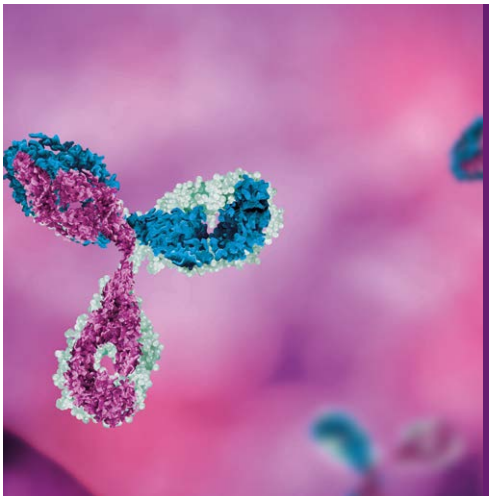
Changes to the manufacturing process of a biopharmaceutical can also influence its immunogenicity profile (see Chapter 2). For instance, a French manufacturer introduced a formulation change to its recombinant human erythropoietin product indicated for patients with kidney disease with anaemia, by switching the product's stabiliser from human serum albumin to polysorbate 80 (see Chapter 5, Box 2).[10,13] This change caused patients receiving the product to develop ADA against the active ingredient, which cross-reacted against natural erythropoietin, neutralising its physiologic action and resulting in 13 cases of PRCA.[10] PRCA also developed after patients received another erythropoietin product; these unwanted effects were traced to a formulation switch involving tungsten microparticles.[4]

Changes of cell line can also lead to important differences in the resultant biopharmaceutical product.[17] Recombinant human granulocyte-macrophage colony-stimulating factor, which is used in patients with cancer for prevention of **neutropenia**, can be produced in various cell lines including Chinese hamster ovary cells, yeast and *Escherichia coli*.[17] The factor produced by the different cell lines varies in propensity to induce immunogenicity.

Clinical practice guidance

While all stages of biopharmaceutical development and testing are geared towards designing, manufacturing and distributing approved products that pose minimal risk of immunogenicity in patients in the real world, immunogenicity remains a constant risk with any biopharmaceutical. Thus, raising awareness of the causes and outcomes of this side effect throughout the multidisciplinary team is advised. Prescribing information for biopharmaceuticals does not typically instruct how or when to monitor patients for the development of ADAs, and besides, appropriate assays may not be routinely available except in specialist laboratories. Although proactive **"therapeutic drug monitoring"** may not be feasible, reactive therapeutic drug monitoring, especially in cases of primary or secondary loss of response, hypersensitivity and injection site or other allergic reactions, is a duty of care for all healthcare professionals dealing with biopharmaceutical products.

Prescribers should be alert and watch closely and continuously even with licensed biopharmaceutical products. Biopharmaceutical-related immunogenicity profiles may differ among the product's licensed indications and at different stages of a particular disease;[1] it is important to remember that immunogenic adverse effects can be acute or delayed. Non-allergic (i.e. not IgE-mediated) infusion reactions are typically observed over the first administration and can be mitigated with appropriate pre-medication. Autoimmune effects, such as cross-reactivity with endogenous proteins with key physiological functions, can also appear and present significant health risks. Many institutions collect serum samples for research purposes, and it may be appropriate to enrol patients who receive biopharmaceuticals in these efforts.



Conclusion

Biologics and biosimilars may stimulate an immune reaction, that is, may be associated with immunogenicity. Immunogenicity due to a biopharmaceutical can impact its efficacy and safety. These large drug molecules, which are typically proteins, may contain antigenic sites that activate immune cells and result in the production of antibodies, both directed against the drug (i.e. ADAs) or the body's other proteins. ADAs can disrupt biopharmaceutical PK, PD or tolerability profiles. Neutralising ADAs directly reduce biopharmaceutical activity, whereas non neutralising ADAs may cause complications such as increasing drug clearance and eliciting cross reactivity. Immunogenicity of a biopharmaceutical is influenced both by its molecular and formulation properties and the immune system of individual patients, with many factors at work including genetic and disease-related inputs. Immunogenicity related to biopharmaceuticals is a highly complex problem and multidisciplinary teams involved in the prescription, preparation and administration of these drugs should be aware of the risks and remain vigilant.

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Chapter 8: Pharmacovigilance

Learning objectives

After completing this chapter, the reader will be able to:

- explain why pharmacovigilance is essential to fully characterise the safety and efficacy of biopharmaceuticals
- demonstrate compliance with pharmacovigilance requirements and prescribing practices

Introduction

Regulatory approval (Chapter 6) of a biosimilar is granted on the basis that its quality characteristics, biological activity, safety and efficacy have been demonstrated as equivalent to those of the reference biopharmaceutical, following a comprehensive comparability exercise. It is also accepted that biosimilars are not completely identical to the reference product as differences in their respective manufacturing processes (Chapter 2) may lead to minor variations in some clinical properties (e.g. their immunogenic potential).[1,2] Differences may also exist between different batches of the same product, and possible reasons for this are detailed in this chapter.

Pre-approval, phase III clinical trials of biosimilars conducted to establish safety and efficacy are not designed to predict whether **post-translational modifications** related to manufacturing conditions (Chapter 1), such as glycosylation, influence immunogenicity.[2] The limited sample size or the rarity of the disease may mean these studies are insufficient to reveal infrequent consequences of immunogenicity prior to authorisation. Because a biosimilar is essentially the same as the reference product, any differences in its clinical performance leading to practice-related adverse effects may be rare and only detectable after prolonged exposure in larger populations.[3] Therefore, clinical safety of biosimilars must be monitored closely during the post-marketing phase.[3] For instance, clinical observation showed that some erythropoietin biosimilars may cause higher-than-expected rates of pure red cell aplasia (Chapter 7) against a background anti-erythropoietin antibody incidence rate of only 0.2–6 cases per 100,000 patient-years.[3]

An illustrative example of this effect is shown in Table 1. A hypothetical study of 1,000 participants has an 82% chance of detecting doubling from 5% to 10% in the true rate of a treatment-related adverse event ([AE] vs. control group), but only a 17% chance of detecting a doubling from 1% to 2%.[4] A study would need to include more than 50,000 people to detect an increase from 0.1% to 0.2% with statistical power of 80%, which is generally considered the acceptable threshold.[4] Although a proportionally small absolute incidence rate, an increase from 0.1% to 0.2% could adversely affect many patients if very large numbers receive the treatment, as happens for approved drugs in the real world.[4]

Table 1. Statistical power to detect a doubling of AE rates, by sample size[4]

Sample size	From 5% to 10% (%)	From 1% to 2% (%)	From 0.1% to 0.2% (%)
1,000	82	17	5
5,000	>99	80	7
10,000	>99	>98	17
50,000	>99	>99	79

AE, adverse event.

Pharmacovigilance

A rare or delayed drug side effect may not emerge until many people have been exposed for a longer time than can be captured in clinical studies, which typically last approximately 6 months to 1 year. As a result, **pharmacovigilance** aims to detect and understand the frequency, nature and potential risk factors for AEs by collecting real-world data after the drug is approved.[5] Pharmacovigilance is mandatory for approved drug products for as long as they remain on the market.[6]

Clinical studies, even those supporting the reference biopharmaceutical, may not fully characterise the test drug's overall safety profile for several reasons, including:[4]

- limited sample size of pre-authorisation studies
- study population may be healthier than the general patient population
- study participants may receive better care than in real-world settings

- drugs for chronic diseases will be given for shorter durations than is clinically typical
- patients in clinical practice may have more comorbidities and receive more concomitant medications than the study population

After marketing authorisation, changes to manufacturing process or quality can potentially alter the safety or efficacy profile of a biological product. Therefore, regulatory authorities require that lifecycle pharmacovigilance activities are put in place for all drugs including biopharmaceuticals.[5] The requirements for the management and reporting of suspected adverse reactions apply equally to biologics and non-biologics. A key requirement for pharmacovigilance of biologics is the need to ensure continuous product and batch traceability in clinical use. Pharmacovigilance includes collection, by the product's manufacturer or **market authorisation holder**, of aggregate reports such as a **periodic safety update report** (PSUR) and introduction of a **risk management plan** (RMP).[7] A PSUR is the source for identification of new safety signals, i.e. a principle to determine changes in the benefit–risk profile of the biosimilar, a method of risk communication to regulators and an indicator of the need for risk-reduction initiatives.[7] An RMP provides documentation necessary to identify, characterise, and minimise important risks throughout the product lifecycle and thereby maximise **benefit–risk balance**.[7]

Pharmacovigilance related to biosimilars often follows the same regulatory requirements as for the originator, but one caveat regards device design. Since biologics are administered parenterally, each product is supplied with its own delivery device (e.g. vial, prefilled syringe, pen), which is proprietary to the manufacturer and may differ in both appearance and function from that used for other biosimilars.[8] Hence patient education is required for each product to ensure appropriate and safe use, especially when switching from originator to biosimilar.[8] Safety issues related to a specific product's device, for example malfunctions and complaints, should also be highlighted in pharmacovigilance monitoring (PSUR, RMP) for that product.[7]

A new biologic or biosimilar is often followed in a **registry study.**[5,9] Patient (or product) registries typically enrol large cohorts of individuals whose clinical, demographic, efficacy and safety data are collected at participating hospitals and clinics, often spread across more than one country or region. This type of study may include many thousands of patients and run for long periods of up to a decade or more, providing a wealth of valuable insights into the product's real-world use and outcomes. Patients enrolled in a registry study are often followed after treatment ends or changes,[9] showing a highly detailed picture of their disease course.

Ensuring traceability

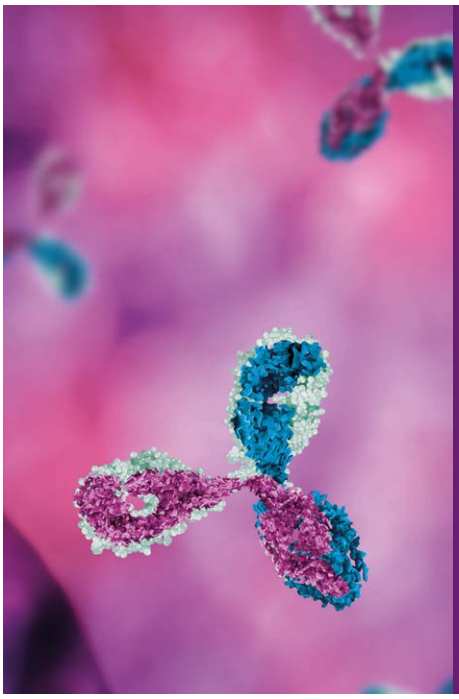
Pharmacovigilance must ensure accurate identification of the drug product associated with any particular AE.[3] Patients treated with biologics may have a number of comorbid disease conditions and often receive polypharmacy, suggesting that tracing causality of side effects to any specific drug is problematic.[7] **Switching** between biosimilars (Chapter 9) complicates attribution of AEs, especially if the product's therapeutic effects are exerted over long time periods, e.g. antibodies.[3]

Many originator biologics are commercially available alongside a range of biosimilars. Therefore, biosimilars should always be prescribed using a **unique name** to ensure traceability of any reported side effects.[2,3] In the USA, reference biopharmaceuticals and biosimilars are given different **international non proprietary names** (INN).[2] Biosimilars are usually noted by a suffix,[2] e.g. for bevacizumab, two of its biosimilars are marketed as bevacizumab-bvzr and bevacizumab-awwb.[10] In the EU, reference biopharmaceuticals and biosimilars have the same INN, so biosimilars are prescribed using their brand name to ensure the intended product is supplied and to enhance traceability of any side effects.[2] Other regional health authorities apply different conventions for naming of biosimilars. In Japan, biosimilars are known by their Japan Approved Name; these drugs are given the INN plus non-proprietary name in parenthesis followed by the letters 'BS' and a number (1, 2, 3…)[11] signifying the ranking order in which the biosimilar was approved. Health Canada proposes that all biopharmaceuticals be identified by their brand name and non-proprietary name, whereas Australian biosimilars are annotated by appending to the INN a second word prefixed by *-sim* and a meaningless syllable.[11]

Naming of biosimilars follows certain INN conventions. Recombinant erythropoietins, for example, are suffixed 'poetin' with a random prefix to indicate changes in the amino acid sequence vs. wild-type protein, e.g. darbepoetin.[5,12] The INN also uses a Greek letter to indicate changes in glycosylation:5 the various products epoetin alpha, beta, omega and delta all have different glycosylation patterns.[13]

Pharmacy dispensing requires recording of both product- and batch-specific exposure information.[14] Recording of exposure information depends on the type of medical records (paper vs. electronic), the extent of linkage between pharmacy and medical records, and local procedures regarding exposure recording and the type of biologic.[14]

As discussed in Chapter 2, the production process for many biopharmaceuticals may undergo one or more modifications during the drug's lifecycle;[15] indeed, the manufacturing process for the infliximab reference biopharmaceutical, REMICADE®, has been altered over 35 times since the drug's inception.[2] A change in the manufacturing process for the etanercept reference product, Enbrel®, meant that two batches with different glycosylation profiles were available simultaneously.2 Therefore, to improve traceability of any reported AE, the batch number, as well as the unique name, of each biopharmaceutical must be recorded in all prescriptions.



Conclusion

Biosimilar drugs, although highly similar by design, are not identical to their reference biopharmaceutical. Minor differences among various biosimilar products can lead to alterations in clinical performance, safety and durability. Pre-approval clinical studies conducted in limited numbers of patients over a constrained period of time may not always reveal the full extent of differences among these products, which may become apparent only once the product reaches the market and has greater exposure in real-world practice.

Pharmacovigilance is the practice of monitoring the performance of approved drugs with the aim of detecting the frequency, nature and potential risk factors for AEs in clinical practice. Pharmacovigilance is mandatory for all prescription drugs including biosimilars. It may include collection of PSURs and introduction of RMPs, providing documentation necessary to identify, characterise, and minimise important risks throughout the product lifecycle and thereby maximise benefit–risk balance.

Several options exist for monitoring real-world drug safety, which may include creating a product registry. Registries usually include large numbers of patients across many geographical areas. Data on these individuals constitute a wealth of valuable information on the product's real-world effectiveness. Pharmacovigilance must also allow traceability to ensure accurate identification of drug product performance. For this reason, all prescriptions must include details of the drug name (specifically related to each biopharmaceutical), batch number and intended length of exposure.

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Chapter 9: Biosimilars in practice

Learning objectives

After completing this chapter, the reader will be able to:

- determine what to consider when reviewing a biosimilar for inclusion in a formulary
- detail the central role of pharmacists in implementing biosimilars in a health service
- discuss concepts of biosimilar interchangeability and regulations pertaining to biosimilar switching and substitution in different regions around the world

Introduction

This chapter introduces several considerations to aid pharmacists and other healthcare professionals (HCPs) when scrutinising **biosimilar** options for **formulary inclusion**. Objective assessments of safety, and clinical and economic outcomes related to candidate biosimilars are performed by **Pharmacy & Therapeutics (P&T) committees** (also known as Drugs & Therapeutics Committees), in which pharmacists play important clinical advisory roles. The aim of P&T committees is to appraise not only each product's characteristics, but also several manufacturer-related factors.[1]

Apart from the topics covered here, HCP and patient education are essential prerogatives (Chapter 10).[1] Pharmacists involved in formulary review of a biosimilar should consider whether the overall evidence justifies the biosimilar's inclusion for each proposed indication, as well as several pricing considerations beyond simply drug acquisition cost (e.g. educational support, **pharmacovigilance** commitments, highly complex interplay of reimbursement permutations among multiple stakeholders).[1] Additionally, switching to a biosimilar may incur non-drug costs including training in its use, administration, storage and handling (e.g. refrigeration and reformulation), and any laboratory tests required for patient monitoring.[2] Overall, cost savings should support conversion from **biologic** to biosimilar. Once included in the formulary, biosimilars should be safely and effectively integrated into treatment algorithms,[1,2] and have safety and clinical monitoring in place.

Procurement of pharmaceuticals including biologics and biosimilars is often subject to **tendering:** competitive bidding, usually at a hospital level, for supplier contracts with the aim of ensuring adequate quantities and high quality while containing spending.[3] In addition to pharmaceuticals, many suppliers also offer support in the form of educational programmes and logistics – so-called value-added services – which may be included in tender awards.[3] Hence tenders do not always focus on price alone; indeed, tendering decisions should be 'value-based'.[3]

Clinical evidence

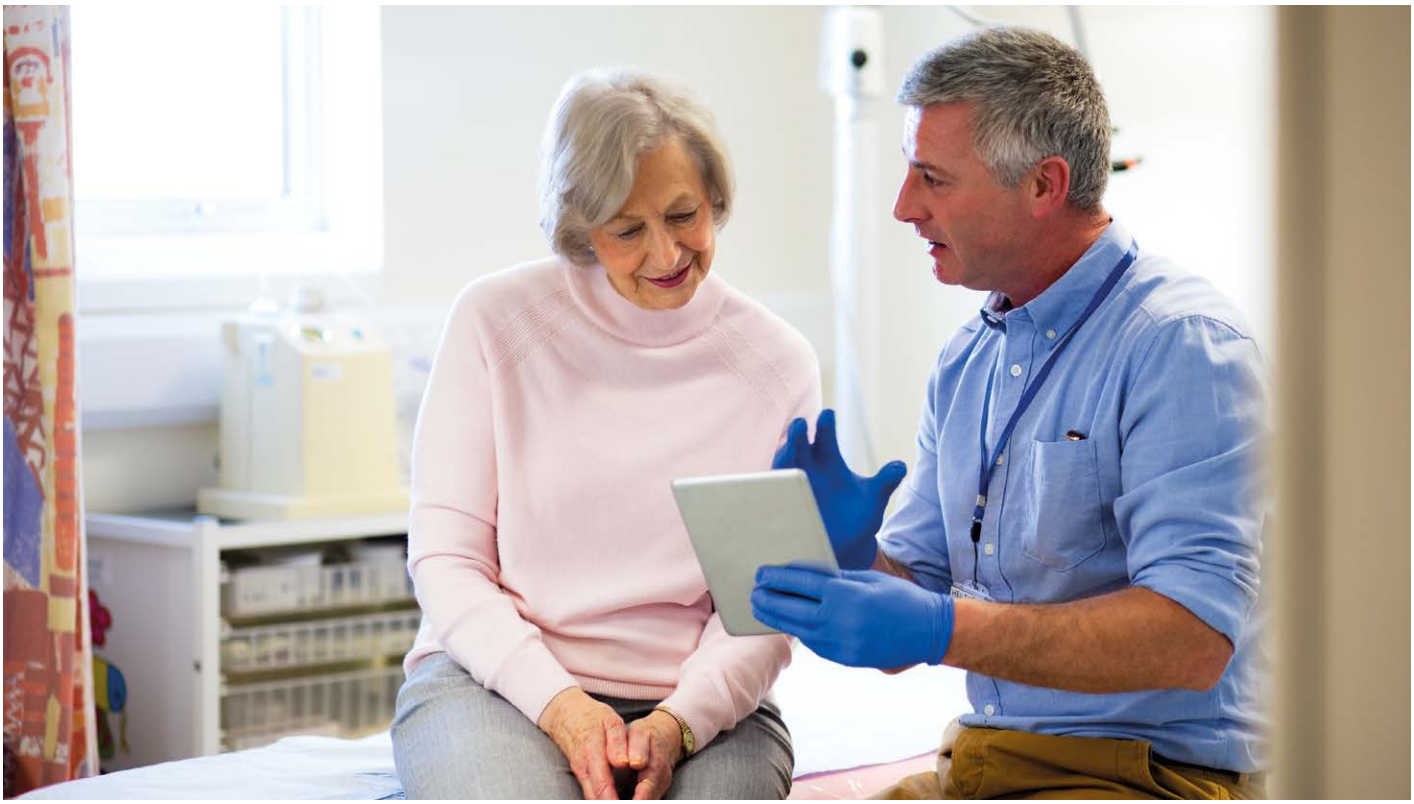
The abbreviated regulatory approval pathway for biosimilars (Chapter 6) often results in the accrual of fewer early phase I–III clinical and laboratory data compared with the reference biopharmaceutical, mostly due to the elimination of phase II (dose finding) trials.[4] Although biosimilars are largely licensed for use in all indications for which the reference biologic (innovator product) is approved, this is not always the case. In general, biosimilars are launched as alternative options in competitive markets with the aim of enhancing patient accessibility and uptake (although they should never be considered identical to their originator biologic and rival biosimilars). Education of all stakeholders (doctors, nurses, pharmacists, healthcare providers and patients) via training materials and programmes is essential and resources are widely available from a variety of sources including biopharmaceutical manufacturers, licensing authorities and medical societies/organisations.[1]

When evaluating a prospective biosimilar for formulary inclusion, it is good practice for pharmacists to familiarise themselves with any differences in product characteristics, particularly in scenarios where multiple alternative biosimilars are available, as well as differences in product presentation and method (dose and route) of administration, which could be confusing for healthcare providers, limit their acceptance and affect patient preference.[1]

Interchangeability – i.e. a designation of whether one biopharmaceutical product can be substituted for another without the knowledge or intervention of the prescribing physician – is subject to regional laws (see below). Extrapolation of indications for biologics is likewise governed according to the mandates of national and regional health authorities (Chapter 6). **Off-label use** of biosimilars in individual patients does happen and should be considered in conjunction with hospital health management policies.

Introducing a new biosimilar clearly has implications for existing patients already receiving ongoing treatment with biologics.[2] Many institutions decide to switch to a biosimilar in all patients both to avoid any confusion and to maximise cost reductions. In some cases, however, hospitals may prefer to gain experience by starting new patients on the biosimilar before considering **switching** established patients, as has happened in some institutions across Europe.

Staying up to date with published **real-world evidence** and pharmacovigilance data (Chapter 8) may provide important insights; rare **adverse events** (AEs), such as changes in **immunogenicity**, may only become apparent post-approval, after large numbers of patients have received the biosimilar.[1,5] In actual clinical practice, multiple switches may occur, including switches between two biosimilars. The effects of multiple switches are largely unknown for many biosimilars; hence vigilance is warranted.[2,6]



Moreover, multiple switching complicates the pharmacovigilance practice of ascribing a particular AE to a specific biosimilar.

Formulation

Pharmacists should consider differences in biosimilars' product characteristics such as their formulation, **excipients** (Chapter 5), containers and method of administration.[1] Different biosimilar products come with a range of delivery devices that are proprietary to the manufacturer, and pharmacists should be aware, and ready to instruct other users, of their correct use (Chapter 10).[7] These considerations may be particularly important in cases where dose adjustments are indicated.

Supply chain

Drug shortages could influence patients' **access to treatment** with an obvious risk of negative effects on clinical outcomes and confidence in the manufacturer.[1] Moreover, supply shortages could increase healthcare costs.[1] When considering adding a new biosimilar to a formulary, pharmacists may consider whether it is manufactured at multiple sites and assess the manufacturer's history of shortages and recalls due to issues with product quality.[1] Other factors to consider include the manufacturer's product handling practices (e.g. controlled temperature during distribution), supply chain security and protection from counterfeit products.[1]

Cost

On introduction to the market, biosimilars are typically priced at a significantly discounted rate – anywhere between 10% and 35% of the reference biopharmaceutical cost.[8,9] Some biosimilars are even cheaper: filgrastim biosimilars, for example, are marketed at greater discounts in the UK due to intense competition. The launch of a biosimilar can also generate price reductions for reference biopharmaceuticals so they can remain competitive.[2,9] However, in Germany there are examples where the cost of the originator supplied to some hospitals was lower than the biosimilar, which made the switch from hospital to outpatient care economically problematic.

Economic analysis of a biosimilar is not confined merely to its acquisition price but may include other factors that incur costs, including:[1,2]

- training and education for HCPs and patients (Chapter 10)
- changes to electronic prescribing systems and drug protocols
- medical information support (e.g. answering questions and maintaining up-to-date systems about new indications and products)
- hospital rules
- pharmacovigilance and laboratory tests (e.g. to monitor **antidrug antibodies**) (Chapter 8)
- technologies for traceability and administrative procedures (e.g. reimbursement and stock control)
- additional monitoring of patients, HCPs and systems
- other infrastructure costs (e.g. storage and handling)

Lastly, drug acquisition prices themselves (and contracts negotiated with manufacturers) can also change over time, and pharmacists should keep abreast of the evolving economic case for stocking each biosimilar.[2]

Infrastructure

Pharmacists should ensure that robust infrastructure supports accurate tracking and tracing to link AEs with a particular biosimilar.[1] Pharmacists must ensure that biosimilars are prescribed and tracked using a unique name (e.g. the brand name in Europe;[10] **international non-proprietary name** [INN], brand name, Drug Identification Number and lot number in Canada;[11] brand name [non-proprietary name suffixed with 'BS'] in Japan;[12] INN in the USA[13]). This may require changes to information technology systems, such as **electronic medical record**s.[1,2]

Storage conditions for a biosimilar may differ from the reference biopharmaceutical, hence training and education are important to avoid inadvertent mishandling.[2] Ideally, each biosimilar and reference biopharmaceutical should be stored separately and clearly marked.[2] Stocking a growing number of biosimilars inevitably places increasing pressure on pharmacy space, which in turn could present another barrier to implementation of these biopharmaceuticals.[1]

Interchangeability

Switching is the conscious decision made by a prescribing physician to discontinue a patient's existing medication and replace it with another medication with the same therapeutic intent.[14] On the other hand, substitution (namely automatic substitution) is when a pharmacist dispenses a different brand of medication (i.e. same pharmaceutical substance made by another manufacturer) to that prescribed, without consulting the prescriber.[14] For different brands of **generic** drugs (small molecule synthetic chemicals), which are considered identical, (automatic) substitution is regarded as inconsequential.[1,2] For biologics and biosimilars, which are not identical but highly similar, substitution is in effect switching and requires complicity of the prescriber, or organisational sign-off and approval.[2] These considerations have given rise to the concept of interchangeability: the extent to which any given biologic and biosimilar can be considered truly equivalent for the same indication, and whether automatic substitution by pharmacists is permissible.[14,15]

Whether biosimilars can be authorised as interchangeable at the pharmacy level is stipulated according to the directives of regional and national health administrators, and P&T (sub)committees.

- In the EU, biosimilars are regarded as interchangeable and the European Medicines Agency delegates that each country determines their own rules on substitution.[14] Indeed, hospitals can devise their own agreements whereby pharmacists can substitute biosimilars for originator biologics as part of an overarching switchover policy.
- In Canada, approved biopharmaceuticals are considered safe and effective for the licensed indications, and the authority to declare two biopharmaceuticals interchangeable rests with each province and territory.[11]
- In Japan, switching of biologics and biosimilars can only be prescribed by physicians and pharmacist substitution is not permitted.[15]
- Pharmacists in Australia can substitute a biosimilar in consultation with the patient, without needing to go back to the prescriber.[16]
- In the USA, the regulations are stricter; switching from biologics to biosimilars is prohibited except for specific biosimilars that have been formally designated interchangeable by the Food and Drug Administration, and even then, substitution is highly restricted in most states.[15]

Evidence abounds that biosimilars are as safe and effective as reference biologics in oncology. For example, analysis of real-world medical records of patients with non-Hodgkin's diffuse large B-cell lymphoma from five European countries showed that biosimilar rituximab is associated with similar response rates to those reported for reference rituximab.[17] Moreover, in another study in the UK, patients could be safely switched from originator to biosimilar rituximab without increasing the risk of infusion reactions.[18]

In practice, **multiple switching** mostly applies to long-term biologic use, in the setting of chronic diseases, and is less common for biologics that are used for a shorter period.[19] Multiple switching may occur for several reasons including changes in pharmaceutical pricing or administrative policy, and non-medical switching from originator to biosimilar then back due to worsening of disease or poor tolerability with the biosimilar.[20]

Maintaining product supply

Healthcare authorities and providers the world over are faced with resource limitations. As such, the main overriding principle of which biologic or biosimilar to hold in formularies is cost reduction. In the UK, the best value biologic product for a given disease is determined as part of a regional tendering process, which helps maintain product supply as well as keep numerous manufacturers of biosimilars in the market. Commissioning rules determine where originators can be used (e.g. to take advantage of a subcutaneous formulation). In Italy, choice of biopharmaceutical is determined by the results of regional tenders, but the originator will normally be available for special cases based on the prescriber's judgement. In some hospital pharmacies across Germany, switching and therefore stocking of only one biosimilar is seen for those biosimilars that have been available for some time, e.g. poietins and filgrastim.

Conclusion

Biosimilars were initially introduced as competitive alternatives to expensive biologics, with the aim of reducing overall cost and improving accessibility of all biopharmaceutical products. This concept, however, introduces many complex considerations beyond lowering drug acquisition prices. Pharmacists play a key role in determining which biosimilars to stock in formularies. Pharmacists advise on clinical and economic assessments of candidate biosimilars in association with P&T committees. In some circumstances, it may be beneficial to introduce a sub-committee or special interest group for biosimilars, where specialists can provide guidelines that deal with the introduction of new biosimilars and switching protocols.

It should always be remembered that biosimilars are highly similar but not identical to their reference biologics. Each biosimilar may have different product characteristics, dosing and method of delivery. Rules on the interchangeability (switching and substitution) of biologics and biosimilars at the physician, pharmacy and, if applicable, patient level are determined by local and regional mandates.

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Chapter 10: Patient considerations and communication

Learning objectives

After completing this chapter, the reader will be able to:

- provide information on and discuss the educational needs of patients regarding biosimilars
- detail the pharmacist's role in delivering advice and support to patients taking biosimilars

Introduction

Between 2019 and 2023, competition due to **biosimilars** entering the **biologics** market is expected to result in savings of approximately US$160 billion in the USA[1] and €100 billion in the EU.[2] In the UK, the NHS has predicted that increasing uptake of best-value biologics and biosimilars could lead to cost savings of at least £400–500 million annually.[3] In Canada, use of established biosimilars was projected to create savings of CAD$294 million in 2021.[4] Meanwhile, in Japan, uptake of biosimilars was slow after the initial launch (2009), but increased steadily thereafter with annual sales reported at approximately JP¥32.4 billion (~US$300 million) in 2020.[5] Clearly there are huge incentives for multiple stakeholders to consider the use of biosimilars.

Patients for whom biologic therapy is indicated should be adequately informed about these products and heavily involved in treatment decisions,[6] such as choice of drug. In a survey of almost 1,700 patients in the USA, 94% of respondents indicated that the decision to switch to a biosimilar should be taken by doctors and patients, rather than payers[7] (e.g. private insurance payers, provincial payers, provincial cancer networks/agencies). Interestingly, fewer than half the respondents indicated that they would be willing to switch from an approved biologic to a biosimilar.[7] Patients as a whole seem poorly informed about biosimilars, contributing to negative attitudes towards their use.[8,9] It is important that pharmaceutical companies and health authorities improve their communication strategies to reassure patients that biosimilars are providing the same benefits as biologics at a lower cost.

Patient needs: education and information

Helpful patient-focused educational initiatives about biosimilars, their approval and use have been released by **regulatory authorities** including the European Commission (EC)[10] and the US Food and Drug Administration (FDA).[11] The EC's approach uses simple terminology to explain the basics of biologics, and how biosimilars are not exact copies but developed by building on the knowledge gained with originator biologics.[10] The EC guideline focuses on initiating biosimilars and transitioning patients from originator biologics to biosimilars (**switching**), as well as on the patient's role in decision-making and reporting side effects.[10] In some countries (e.g. France and the UK), patients are unaware of the price of pharmaceuticals as they do not pay for them directly; as such, patients can be less concerned about the cost savings offered by biosimilars. Materials provided by both the EC and FDA emphasise that the cost reductions associated with using biosimilars can be put back into the healthcare system to provide patients with more options and better access to expensive, novel treatments.[10,11]

Multiple surveys conducted in patients with a broad range of conditions for which biologics and biosimilars may be indicated reveal the importance of education in increasing acceptance and uptake of these drugs.[12] Many patients report having no prior knowledge of biosimilars,[7] suggesting that fundamental education programmes are most appropriate. Indeed, one educational initiative designed to enhance patients' knowledge and awareness of biosimilars, which was followed by an online assessment, showed a marked increase in learning and understanding.[13]

Although surveys can provide conflicting insights into the knowledge of biosimilars held by various groups of patients – ranging from poor to very well informed – a clear pattern emerges. Patients are more likely to accept switching to a biosimilar and adhere to biosimilar therapy if they receive sufficient information about them.[12] For example, patients with cancer may perceive that their disease is "too serious to take any chances" with a cheaper medication, even if they do accept that more expensive drugs are not necessarily better;[14] therefore, patients may need reassurance that the lower cost of biosimilars does not imply inferior quality.[12] Interestingly, hardly any patient concerns over biosimilar cost were connected with their not receiving the best possible treatment. This suggests other negative associations seem to persist around biosimilars, which could be allayed by improved communication.

A study that combined a structured **literature review** along with interviews conducted in a range of stakeholders including physicians, pharmacists and patients revealed a wealth of insights regarding participants' knowledge and acceptance of biosimilars.[12] On the whole, while physicians and patients could be uncomfortable about switching to biosimilars, patients who were switched generally reported positive experiences.[12] Patients rely heavily on the physician's decision to use a biosimilar, and it was suggested that having clear, simple communication and more involvement in clinical decision-making may increase patient acceptance of these drugs.[12] Patients and physicians indicated that a significant

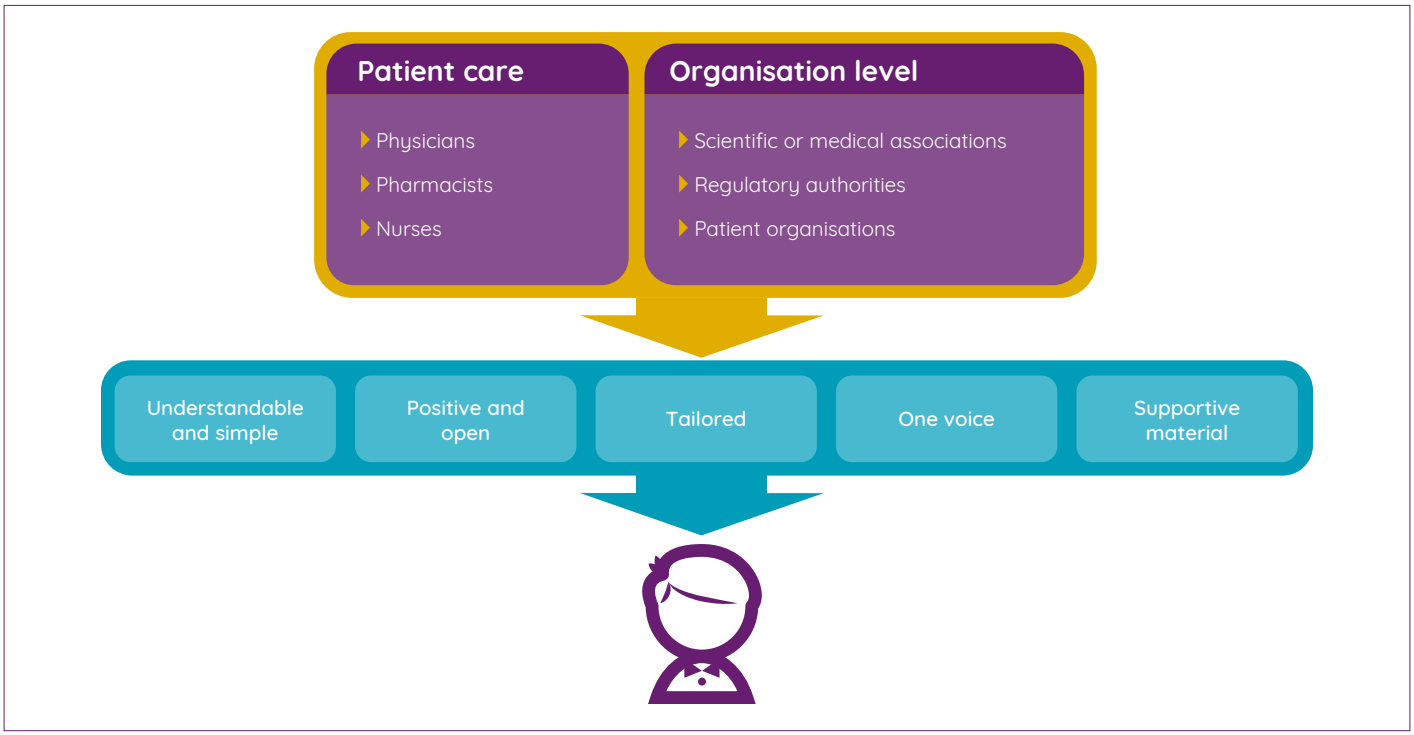


Figure 1. Recommended strategies for informing patients about biosimilars (adapted from Vandenplas Y, et al. 2021)[9]

hurdle to acceptance of biosimilars is understanding regulatory concepts such as approval pathways, particularly regarding robustness.[12]

There are copious amounts of guidance on how to provide patient education about biosimilars from regulatory authorities, scientific or medical professional societies, and **patient advocacy groups**. The amount of information available, especially on the internet and social media, can be disconcerting and make healthcare professionals (HCPs) who wish to communicate with patients unsure of where to start. To counter this, a mapping exercise was performed to provide an overview of what materials exist and to evaluate their tone.[9] This mapping exercise suggested the following actions should be taken when communicating with patients (Figure 1):[9]

- provide understandable and up-to-date information
- communicate positively by stating the similarities between biologics and biosimilars and avoiding negative associations (e.g. mentioning all possible side effects)
- tailor information to individual patient needs
- make messaging coherent and consistent
- use supportive materials such as audio-visual aids (i.e. videos, infographics, podcasts, pictures).

The mapping exercise selected some key, unbiased materials that are suitable to use with patients.[9]

- The European Society for Medical Oncology has developed a series of leaflets using infographics and understandable language.[9]
- The EC/European Medicines Agency's multi-language brochures are standard reference materials and also available online in video format.[9,10]
- Patient associations such as the European Patients' Forum15 and International Alliance of Patients' Organizations16 serve as reliable discussion boards for users to share their experiences with biosimilars.[9]

With the prevalence of "fake news" published on social media or by lobbyists, it is crucial to ensure that scientifically sound information is readily available to combat misinformation and help patients to understand.

Patients who harbour negative expectations about biosimilars could experience a phenomenon known as the **nocebo effect**, where their misperceptions of inferior efficacy and tolerability interfere with the biosimilar's intended pharmacological effects and lead to actual psychological and physiological harm.[17] Causes of the nocebo effect include biased ideas, warnings about a medication and economic information, such as cost in comparison to originator product. Lack of biosimilar therapeutic benefit has been attributed to the nocebo effect in studies that investigated non-medical switchover from originator biologics, where persistence with the biosimilar was curtailed despite it showing similar objective improvements on disease activity as the originator. Strategies to address the nocebo effect in patients receiving biosimilars include providing and emphasising positive information, having more open patient–clinician interactions, alleviating patients' emotional burden, and managing patients' beliefs and expectations.[17] Patients may even benefit from learning about the nocebo effect and its potential psychophysiological mechanisms, including a detrimental impact of anxiety.[17] When discussing treatment, patients who are encouraged to have a sense of control and ownership over the decision-making process may also be less susceptible to nocebo effects.[17]

Elements of biosimilar education

Education and structured communication may increase patients' confidence about and adherence to treatment with biosimilars, e.g. nurse-led education.[18] It follows that HCPs, as primary information resources, should be knowledgeable about biosimilars, guidelines on their use and understand the differences compared with reference

biologics.[18] However, some HCPs lack familiarity with using biosimilars, which could undermine patient confidence as well as lead to medication errors, inflate risk of side effects, delay therapeutic benefit[5] and slow adoption into clinical practice, resulting in delayed economic benefit. A 2016 survey of physicians working in the USA who prescribed biosimilars identified major knowledge gaps surrounding the definition of biologics and biosimilars/biosimilarity, understanding the safety/**immunogenicity** of biosimilars, the totality of evidence, the rationale for **extrapolation of indications**, and definitions of **interchangeability** and related rules.[19] Moreover, an Italian study reported that 74% of hospital specialists and pharmacists considered they had poor knowledge of the scientific principles for the provision of **marketing authorisation** for biosimilars.[20] HCPs should be able to appropriately explain the difference between a generic drug and a biosimilar, and a biosimilar and an originator, as well as how biosimilars can be extrapolated to other indications, which is a new concept in the market authorisation field.

Information for HCPs and patients should be unbiased to allow informed treatment choices.[6] Several interested organisations including the EC,[10] European Society for Medical Oncology,[21] American Society of Clinical Oncology[22] and the pan-Canadian Oncology Biosimilars Initiative[23] have developed educational materials about biosimilars for HCPs. HCPs should be able to articulate arguments in favour of prescribing biosimilars in a manner that is relevant to the patient. For example, patients may rank their ability to perform **activities of daily living** higher than any improvement in **disease rating scales** used by HCPs.[8] Communication about biosimilars with patients must be clear, concise and free from unnecessary **medical jargon**.[9] HCPs should be aware that some patients have an 'emotional bond' with a pharmaceutical brand;[8] indeed, knowledge that they are receiving a particular pharmaceutical brand can have a marked **placebo effect**.[24,25]

Adequately informing patients before considering switching to a biosimilar is associated with positive outcomes;[9] structured communication and management of expectations through patient empowerment may help achieve these positive results.[9,26] Education about biosimilars should be tailored to each individual patient, focus on direct benefits such as increased access to medicines, and should not imply that a switch is done solely to reduce treatment costs.[9] An example of communication strategies to use with patients who are candidates for biosimilars is shown in Table 1. Although originally designed for gastroenterology specialists treating patients with inflammatory bowel disease, the principles may be equally applied to HCPs managing patients who may be suitable for biosimilars.

Pharmacists' role in education and patient support

Pharmacists occupy a key position as providers of information and education about biologics.[9] Typically, physicians provide the first information that patients receive about biologics and biosimilars in the context of

Table 1. Suggested communication strategies and top tips to convey knowledge of biosimilars to patients (adapted from Armuzzi A, *et al.* 2019)[18]

Aim	Communication strategy
Enhance patients' knowledge of their condition via HCP-led education programmes	• Provide comprehensive information on disease pathology and symptomatology
Aid patients' understanding of biosimilars	• Explain the development process for biosimilars • Detail clinical data demonstrating effectiveness and safety of biosimilars • Explain the purpose of biosimilars and their mechanisms of action
Aid successful switching	• Send letters to inform patients about a request or plan to switch • Complete follow-up telephone calls • Suggest online videos • Provide written information • Direct patients to country-specific support groups and charities
Deliver information on a specific biosimilar	• Use instructional videos • Provide biosimilar device-handling leaflet • Give a live demonstration • Provide information on correct storage • Supply information on the most common adverse reactions and how to manage them
Top tips when communicating the concept of biosimilars to patients	• Keep the information simple and use familiar language instead of complex medical terminology • Use visual aids including pictures, graphs and arrays • Check and clarify the patient's understanding by asking them to repeat the information in their own words • Avoid negative associations

their disease. Since discussions about disease and treatments soon after a diagnosis can be highly stressful and overwhelming, especially in patients with cancer, further time may be needed to consider the most suitable option. Follow-up reviews with pharmacists should ideally be scheduled for when patients feel less anxious and have had more time to reflect on their condition and any questions they may have. The role of the pharmacist is to clarify, complement and reassure patients about the information provided by the treating physician.

Hospital pharmacists can help to educate colleagues about biosimilars and implement them in clinical practice (Chapter 9).[9] For example, pharmacists could consider issuing a letter to patients that clearly, in non-medical terminology, describes the reason for the switch to the biosimilar.[6] It has been shown that few patients switch back to the reference biologic after receiving this type of communication.[6]

Availability of biologics and biosimilars across different countries is governed by **marketing authorisation** agreements, which determine whether these medicines can be procured; however, this does not automatically lead to funding, so restrictions are mostly determined by local healthcare systems.[27]

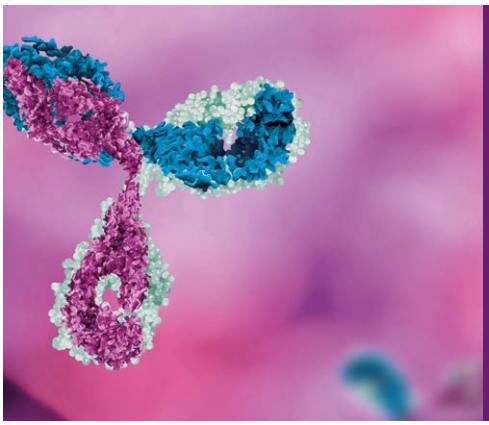
As partners in integrated healthcare systems that determine what products to include in formularies, pharmacists may have an interest in promoting **gainsharing:** the practice of incentivising investment in lower-cost biosimilars by guaranteed redistribution of some of the savings to the hospital or department, and ultimately to physicians and patients, as a means of supporting sustainable healthcare.[27]

In the field of oncology, approved biologics either have direct anticancer effects or are used as supportive management in patients whose bone marrow is weakened due to the underlying cancer or other treatments (e.g. chemotherapy). Although biologics for the treatment of cancer are normally dispensed and administered in hospitals, community pharmacists can play a role in helping patients who have questions about biosimilars and thereby improve their confidence in accepting them as a safe and effective treatment option. Patients wish for and deserve high-quality information to inform their decisions about treatment with biosimilars, and as local, approachable health advisors, community pharmacists should be sufficiently knowledgeable to provide answers to their questions.

Potential roles for new technology

Pharmacovigilance is a key consideration in the use of biosimilar drugs to monitor for rare adverse events (see Chapter 8). Patients must be active participants in the pharmacovigilance process by declaring adverse events or side effects. To facilitate patient feedback, easy-to-use, anonymous platforms or mobile applications would be useful resources. Analysis of the additional pharmacovigilance data would be most effective if done in real time with a return of information and action to the patient. A real-world analysis of efficacy could potentially be completed to create a large database.

Other technological platforms, such as mobile applications to help patients discharge from hospital, or telemedicine or telepharmacy platforms could also be developed to create a strong link between HCPs and outpatients and hospitalised patients. Information transfer to the community pharmacy is crucial as local pharmacists will see the patients frequently.



Conclusion

The entry of biosimilars into the biologics market is expected to result in substantial economic savings. However, there needs to be more patient education available to allay fears over suspected inferiority of efficacy and safety in comparison to the originator. There are different and complimentary routes for dissemination – either patient-care-team-led education (physicians, pharmacists and nurses) and organisation-led education (scientific or medical associations, regulatory authorities and patient organisations). The education provided should explain safety/immunogenicity, totality of evidence and the difference between a generic drug and a biosimilar. Adequately informing patients before considering switching to a biosimilar is associated with positive outcomes during treatment. As always, pharmacovigilance is important for monitoring for adverse events, with patients actively encouraged to participate in the process.

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Glossary

Access to treatment: Access to safe, quality and appropriate services, treatments, preventive care and health promotion activities

Activities of daily living: The tasks of everyday life. These activities include eating, dressing, getting into or out of a bed or chair, taking a bath or shower, and using the toilet

ADA titre: A quasi-quantitative assay providing titre as the unit of the amount of anti-drug antibody in a sample

Adverse event: An untoward medical occurrence after exposure to a medicine, which is not necessarily caused by that medicine

Anaphylaxis: An acute allergic reaction to an antigen (e.g. a bee sting) to which the body has become hypersensitive

Anti-drug antibody: An antibody binding to the idiotope of another antibody, generally an antibody drug. Unwanted immunogenicity is an immune response by an organism against a therapeutic antigen. This reaction leads to production of anti-drug-antibodies, inactivating the therapeutic effects of the treatment and potentially inducing adverse effects

Antigen-presenting cell: A heterogeneous group of immune cells that mediate the cellular immune response by processing and presenting antigens for recognition by certain lymphocytes such as T cells

Benefit–risk balance: The comparative evaluation or weighing of benefits (positive effects) and risks (potential harm) of various medical options for treatment, prophylaxis, prevention or diagnosis done during research and development on new medical products or procedures, or by a regulatory authority deliberating the approval or withdrawal of a product or some intermediate action

Biologic: A preparation, such as a drug, a vaccine, or an antitoxin, that is synthesized from living organisms or their products and used as a diagnostic, preventive, or therapeutic agent.

Biopharmaceutical: Drugs created by means of biotechnology, especially genetic engineering

Biosimilarity: The relationship between a proposed protein therapeutic (biologic) product and an approved reference product

Biosimilar: A biopharmaceutical that is very similar, but not identical, to a previously manufactured one

Bulking: The process of adding excipients to active ingredients to allow convenient and accurate dispensation of a drug substance when producing a dosage form

CD4+ T-cell: Cell that recognises peptides presented on MHC class II molecules, which are found on antigen presenting cells. As a whole, they play a major role in instigating and shaping adaptive immune responses

Chemical instability: The reactive and decomposition ability of substances or species. Chemical instability of a protein involves an undesired covalent modification, such as oxidation, asparagine deamidation, aspartic acid isomerization, or peptide backbone hydrolysis

Cold chain: The cold temperature conditions in which certain products need to be kept during storage and distribution

Co-translational modification: The process of covalently altering one or more amino acids in a protein after translation has begun but before the protein has been released from the ribosome.

Critical Quality Attribute: A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality

Cytokine: Small proteins that are crucial in controlling the growth and activity of other immune system cells and blood cells. Their primary function is to regulate inflammation which is an important part of regulating the immune response

Deglycosylation: The removal of the sugar entity from a glycogen

Disease-rating scale: A rating tool used by healthcare professionals to gauge the course of a particular disease in patients

Electronic medical record: A collection of medical information about a person that is stored on a computer, including information about a patient's health history, such as diagnoses, medicines, tests, allergies, immunisations and treatment plans

Enzyme/zymogen: A zymogen, also called a proenzyme, is an inactive precursor of an enzyme. A zymogen requires a biochemical change for it to become an active enzyme. The biochemical change usually occurs in Golgi bodies, where a specific part of the precursor enzyme is cleaved in order to activate it. Enzymes are proteins that act as biological catalysts

Epitope: The surface portion of antigens capable of eliciting an immune response and of combining with the antibody produced to counter that response

Excipient: Pharmacologically inert, adhesive substances, as honey, syrup, or gum arabic, used to bind the contents of a pill or tablet

Expression system: a genetic construct (a gene encoded by DNA) designed to produce a protein, or an RNA (ribonucleic acid), either inside or outside a cell. Expression systems are used in research and in the commercial production of enzymes or therapeutics

Expression vector: A vector, such as a plasmid, yeast, or animal virus genome, used to introduce foreign genetic material into a host cell in order to replicate and amplify the foreign DNA sequences as a recombinant molecule

Extended stability data: Data that demonstrates the stability of a product that extends beyond the period covered by "available data from the stability study under the long-term storage condition", i.e. it's beyond its recommended shelf-life

Extrapolation: An estimation of a value based on extending a known sequence of values or facts beyond the area that is certainly known

Extrapolation of indication: Approval of a biosimilar for use in an indication held by the reference product but not directly studied in a comparative clinical trial with a biosimilar

Formulary inclusion: Inclusion on the list of medicines prescribed by a particular pharmacy

Fusion protein: Proteins created through the joining of two or more genes that originally coded for separate proteins

Gainsharing: the practice of incentivising investment in lower-cost biosimilars by guaranteed redistribution of some of the savings to the hospital or department, and ultimately to physicians and patients, as a means of supporting sustainable healthcare

Gene expression: The process by which information from a gene is used in the synthesis of a functional gene product that enables it to produce end products, protein or non-coding RNA, and ultimately affect a phenotype.

Gene regulation: The process of turning genes on and off. During early development, cells begin to take on specific functions. Gene regulation ensures that the appropriate genes are expressed at the proper times. Gene regulation can also help an organism respond to its environment.

Generic: A drug that does not have a trademark

Glycosylation: The reaction in which a carbohydrate, i.e. a glycosyl donor, is attached to a hydroxyl or other functional group of another molecule in order to form a glycoconjugate. This reaction is usually catalysed by an enzyme

Hormone: Regulatory substance produced in an organism and transported in tissue fluids such as blood or sap to stimulate specific cells or tissues into action

Host cell: A cell that has been introduced with DNA (or RNA), such as a bacterial cell acting as a host cell for the DNA isolated from a bacteriophage

Hydrolysis: Decomposition of a chemical compound by reaction with water, such as the dissociation of a dissolved salt or the catalytic conversion of starch to glucose

Immunogenicity: The degree to which a substance induces an immune response

Immunoglobulin: Any of several classes of structurally related proteins that function as antibodies or receptors and are found in plasma and other body fluids and in the membrane of certain cells

Interchangeability: A condition in which the biologic product "may be substituted for the reference product without the intervention of the healthcare providers who prescribed the reference product

International non-proprietary name (INN): An INN identifies a pharmaceutical substance or active pharmaceutical ingredient by a unique name that is globally recognised and is public property

Literature review: An overview of the previously published works on a specific topic

Living cell: Cell within a live organism that can achieve homeostasis

Maillard reaction: Also known as non-enzymatic browning, is the reaction between reducing sugars and proteins by the impact of heat. It starts with the reaction of a reducing sugar with an amine, creating glycosylamine

Major histocompatibility complex (MHC): A group of genes that encode proteins on the cell surface that have an important role in immune response. The MHC complex on the cell surface is necessary for cell self-recognition and the prevention of the immune system targeting its own cells

Manufacture: The production of goods using labour, machines, tools, and chemical or biological processing or formulation

Market authorisation holder: A company, firm or non-profit organisation that has been granted a marketing authorisation. The marketing authorisation allows the holder to market a specific medicinal product in a particular country or region

Marketing authorisation: The process of reviewing and assessing the evidence to support a medicinal product in relation to its marketing, finalised by granting of a licence by a regulatory authority for the product to be sold

Martindale monograph: Product monographs detailed in the Martindale reference book published by the Royal Pharmaceutical Society of Great Britain. The Martindale reference book lists over 6,000 drugs and medicines used throughout the world, including details of over 180,000 proprietary preparations

Material Safety Data Sheet (MSDS): Safety document that is provided by manufacturers about particular products

Medical jargon: Any medical terminology which may be unfamiliar to persons without clinical experience

Monoclonal antibody: Antibodies produced by a single clone of cells or cell line and consisting of identical antibody molecules. Monoclonal antibodies are made so that they bind to only one substance

Multiple switching: More than one switch between an originator and a single biosimilar for non-medical reasons

Neutropenia: A condition where a person has a low level of neutrophils (a type of white blood cell)

Nocebo effect: A situation in which a patient develops side effects or symptoms that can occur with a drug or other therapy just because the patient believes they may occur

Off-label use: Use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration

Originator: the original/reference approved biologic pharmaceutical on which a biosimilar drug is based

Patient advocacy group: A formally organised non-profit group that concerns itself with a medical condition or potential medical condition, and that has a mission and takes actions that seek to help people affected by that medical condition or to help their families

Periodic safety update report: Pharmacovigilance documents intended to provide an evaluation of the risk–benefit balance of a medicinal product at defined time points after its authorisation

Pharmacodynamic: The study of a drug's molecular, biochemical, and physiologic effects or actions

Pharmacokinetic: The study of the time course of drug absorption, distribution, metabolism, and excretion

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem

Pharmacy & Therapeutics (P&T) committee: The medical staff committee responsible for managing the formulary system who provide an evaluative, educational and advisory

service to the medical staff and organisational administration in matters pertaining to the use of available medications

Physical instability: Varying degrees and forms of unfolding, aggregation, fragmentation, or adsorptive losses of proteins

Placebo effect: A beneficial effect produced by a placebo drug or treatment, which cannot be attributed to the properties of the placebo itself, and must therefore be due to the patient's belief in that treatment

Poolability testing: Analysing the stability of the parameters (it can be performed across individuals and over time). In simple words, the goal of the testing is to analyse if the same coefficients are applicable for all individuals and time

Post-transcriptional modification / co-transcriptional modification: A biological process common to most eukaryotic cells by which an RNA primary transcript is chemically altered following transcription from a gene to produce a mature, functional RNA molecule that can then leave the nucleus and perform any of a variety of different functions in the cell

Post-translational modification: Covalent and generally enzymatic modification of proteins following protein biosynthesis to form the mature protein product

Product drift: A change in the product and its characteristics that can occur over time as a result of manufacturing changes

Protein modification: Any change in the chemical composition of proteins following translation, also known as post-translational modifications

Protein synthesis: The process by which amino acids are linearly arranged into proteins through the involvement of ribosomal RNA, transfer RNA, messenger RNA, and various enzymes

Purification: The process of removing extraneous matter to avoid contamination

Real-world evidence: Data that are collected outside the constraints of conventional randomised clinical trials

Recombinant: A cell or organism whose genetic complement results from recombination

Reference product: The original/reference approved biologic pharmaceutical on which a biosimilar drug is based

Registry study: An investigation of a research question using the infrastructure of a new or existing registry(-ies) for patient recruitment and data collection

Regulatory approval: Approval of a drug for use in patients by a country or region's competent regulatory authority (e.g., EMA or Health Canada)

Regulatory authority: A body that carries out regulatory activities relating to medicines, including the processing of marketing authorisations, the monitoring of side effects, inspections, quality testing and monitoring the use of medicines

Regulatory T-cell: A specialized subpopulation of T cells that act to suppress immune response, thereby maintaining homeostasis and self-tolerance

Ribosome: A minute round cytoplasmic particle composed of RNA and protein that is the site of protein synthesis as directed by mRNA.

Risk management plan: A document that includes information on a medicine's safety profile; how its risks will be prevented or minimised in patients; plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine; measuring the effectiveness of risk-minimisation measures

Self-tolerance: the ability of the immune system to recognize self-produced antigens as a non-threat while appropriately mounting a response to foreign substances

Separating method: Method that converts a mixture or solution of chemical substances into two or more distinct product mixtures

Shelf-life: The term or period during which a stored commodity remains effective, useful, or suitable for consumption

Stabilisation: The processes used to retain a product's properties and characteristics that it possessed at the time of its manufacture

Substitution: The practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber

Switching: A change from routine use of one specific product to routine use of another specific product with the same therapeutic intent

Target protein: A functional protein which a given drug binds to, resulting in an alteration of the normal function of the bound protein and a desirable therapeutic effect

T-cell receptor: Protein complex found on the surface of T cells, that are responsible for recognizing fragments of antigen as peptides bound to major histocompatibility complex molecules

Tendering: The process where hospitals invite bids for large contracts that must be submitted within a finite deadline

T helper cell: A type of T cell that plays an important role in the immune system "helping" the activity of other immune cells by releasing cytokines

Therapeutic drug monitoring: the clinical practice of measuring specific drugs at designated intervals to maintain a constant concentration in a patient's bloodstream, thereby optimizing individual dosage regimens

Transcription: The process by which mRNA is synthesized from a DNA template resulting in the transfer of genetic information from the DNA molecule to mRNA

Translation: The process by which mRNA, tRNA, and ribosomes effect the production of a protein molecule from amino acids, the specificity of synthesis being controlled by the base sequences of the mRNA

Type 1 hypersensitivity: Also known as an immediate reaction, involves immunoglobulin E mediated release of antibodies against the soluble antigen. This results in mast cell degranulation and release of histamine and other inflammatory mediators

Unique name: The name that the drug manufacturers uses to differentiate different formulations

Zero-order kinetics: A way of describing how the body uses and breaks down some medicines. While the rate at which the body eliminates most drugs is proportional to the concentration administered, known as first order kinetics, drugs that work by zero order kinetics work at a predictable, constant rate

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