

WHAT IS A BIOSIMILAR?

> A biosimilar is a biological product

FDA-approved biosimilars have been compared to an FDA-approved biologic, known as the reference product.

Reference and biosimilar products are:



Large and generally complex molecules



Produced from living organisms



Carefully monitored to ensure consistent quality

> A biosimilar is highly similar to a reference product

For approval, the structure and function of an approved biosimilar were compared to a reference product, looking at key characteristics such as:



Purity



Molecular structure



Bioactivity

The data from these comparisons must show that the biosimilar is highly similar to the reference product.

> A biosimilar has no clinically meaningful differences from a reference product

Studies were performed to show that biosimilars have no clinically meaningful differences in safety, purity, or potency (safety and effectiveness) compared to the reference product:



Pharmacokinetic
and, if needed,
pharmacodynamic studies



Immunogenicity
assessment



Additional clinical
studies as needed

Studies may be done independently or combined.

> A biosimilar is approved by FDA after rigorous evaluation and testing by the applicant

Prescribers and patients should have no concerns about using these medications instead of reference products because biosimilars:



Meet FDA's
rigorous standards
for approval



Are manufactured
in FDA-licensed
facilities



Are tracked as part
of post-market
surveillance to ensure
continued safety

Introduction

- Biological medicines are derived from living cells or organisms and consist of large, highly complex molecular entities which may be difficult to characterise.
- Due to the variability of the biological system and the manufacturing process, biological medicines may show a certain degree of variation, even between batches of the same product



- ▶ A biosimilar medicine is a biological medicine that is developed to be highly similar and clinically equivalent to an existing biological medicine.
- ▶ A biosimilar contains a version of an active substance of an already approved biological medicine, which is referred to as the 'reference medicine' or 'originator medicine'.
- ▶ Similarity to the reference medicine in terms of quality, structural characteristics, biological activity, safety and efficacy must be established based on a comprehensive scientific comparability exercise such that they do not have any clinically meaningful differences from the reference medicine in terms of quality, safety and efficacy

Biologic Medicines ?

- A large Protein molecule typically derived from living cells and used in the treatment or prevention of disease
- Include therapeutic proteins, DNA, monoclonal antibodies and fusion proteins.
- Often 200 to 1,000 times the size of a small molecule drug and far more complex structurally.

Examples :

- Human Growth hormone
- Human insulin
- Erythropoietin
- Vaccines
- Monoclonal antibodies



Biologicals : Differences to Small molecules


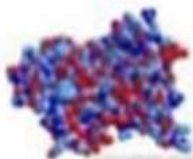
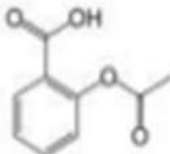
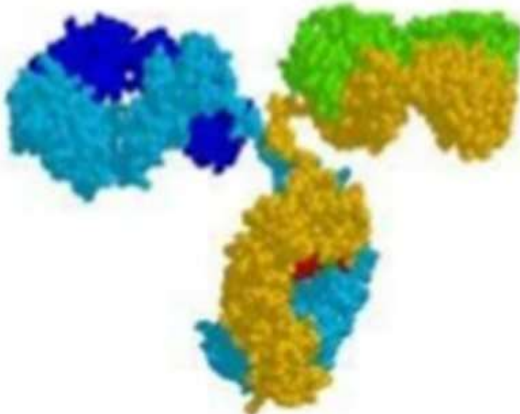
Size			
			
	Aspirin 21 atoms	Growth hormone 3,000 atoms	Monoclonal Antibody 25,000 atoms
Structure	1 ^o	1 ^o , 2 ^o , 3 ^o , 4 ^o	
Bonding	Strong (covalent)	Strong & Weak (covalent & non-covalent)	

Table 2 Comparison of generic, biosimilar, and innovator products

Process	Biologic	Biosimilar	Generic
Manufacturing	Produced by biological process in host cell lines Sensitive to production process changes – expensive and specialized production facilities Reproducibility difficult to establish	Produced by biological process in host cell lines Sensitive to production process changes – expensive and specialized production facilities Reproducibility difficult to establish	Produced by using chemical synthesis Less sensitive to production process changes Reproducibility easy to establish
Clinical development	Extensive clinical studies, including Phase I–III Pharmacovigilance and periodic safety updates needed	Extensive clinical studies, including Phase I–III Pharmacovigilance and periodic safety updates needed	Often only Phase I studies Short timeline for approval
Regulation	Needs to demonstrate “comparability” Regulatory pathway defined by Europe (EMA) Currently no automatic substitution intended	Needs to demonstrate “similarity” Regulatory pathway defined by Europe (EMA) No automatic substitution allowed	Needs to show bioequivalence Abbreviated registration procedures in Europe and US Automatic substitution allowed

Abbreviation: EMA, European Medicines Agency.

Table 5 Biosimilars approved or rejected timeline

Biosimilar	Reference	Approval/Rejection year
Omnitrope	Somatropin	2006*
Valtropin	Somatropin	2006*
Binocrit	Epoetin alpha	2007*
Epoetin alpha	Epoetin alpha	2007*
Hexal		
Abseamed	Epoetin alpha	2007*
Silapo	Epoetin zeta	2007*
Retacrit	Epoetin zeta	2007*
Filgrastim	Filgrastim	2008*
Ratiopharm		
Ratiograstim	Filgrastim	2008*
Biograstim	Filgrastim	2008*
Tevagrastim	Filgrastim	2008*
Filgrastim hexal	Filgrastim	2009*
Zarzio	Filgrastim	2009*
Nivestim	Filgrastim	2010*
Alpheon	Roferon-A	2006**
Human insulin	Humulin	2007**

Notes: *Approved, **Rejected

Comparison of Traditional Small molecule drugs and Biologic drugs

Feature	Small Molecule Drug	Biologic Agent
Example	Acetylsalicylic acid (180 Da)	Monoclonal antibody (~150,000 Da)
Entity	Chemical	Protein
Structure	Small, simple, well characterized	Large, complex, heterogeneous
Stability	Stable	Unstable
Mode of administration	Usually amenable to ingestion	Usually requires injection or infusion
Manufacturing process	Predictable and precise method; identical copies in batches	Living cell-based complex technology; batch-to-batch variation, sensitive to storage and handling
Immunogenicity	Mostly nonimmunogenic	Immunogenic

What are biosimilars?



- Legally approved ***subsequent versions*** of innovator biopharmaceutical products made by a different sponsor ***following patent & exclusivity expiry*** of the innovator product.
- Because of structural & manufacturing complexities, these biological products are considered as ***similar, but not generic equivalents*** of innovator biopharmaceuticals



DEFINITION OF BIOSIMILARS



World Health
Organization



U.S. Food and Drug
Administration

SBP (Similar Biologic Product)

Abiotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product

FOB (Follow-On Biologic)

Abiological product that is highly similar to a U.S.licensed reference biological product with no clinically meaningful differences in terms of the safety, purity and potency .

Based on these different definitions,
Three determinants in definition of
biosimilar product:



1. It should be a ***biologic product***

Reference product should be an already ***licensed***
biologic product

3. Demonstration of ***high similarity*** in safety, quality &
efficacy is necessary

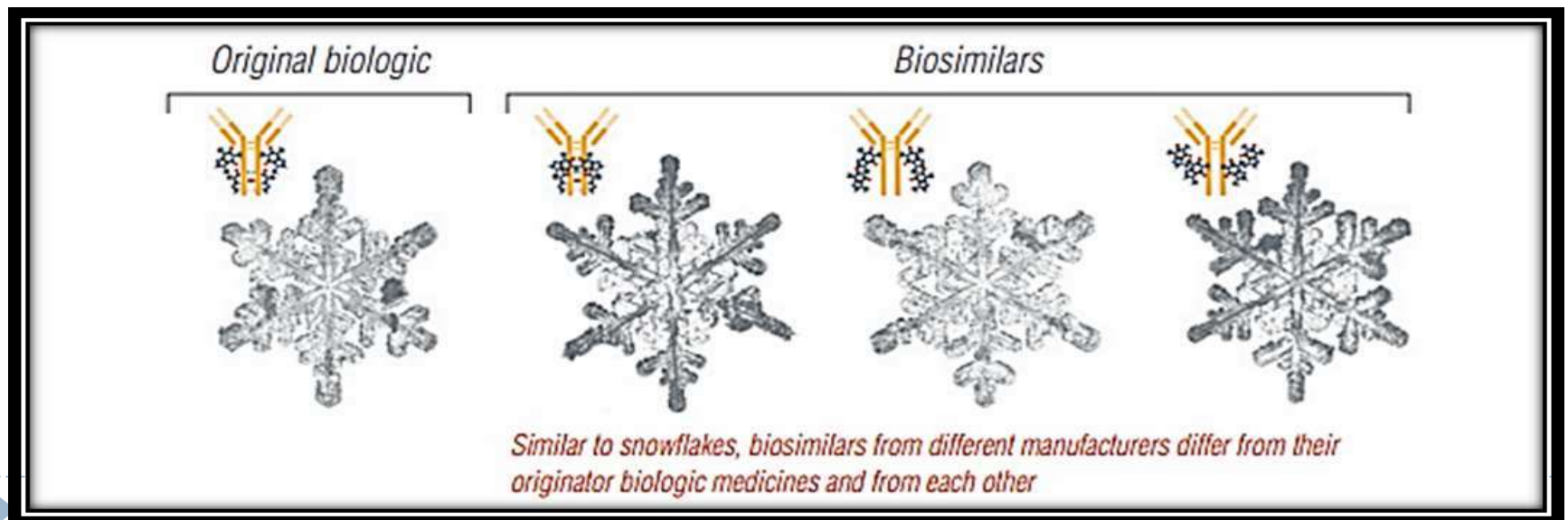
➤ *Similarity should be demonstrated using a set of
comprehensive comparability exercises at the quality,
non-clinical & clinical level*



Biosimilars

Unlike generic medicines where the active ingredients are identical, biosimilars – by definition are not likely to be identical to the originator biologic.

Similar to Snowflakes Biologics made by different manufacturers differ from the original product and from each other.



Structure of mAb's

Primary Structure

– the amino acid sequence

Secondary Structure

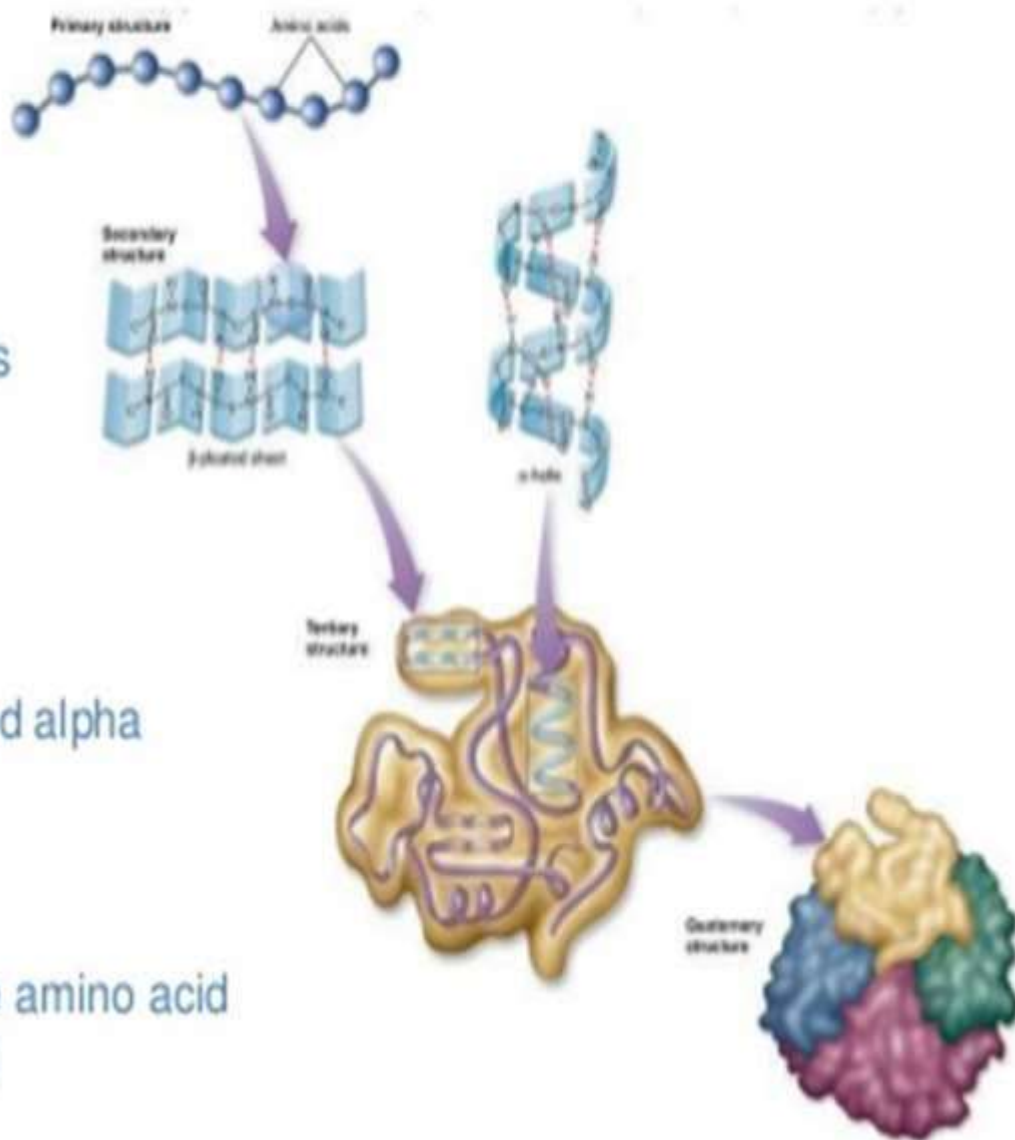
– linking of sequences of amino acids by hydrogen bonding (beta sheets, alpha helices)

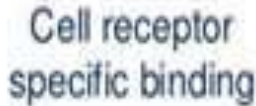
Tertiary Structure

– attractions between beta sheets and alpha helices to give 3-D structures

Quaternary Structures

– protein consisting of more than one amino acid chain (complex of protein molecules)





- Therapeutic mAb's predominantly of Ig G1 class & subtypes.
- Ig G consists of 2 Heavy and light chains
- Around 150 kDa in Size.
- Chains held together by disulfide bond between conserved cysteine residues at the Hinge region.
- Fc region binding cell surface Ig receptor
- Antigen binding variable region.

Classes of Biologicals

- ↖ “Biologic”s is a generic term used to refer to numerous types of peptide and protein based therapeutic molecules.
- ↖ Biologicals themselves can differ significantly in size and complexity.
- ↖ **Examples:**

- | | |
|--------------------|---------------------|
| ➤ Small peptides: | Insulin, Fuzen |
| ➤ Medium proteins: | Epogen, Neupogen. |
| ➤ Large Proteins: | Herceptin, Avastin. |

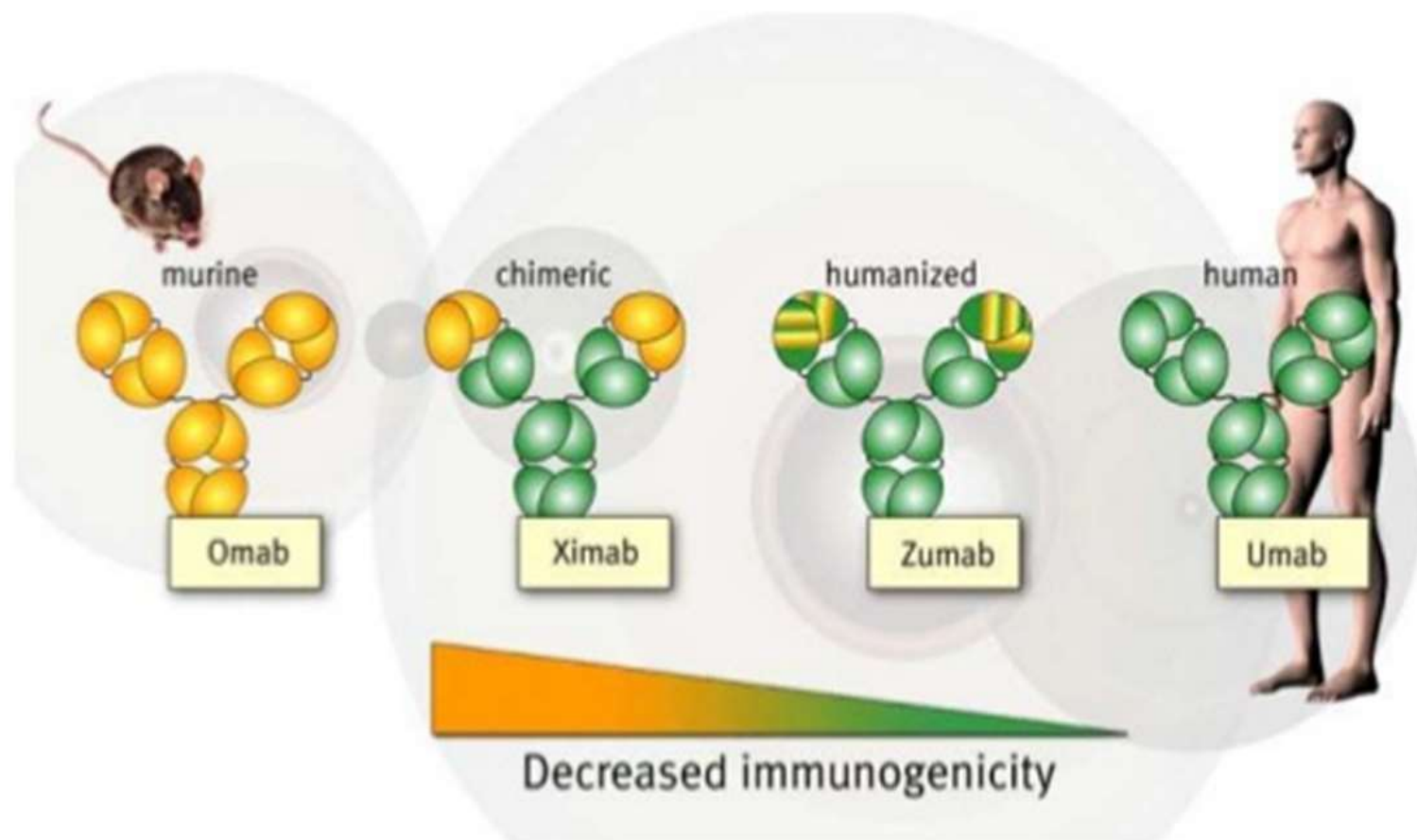


Increasing size and
complexity



Types of monoclonal antibodies

- mAb's can be raised from a number of species
- Being **protein based**, they will be recognised by our immune system

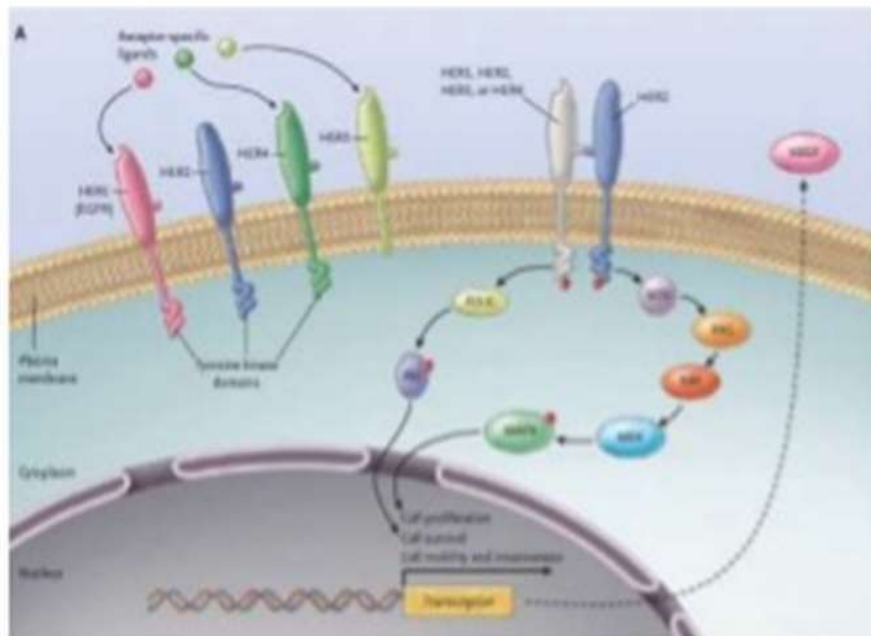


Mechanisms of action

- mAb's often act by triggering a series of biochemical pathways in a cell
- Firstly, this requires binding to their target receptor.

○ Example: Herceptin

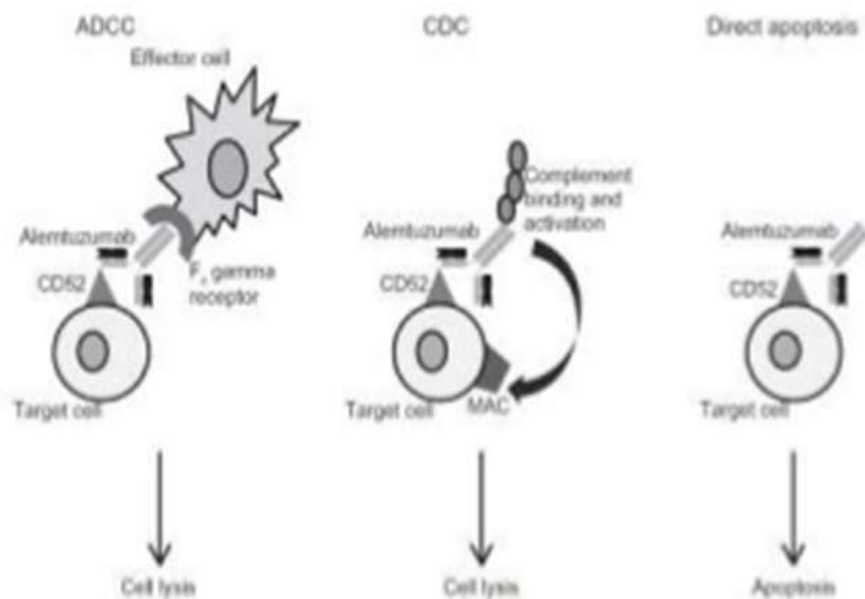
- Herceptin binds to Her2 receptor.
- Causes a series of intracellular signalling events.
- Results in reduced cell proliferation and increased cell death.



Shape of the drug is essential for receptor binding → therapeutic effect!

Mechanisms of action

- mAb's can also act through multiple pathways, each involving binding of Fc or Fv domains to different targets, i.e. Alemtuzumab
 - Fc binding to an effector cell → Antibody Dependant Cellular Cytotoxicity
 - Fc binding to complement → Complement Dependant Cytotoxicity
 - Fv binding to CD52 receptor → Direct apoptosis



Shape of the drug is essential for receptor binding → therapeutic effect!

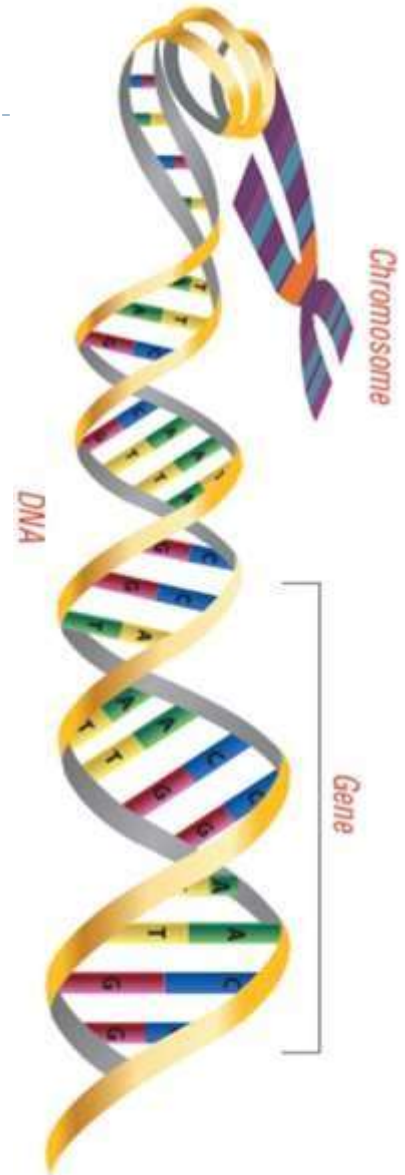
Therapeutic effects of BRMs.

- 1.Regulation and/or increased immune response.
- 2.Cytotoxic or cytostatic activity against tumor cells.
- 3.Inhibition of metastasis, or cell maturation.
- 4.Stimulation of BM stem cells, required for recuperation from cytotoxic insult secondary to chemotherapy.



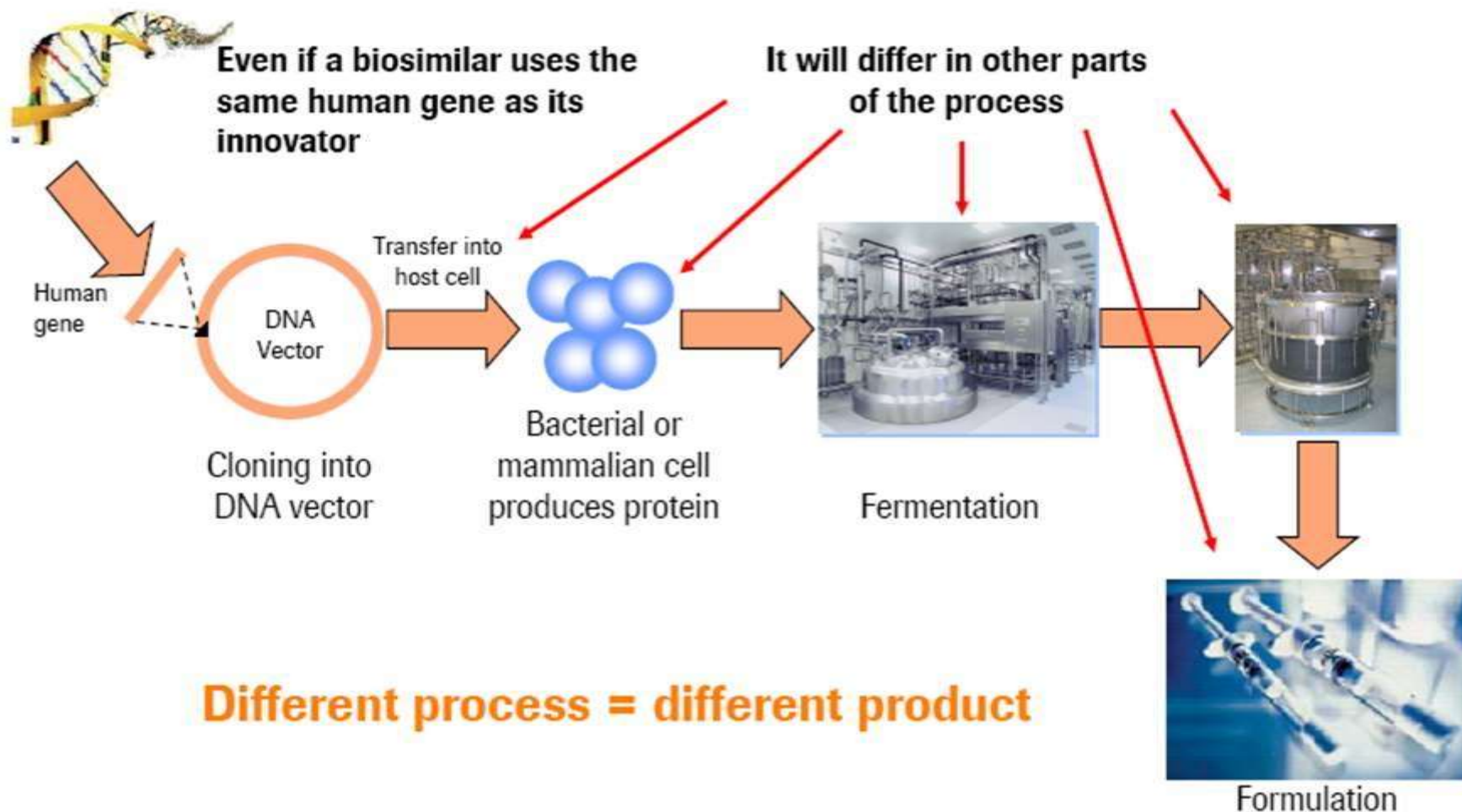
Production of biologic

- The genetic code of a chosen protein, such as immune system antibody is identified and replicated by combining different segments of DNA to build a **functional DNA sequence**
- This DNA sequence is **introduced into the host cell** of a living organism, such as mammal cells altering the cell to produce the chosen protein.
- These genetically modified cell lines are carefully selected (**MASTER CELL LINE**) and cultured in large **bioreactors** before the biologic medicine is extracted through complex and lengthy purification process



Biologic manufacturing is complex

Biosimilars will always be different from the original



Key challenges of biosimilar monoclonalAb development

- Correct amino acid sequence
- Similar Glycoform structure
- Comparable pre-clinical activity
- High-yield master cell bank/working cell bank
- Scalable manufacturing process



Differences between chemical generics & biosimilars

1. Heavier

Unlike structurally well-defined, low molecular weight chemical drugs, biopharmaceuticals are:

High molecular weight compounds with complex three-dimensional structure

- For example, the molecular weight of Aspirin is 180 Da whereas Interferon- β is 19,000 Da



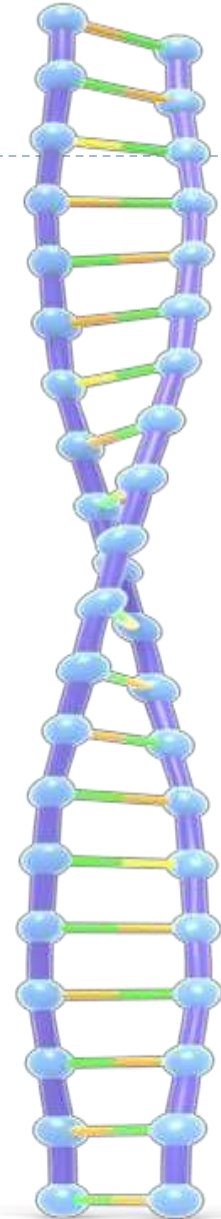
2. Larger

- Typical biologic drug is 100 to 1000 times larger than small molecule chemical drugs.
- Possesses fragile three-dimensional structure as compared to well-characterized one-dimensional structure of chemical drug.



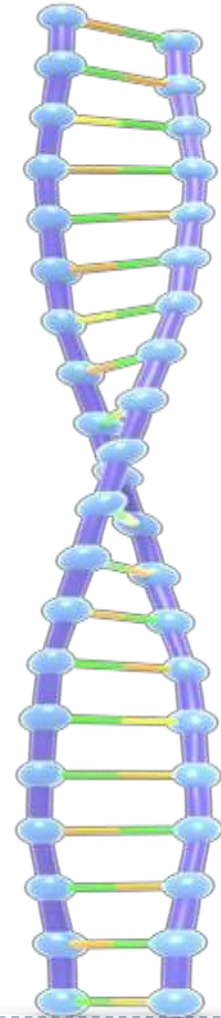
3. *Difficult to define structure*

- Small Molecule drugs → easy to reproduce & specify by mass spectroscopy & other techniques.
- Lack of appropriate investigative tools to define composite structure of large proteins



4. Complex manufacturing processes

- Manufacturers of biosimilar products will not have access to manufacturing process of innovator products → *Proprietary knowledge*
- *Impossible to accurately duplicate any protein product*
- Different manufacturing processes use different cell lines, protein sources & extraction & purification techniques → *heterogeneity of biopharmaceuticals*



continued

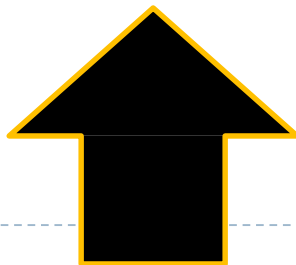
- Versatile cell lines used to produce the proteins have an impact on the gross structure of the protein
 - Such alterations may significantly impact: Receptor binding, Stability, Pharmacokinetics & Safety
 - Immunogenic potential of therapeutic proteins → Unique safety issue → Not observed with chemical generics
-



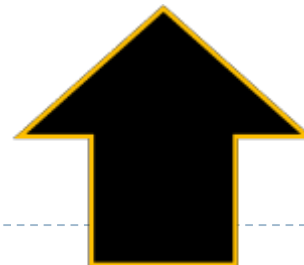
Benefits of Biosimilars

- ▶ “The development of biosimilars allows for wider and, as important, earlier access to these agents because of their lower cost and consequently greater affordability”
- ▶ “lower cost is expected not only to improve cost- efficacy ratios, but also to improve drug access,”

**Greater
affordability**

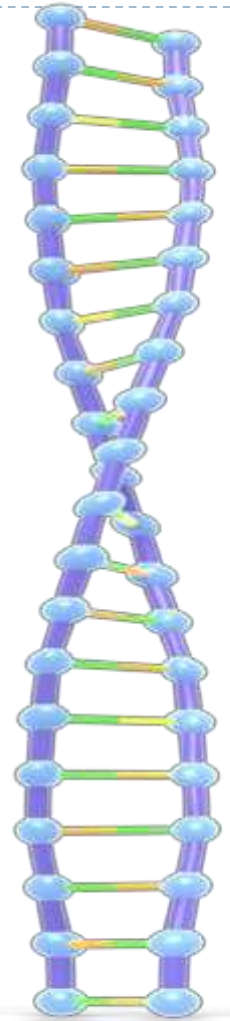


**Improved drug
access**



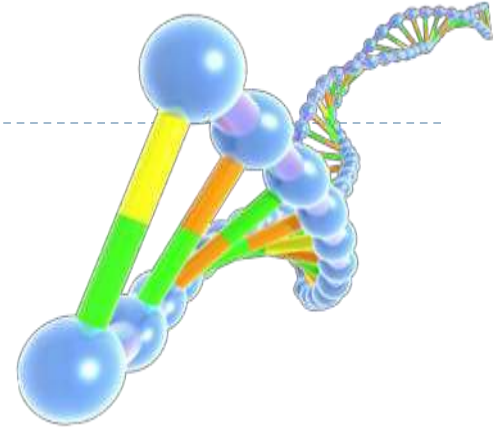
Emerging Role of Biosimilars

- Countries around the world- growing, aging population ---> ↑ in chronic disease.
- Expanding demand for good-quality healthcare ---> challenge of controlling healthcare expenditure.
- The safe and regulated introduction of biosimilars into the market has been forecasted to increase access to much needed biologic medicines and reduce costs.



Concerns with Biosimilars

- The two biosimilar products have different origin.
- The two biosimilars may have same therapeutic effect.
- They may have different side effect and toxicology.



Hence Biosimilars require thorough testing.

- Similarity between a biosimilar and its reference biotherapeutic product should be evaluated in all respects (quality, safety and efficacy).
- Purported copies of biotherapeutic medicines that have not undergone head-to-head comparisons with an appropriate reference product put patient safety at risk and should not be licensed via biosimilar pathways.

Issues of concern with use of biosimilars

1. Efficacy issues

- Differences between the bioactivity of the biosimilars & their innovator products

Example:

- 11 epoetin alfa products from 4 different countries (Korea, Argentina, China, India)
- Significant diversions from specification for in vivo bioactivity

Ranged from 71-226%



2. Safety issues

Concerns regarding immunogenicity

Example:

Pure Red Cell Aplasia
epoetin α

neutralizing

antibodies



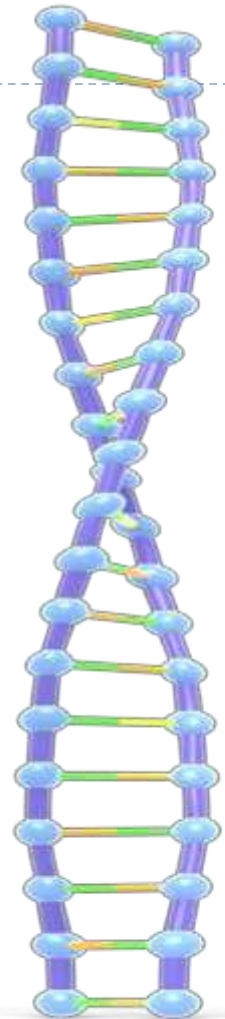
3. Pharmacovigilance

- Due to limited clinical database at the time of approval→ Vigorous pharmacovigilance required

Immunogenicity is a unique safety issue

Adverse drugs reactions monitoring data should be exhaustive

- Type of adverse event & data about drug such as:
Proprietary name, International nonproprietary name (INN) & dosage



4. *Substitution*

- Allows dispensing of generic drugs in place of prescribed IP

Rationale for generics→ Original drugs & their generics are identical & have the same therapeutic effect

- Produce cost savings



Same substitution rules should not be applied:

Decrease the safety of therapy or cause therapeutic failure

- Uncontrolled substitution → confounds accurate pharmacovigilance
- Adverse event emerges after switching from IP to its biosimilar without documentation → event will not be associated to a specific product or it will be ascribed to a wrong product



Naming and labeling

- Generic adaptation of chemical medicines is assigned the same name → identical copies of the reference products
- Biosimilars require *unique INNs*, as this would facilitate:
 - Prescribing & dispensing of biopharmaceuticals:
 - Precise pharmacovigilance
- Need for Comprehensive labeling of biosimilars including deviations from IP & unique safety & efficacy data

Assist the physician & pharmacist in making informed decisions



Regulation of Biosimilars

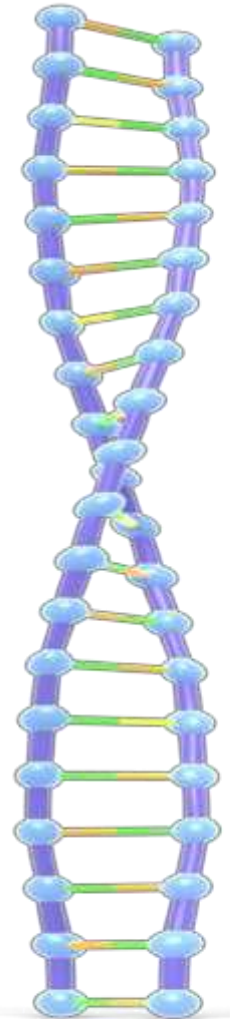
“The approach established for generic medicines is not suitable for development, evaluation and licensing of similar biotherapeutic products (SBPs) since biotherapeutics consist of relatively large and complex proteins that are difficult to characterize”.⁽⁸⁾

The World Health Organization



WHO regulations for Biosimilars

- In 2009 the World Health Organization developed a set of globally accepted standards to assure the safety, efficacy and quality of biosimilar medicines.
- These have been developed in the wake of increased interest in biosimilars by local regulatory authorities seeking to develop national standards.



What is biosimilarity?

- “Biosimilarity” is the regulatory term used to denote the comparability between a biosimilar and its reference medicinal product.
- Regulatory bodies across the world including India, recommends a stepwise approach to demonstrate biosimilarity between a proposed medicine and the original biologic
- The aim is to demonstrate no clinically meaningful difference in terms of safety, potency and purity



WHO regulations

Reference product

The reference product should be authorized in the country or region in question

Quality

All aspects of quality and heterogeneity should be assessed including head-to-head comparisons with the reference product

Non-clinical data

Should include pharmacodynamic, pharmacokinetic and comparative repeat-dose toxicity studies in a relevant species

Clinical studies

Required to demonstrate similar safety and efficacy. Immunogenicity should always be investigated in humans before authorization

Pharmacovigilance and risk management

A pharmacovigilance plan is required when an application is submitted and a risk management plan may be necessary in some cases

Mostly Commonly used BRM's in Rheumatology

1. **Infliximab:** A monoclonal Ab to TNF, proinflammatory cytokine.

Toxicity: Respiratory infection, fever, hypotension.

Predisposes to infections (reactivation of latent TB).

CD20 surface

immunoglobulin. Clinical use: Lymphoma.

3. **Etanercept:** Recombinant form of human TNF receptor that binds TNF.



Ranbaxy launched India's first Biosimilar of Infliximab – *Infimab* in Dec 01 2014

- Clinical effectiveness of Infimab coupled with cost effective pricing will enable more number of patients to get access to biologic treatment in India.



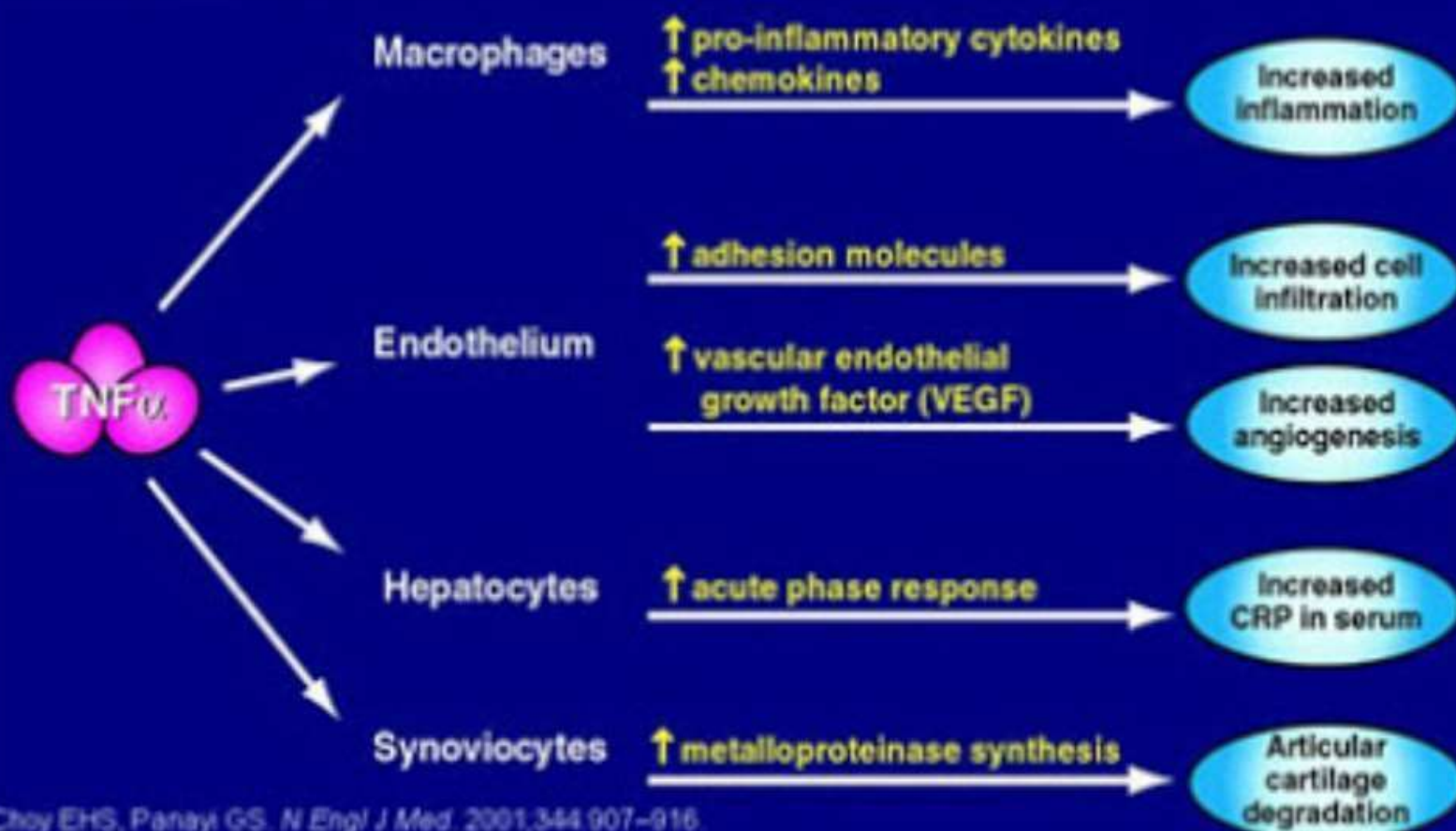
Etanercept

Etacept

- Cipla one of leading pharmaceutical company announced the launch of first biosimilar of etanercept in India, known as *etacept*, in April 2013.



Key Actions Attributed to TNF-alpha



Choy EHS, Panayi GS. *N Engl J Med*. 2001;344:907-916.

Feldmann M et al. *Annu Rev Immunol*. 1996;14:397-440.

Gravallese EM, Goldring SR. *Arthritis Rheum*. 2000;43:2143-2151.

Rituxumab

Intas launched biosimilar version of Rituxumab – Mabtas in India in April 2013 in order to make treatment of NHL cost effective.



limitations of patent Biologics

- Injection-site reactions are the most frequent adverse events. The severity varies from mild redness to deep inflammation and necrosis.
- In most cases, the treatment can be continued and the severity of reactions will decrease with time.
- Like all foreign proteins, monoclonal antibodies may induce urticaria, angioedema, anaphylactic reactions, and serum sickness.
- Production of inactivating antibodies to the drug may occur, classically with infliximab, and may be prevented by concomitant administration of low-dose methotrexate.

