Biologic and Biosimilar Medicines

Their Purpose, Development, Structure, and Effects

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Introduction

Philip Schneider, MS, FASHP, FFIP

- Vice President, International Pharmaceutical Federation (FIP)
- Recently retired as Professor/Associate Dean, University of AZ College of Pharmacy
- Past-President, American Society of Health-system Pharmacists
- Advisory Board Chair, Alliance for Safe Biologic Medicines

Biosimilars Pop Quiz

How familiar are you with BIOLOGIC medicines?

1. Very Familiar-complete understanding,
2. Familiar-basic understanding,
3. I have heard of them but could not define
4. I have never heard of them

How familiar are you with BIOSIMILAR medicines?

1. Very Familiar-complete understanding,
2. Familiar-basic understanding,
3. I have heard of them but could not define
4. I have never heard of them

How many biosimilars been approved by the FDA for use in the U.S.?

1. None
2. ~4
3. ~12
4. ~30

“Biosimilars are structurally identical to the reference biologic product upon which they are based.”

1. TRUE
2. FALSE

“In the U.S., biosimilars share the same non-proprietary name as their reference product, as with generics.”

1. TRUE
2. FALSE
3. NOT SURE

“A biosimilar is by definition interchangeable with its reference biologic product.”

1. TRUE
2. FALSE
3. NOT SURE

“A pharmacist can substitute any FDA-approved biosimilar in place of the prescribed originator biologic”

1. TRUE
2. FALSE

“As a pharmacist, I believe I will have a role in making decisions about the choice of biologics for specific indications.”

1. YES
2. NO
3. NOT SURE

“I believe the safe use of biosimilars will reduce healthcare costs.”

1. YES
2. NO
3. NOT SURE

Which of the following tools will you use to realize the potential cost benefits of biosimilars:

1. The formulary system
2. Clinical practice guidelines that specify the choice of drugs
3. Therapeutic interchange policy
4. Patient-specific dialog with the prescriber on a case-by-case basis
5. All of the above

“I need and plan to learn more about biologics to prepare myself for a role in the safe use of biosimilars.”

1. TRUE
2. FALSE

Biologics and Biosimilars: Overview

What is a Biologic Medicine?

A **biologic medicine** is a **substance** that is made **from** a **living organism** or its products and is used in the prevention, diagnosis, treatment, or cure of a disease. Biologic medicines include:

- antibodies
- vaccines
- interleukins (these can regulate immune responses)
- hormones
- blood and blood products

At a molecular level, biologic medicines are often 200–1000 times the size of a chemical drug molecule and are far more complex structurally. They are highly sensitive to handling and their environment.

Biologics are more difficult to characterize and manufacture than chemical drugs.

Due to their size and sensitivity, biologic medicines are almost always injected into a patient's body.

What is a Biosimilar?

- Developing a biosimilar requires reverse-engineering an innovator biologic. **Biosimilars are often mistakenly referred to as "generic" biologics.**
- Unlike with generic copies of chemical medicines, the fact that they are made using living cells means biologic medicines **cannot be copied exactly. It can only ever be "similar" to its reference biologic.**
- Cost savings vary from 15%-60% over reference product depending on country.
- In January 2017, FDA issued draft guidance on how similar a biosimilar must be to earn a designation of **"interchangeable"**, meaning that the biosimilar has the **same clinical effects in a patient without additional risks. Dr. Partha Roy** of PAREXEL Consulting will present a regulatory overview later today.
- **"Interchangeable" biosimilars are those which pharmacists will potentially be able to substitute.** Biosimilar substitution policy will be discussed in more detail later today.

How Are Biologics Used?

Benefits of Biologic Medicines

- Biologic medicines have made a significant difference in the lives of patients with serious illnesses, including cancer, blood conditions, auto-immune disorders such as rheumatoid arthritis (RA) and psoriasis, and neurological disorders like multiple sclerosis (MS).

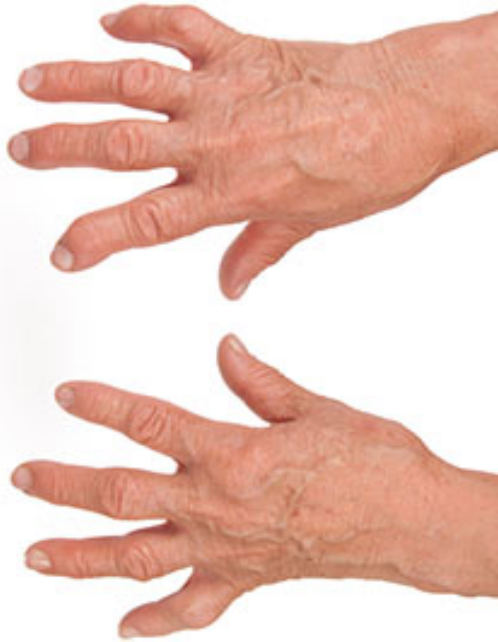
- By understanding the mechanisms of diseases, companies have developed biologic medicines to target and modify the underlying causes of disease, potentially altering the course of the disease rather than simply treating symptoms.

- The development of new biologic medicines may be the best hope for effectively treating diseases for which there are currently no cures.

Example: Rheumatoid Arthritis

- Advances in the understanding of RA over the last 20 years have led to a new treatment paradigm, where reducing disability and achieving remission are now possible goals.

- Once researchers understood the underlying inflammatory mechanisms of RA, scientists developed disease-modifying biologic medicines to target the proteins that regulate inflammation. Biologic medicines have proved effective in slowing down disease progression and joint damage, helping to improve daily function.

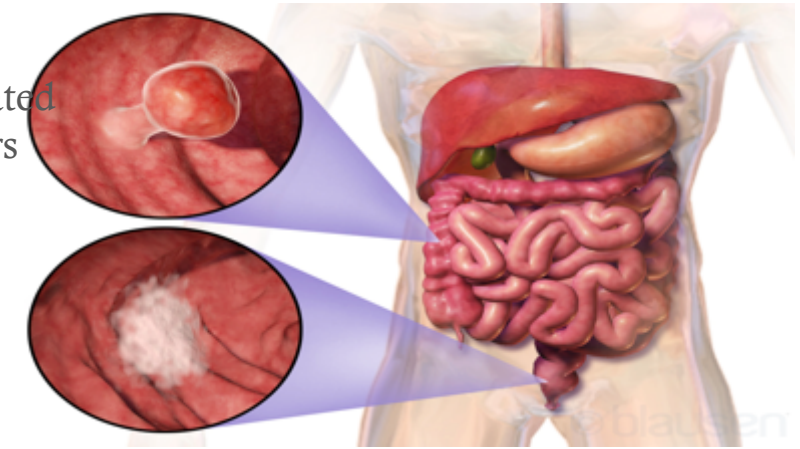


Example: Colorectal Cancer

- Investigating cancer pathways and determining the molecular basis of cancer has led to the development of new targeted diagnostics and treatments. Traditionally, cancer has been treated with surgery, radiation, and chemotherapy. Biotechnology has contributed to significant advances in cancer treatment, including hormone therapies, biologics, and targeted therapies such as monoclonal antibodies.

- Some kinds of colorectal cancer are caused by the overexpression of epidermal growth factor receptors (EGFR), causing the overly rapid cell growth associated with most cancers. There are several EGFR inhibitors available to patients.

- Patient advocate Scott Kahn, PhD, from the International Cancer Advocacy Network (ICAN), will provide a patient perspective on biologic medicines later today.



Two Sources of Biologic Medicines

NATURAL:

- Eggs
- Pigs
- Cows
- Humans

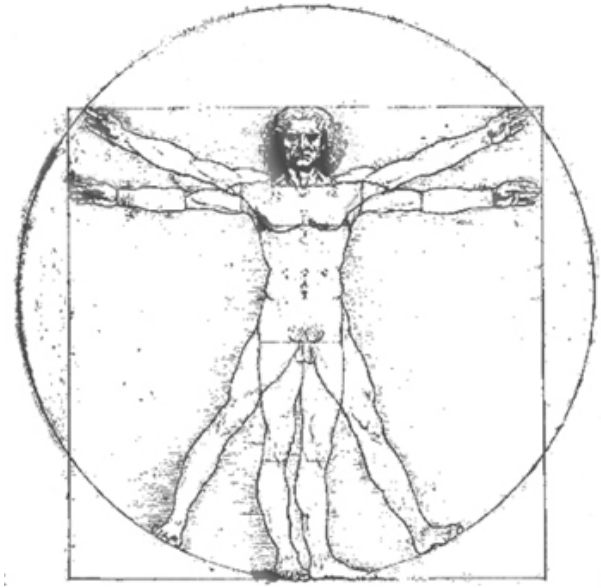
RECOMBINANT:

- Bacteria
- Yeast
- Mammalian Cells
- Transgenic Plants
- Transgenic Animals

Two Types of Biologic Therapy

REPLACEMENT therapy:
A patient is administered an *endogenous* (i.e., naturally occurring) protein or hormone to compensate for the loss, due to disease, genetic or otherwise, or surgery of a gland or tissue that would normally produce the substance

INTERVENTION therapy:
A novel biologic molecule is designed to specifically bind a chosen target.



Biologic Medicine Source and Therapy Types

	NATURAL SOURCE	RECOMBINANT SOURCE
REPLACEMENT THERAPY	Insulin from pigs and cows Human blood for Factor VIII (clotting factor), Immunoglobulin G antibodies, and Albumin	Recombinant technology has made possible the synthesis of insulin and granulocyte colony-stimulating factor (used to assist in minimizing the immunosuppressive effects of chemotherapy) Yeast has also become a source of recombinant forms of insulin and human growth hormone (HGH). Factor VIII (used in the treatment of blood clotting disorder Hemophilia A) Erythropoietins (used to treat anemia due to cancer or kidney disease). “Enzyme replacement therapy,” including Ceredase for the treatment of Gaucher disease.
INTERVENTION THERAPY	Flu Vaccine grown within egg	Treatment of myocardial infarction using tissue plasminogen activator Treatment of multiple sclerosis or Hepatitis C using interferons Treatment of cancer (trastuzumab, panitumumab, etc.) Treatment of rheumatoid arthritis (etanercept, adalimumab)

Europe Leads in Biosimilar Approvals

50 biosimilars

Abasaglar insulin glargine
Abseamed epoetin alfa
Accofil filgrastim
Amgevita adalimumab
Bemfola follitropin alfa
Benepali etanercept
Binocrit epoetin alfa
~~Biograstim filgrastim~~ (withdrawn)
Blitzima rituximab
Cyltezo adalimumab
Epoetin alfa Hexal epoetin alfa
Erelzi etanercept
Filgrastim Hexal
~~Filgrastim ratiopharm~~ (withdrawn)
Flixabi infliximab
Grastofil filgrastim
Halimatoz adalimumab
Hefiya adalimumab
Herzuma trastuzumab
Hulio adalimumab
Hyrimoz adalimumab
Imraldi adalimumab
Inflectra infliximab
Inhixa enoxaparin sodium
Insulin lispro Sanofi
Kanjinti trastuzumab
Lusduna insulin glargine
Movymia teriparatide
Mvasi bevacizumab
Nivestim filgrastim
Omnitrope somatropin
Ontruzant trastuzumab
Ovaleap follitropin alfa
Pelgraz pegfilgrastim
Ratiograstim filgrastim
Remsima infliximab
Retacrit epoetin zeta
Ritemvia rituximab
Rituzena rituximab
Rixathon rituximab
Riximyo rituximab
Semglee insulin glargine
Silapo epoetin zeta
Solymbic adalimumab
Terrosa teriparatide
Tevagrastim filgrastim
Thorinane enoxaparin sodium
Trazimera trastuzumab
Truxima rituximab
Udenyca pegfilgrastim
~~Valtropin somatropin~~ (withdrawn)
Zarzio filgrastim
Zessly infliximab

http://gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe accessed 8/28/18

Australian Biosimilar Approvals

Australian Government
Department of Health
Therapeutic Goods Administration

16 biosimilars

Aczicrit	epoetin lambda
Amgevita	adalimumab
Basaglar	insulin glargine
Bemfola	follitropin alfa
Brenzys	etanercept
Erelzi	etanercept
Grandicrit	epoetin lambda
Inflectra#	infliximab
Nivestim#	filgrastim
Novicrit#	epoetin lambda
Omnitrope#	somatropin
Renflexis	infliximab
Riximyo	rituximab
SciTropin A	somatropin
Tevagrastim#	filgrastim
Zarzio#	filgrastim

Canadian Biosimilar Approvals

Health Canada

6 biosimilars, 1 FOB

Brenzys Etanercept

Erelzi Etanercept

Grastofil filgrastim

Inflectra infliximab

Omnitrope Somatroptin

Remsima infliximab

Lapelga pegfilgrastim

http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Canada accessed 8/28/18

Latin America Biosimilar Approvals

10 biosimilars

Etanar	etanercept
Etart	etanercept
Fiprima	filgrastim
Infinitam	etanercept
Kikuzubam	rituximab
Novex	rituximab
Reditux/ Tidecron	rituximab
Remsima	infliximab
Usmal	rituximab
Zedora	trastuzumab

http://www.gabionline.net/Biosimilars/General/Similar-biotherapeutic-products-approved-and-marketed-in-Latin-America accessed 8/28/18

Twelve Biosimilars Currently Approved in U.S.

12 biosimilars, 2 FOBs

Admelog insulin lispro*
Basaglar insulin glargine*
Epoetin Hospira epoetin alfa
Amjevita (adalimumab-atto)
Cyltezo (adalimumab-adbm)
Erelzi (etanercept-szzs)
Fulphilia (pegfilgrastim-jmdb)
Inflectra (infliximab- dyyb)
Ixifi (infliximab-qbtx)
Mvasi (bevacizumab-awwb)
Nivestym (filgrastim-aafi)
Ogivri (trastuzumab-dkst)
Renflexis (infliximab-abda)
Retacrit (epoetin alfa-epbx)
Zarxio (filgrastim-sndz)

http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-the-US accessed 8/28/18

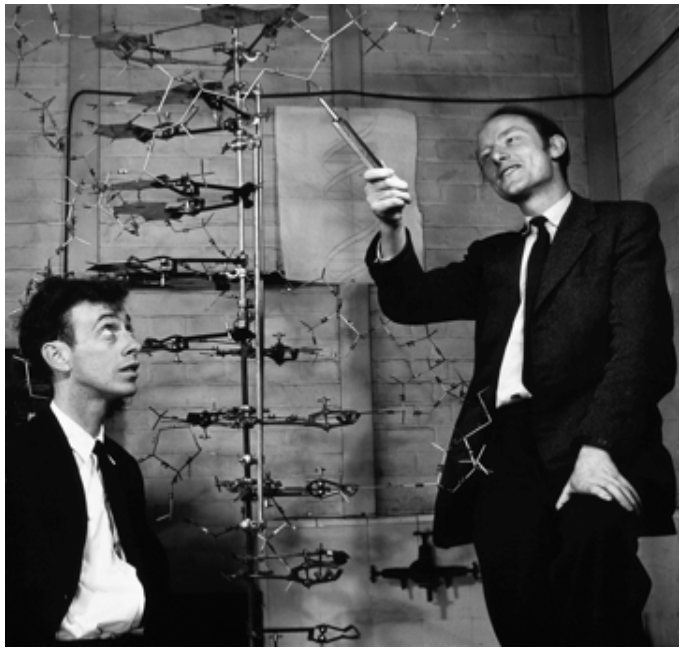
Evolution of Biologic Therapies

History of Biologic Medicines
Early 20th Century

- 1920s: Biologics derived from Animal Sources- insulin from cow and pig pancreas.
- 1940s: influenza vaccines manufactured within eggs.
- 1950: human blood-derived proteins used in treatment of hemophilia and primary immune deficiency.

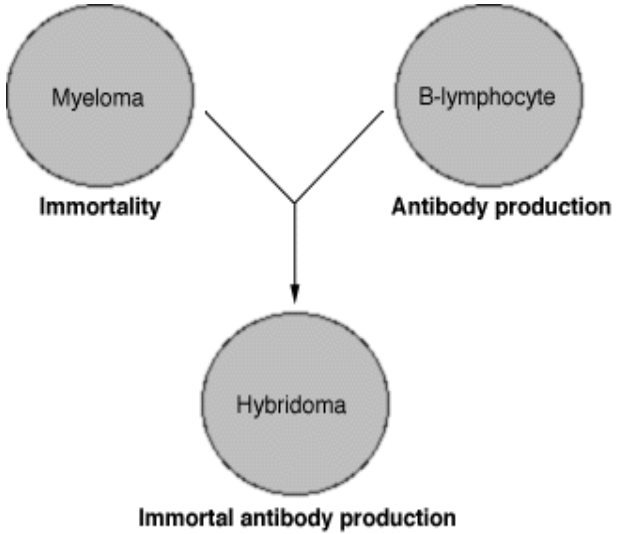
History of Biologic Medicines
Mid 20th Century

- 1953: Drs. Watson and Crick reveal structure of DNA, commencing era of modern biotechnology.
- 1960s: scientists fully understand the genetic code.
- 1973: Bacterial genes used to insert recombinant DNA into a cell for replication.
- 1973: "Southern blot" technique developed to study DNA structure.



History of Biologic Medicines
Late 20th Century

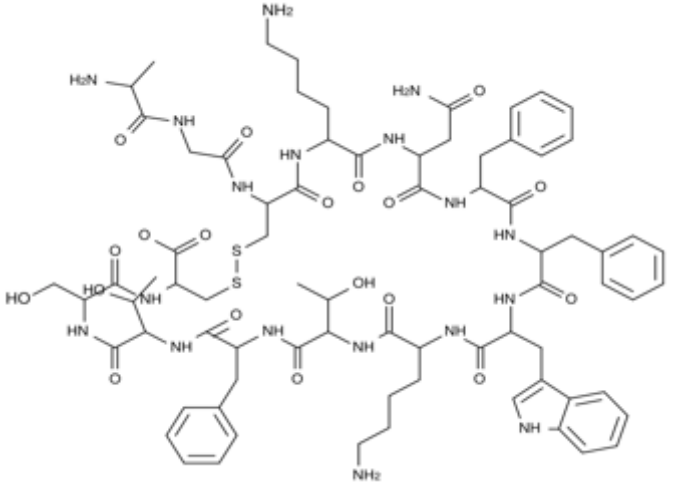
- 1975: Colony hybridization and Southern blotting developed for detecting specific DNA sequences.
- 1975: first **monoclonal antibody** developed by fusing immortal tumor cells with antibody-producing B-lymphocyte cells to produce hybrid cells (hybridomas) that synthesize identical (or "monoclonal") antibodies.



History of Biologic Medicines
Late 20th Century

- 1977: Long sequences of DNA can now be sequenced. Genetically engineered bacteria used to synthesize peptide hormone **somatostatin.**

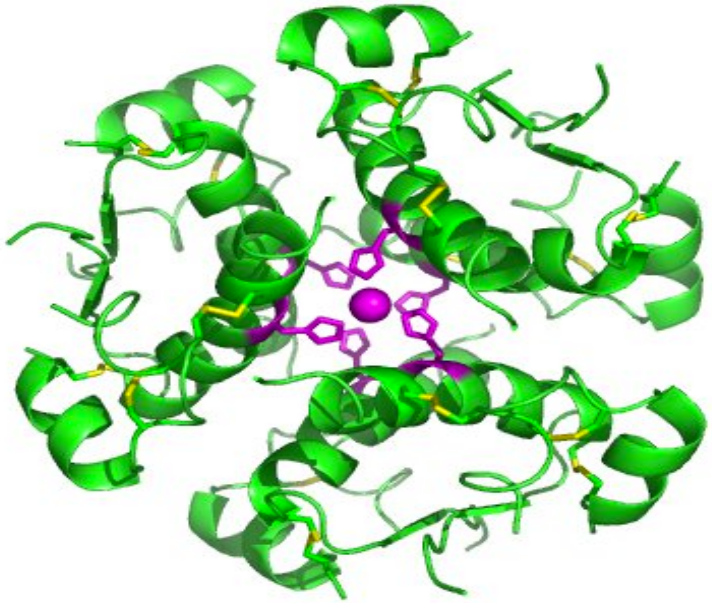
  For the first time a synthetic recombinant gene had been used to clone a protein. Many consider this the beginning of the Age of Biotechnology.



History of Biologic Medicines
Late 20th Century

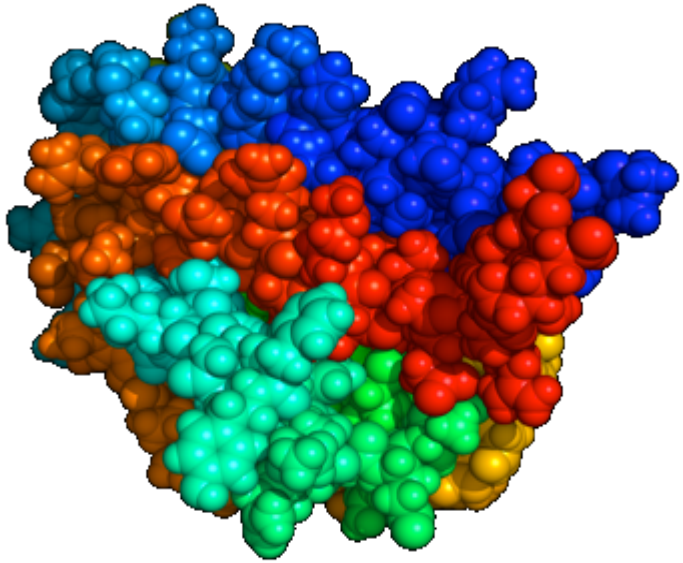
- 1982: **Insulin** becomes **first-ever approved human therapeutic manufactured using recombinant technology** in *E.coli* bacteria, rather than mammal cells.

  Today, recombinant insulin is made within both bacteria and yeast.



History of Biologic Medicines
Late 20th Century

- 1987: FDA approves genetically engineered plasminogen activator to treat heart attacks.
- 1989: FDA approves **Erythropoietin** (EPO), a complex glycoprotein used to treat anemia in patients with cancer or kidney damage.



History of Biologic Medicines
1990s-Present

- Nearly 200 biologic and recombinant biotechnology medicines are helping 800 million patients worldwide.
- 907 medicines and vaccines targeting more than 100 diseases are in human clinical trials or under FDA review.
- This includes 338 monoclonal antibodies, 250 vaccines, 93 recombinant proteins, 60 cell therapies, 46 gene therapies and 30 antisense medicines.

How Do Biologics Differ From Chemical Medicines?

Differences Between Biologic and Chemical Medicines

- **SIZE: Chemical compounds are generally much smaller in size than biologics and are generally unseen by the human immune system.**

- **STRUCTURE:** The structure and function of a chemical compound are simple and straightforward, but **a biologic protein has a complex three-dimensional structure.** Some of the proteins have post-translational modifications in the form of sugar attachments (called glycosylation) at specific sites, or they may have chemical modifications. Due to the structural complexity of biologics, the relationship between structure and function is often unclear (as explained on the subsequent slide under characterization).

Differences Between Biologic and Chemical Medicines
(Continued)

- **STABILITY:** Chemical drug structure is defined by rigid and stable covalent bonds, whereas a protein's structure is defined by the sequence (relatively stable covalent bonds) AND the three-dimensional folding into a structure stabilized by weak non-covalent bonds. The interactions of many weak bonds give proteins a three-dimensional structure and functional flexibility but also make it **sensitive to chemical and physical degradation.**

- **VARIABILITY:** While an active pharmaceutical ingredient of a drug consists of a single, well-defined structure, a biologic medicine exhibits a diversity of structures due to being prone to weak non-covalent bonds as well as the diversity of enzymatic and chemical modifications that can occur. **Consequently, a biologic medicine is a heterogeneous mixture of product and its related components as well as impurities from the manufacturing process.**

Differences Between Biologic and Chemical Medicines
(Continued)

- **MANUFACTURING:** Chemical compounds are manufactured using chemical reactions that are predictable and robustly reproducible, so an identical copy can be made. However, biotechnology medicines are made using living cells. **Therefore, an identical copy of a biologic medicine using a different cell line and/or different manufacturing process is not possible.**

- **CHARACTERIZATION:** Chemical compounds are easy to fully characterize. In addition, since the structure of the active ingredient in the chemical drug is precisely known, we can expect to see the same pharmaceutical function in vivo.

Differences Between Biologic and Chemical Medicines
(Continued)

- **CHARACTERIZATION (continued):** Characterization of biologic medicines requires multiple, orthogonal, advanced analytical methods. **While many biologic products have been well-characterized, complete characterization to the last atom is impossible.** In addition, correlating the diverse structures in a biologic medicine to function is quite difficult.

- **IMMUNOGENICITY**: Immunogenicity is the reaction of the body's immune system to a foreign substance. Chemical compounds have a lower potential while **biologics have higher potential for immunogenicity.**

Proteins: Size, Structure & Complexity

	Small Molecule Drug	Large Molecule Drug	Large Biologic
Size	Aspirin 21 atoms	hGH ~ 3000 atoms	IgG Antibody ~ 25,000 atoms
Complexity	Bike ~ 20 lbs	Car ~ 3000 lbs	F16 Jet ~ 25,000 lbs (without fuel)

Source: Genentech

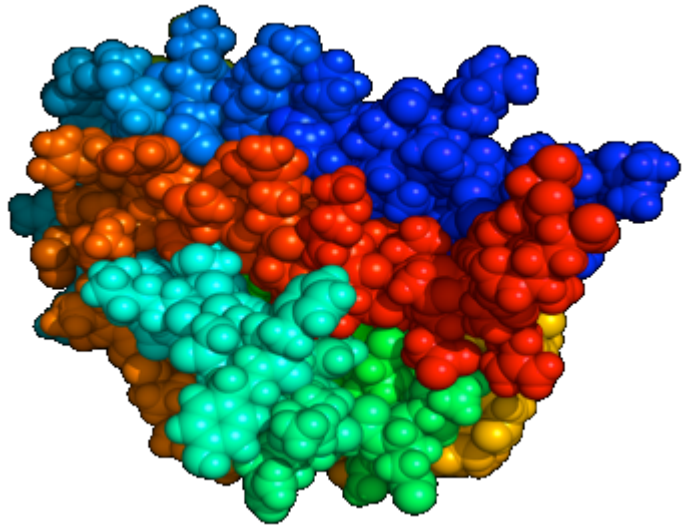
Size and Complexity of Biologics

"Biologics [and biosimilars] are like the Empire State Building, compared to a regular drug, which is like a small house"

-Dr. Janet Woodcock,
Director of the Center for Drug Evaluation and Research (CDER), FDA
February 4, 2016

Advantages of Large Size/Complexity of Biologic Medicines

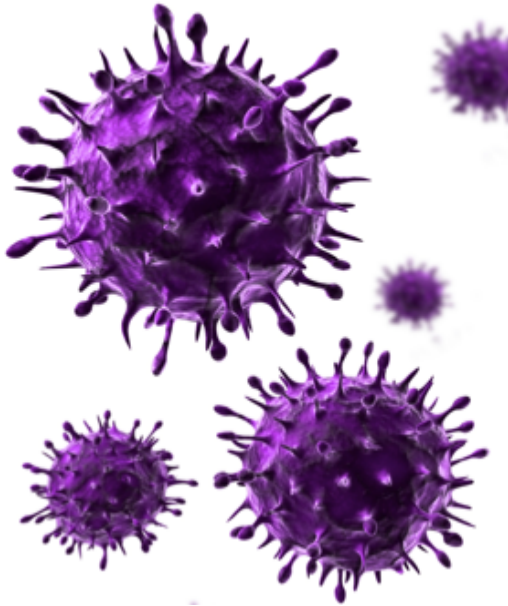
- **More precise fit to a large target (disease)**
- Can interact with multiple targets (such as binding to two receptors) simultaneously
- Large molecule can stay in body longer



One Disadvantage of Large Size/Complexity: Immunogenicity

- **Biologics have provided new options in the prevention and treatment of diseases in which previous therapies treated only the symptoms.** However, because of their complexity, biologics are associated with additional risks. The most important of these risks is **the potential to cause immunogenicity.**

- Immunogenicity occurs when the immune system in the human body mounts an attack when a foreign substance enters the body. For example, when we catch a common cold (i.e. rhinovirus) or the flu (i.e., influenza virus), **our body responds by attacking these viruses, thereby neutralizing them.**



Potential for Immunogenicity is a Major Concern

- All biologic medicines are fairly large molecules, sometimes resembling a virus, and have the potential to induce unwanted antibody responses (i.e., be immunogenic).
- The unwanted immune response may be of no consequence for a patient or of serious consequence.
  - Immunogenicity may neutralize the medicine, minimizing or eliminating the intended effect of the medicine.
  - One of the main concerns is that the immune system may attack the endogenous protein, making the patient's condition worse than before the medicine was introduced.

Example of Immunogenic Response: PRCA

- Many biologic products are engineered and manufactured to be as similar as possible to an already existing endogenous protein in the body.

- However, if there is some small difference that allows the body to differentiate or discriminate between the drug and the endogenous protein, the immune system may develop an antibody or immunogenic response against that protein. In addition, that immunogenic response may broaden and actually cross-react with the endogenous protein.

- In many cases the presence of antibody may not cause clinical consequences, but in some cases it can result in significant consequences. One such example is a condition called **Pure Red Blood Cell Aplasia (PRCA)**, a syndrome characterized by severe anemia and absence of erythroblasts from an otherwise normal bone marrow.

- The immune reaction neutralizes the endogenous protein necessary for red blood cell product and the patient needs blood transfusions to address the anemia.

Immunogenicity: Causes and Monitoring

- Antibody reactions cannot be predicted via other means (e.g., animal studies), which is why **clinical data are necessary.**
- Processes and conditions could influence molecular structures in unexpected ways, leading to an unwanted immunogenic reaction.
- **Monitoring patients for an immune reaction to the biologic is important both before and after regulatory approval.**

Domains of Selecting a Medicine

Approval Process of Biologics

Approval: Pre-Clinical Phase

- Researchers look for potential new compounds to treat targeted diseases.
- Toxicology is tested in animals and living tissue.
- During this phase researchers look for:
  - a correct dosage level
  - appropriate frequency of administration
  - the best delivery system (oral, topical, intravenous, etc.)
  - short- and long-term survival of animals
- Following animal testing, manufacturer files an Investigational New Drug Application (IND) or Clinical Trials Application (CTA) with FDA.

Approval Process: Phase I Human Testing

- After the approval of the IND/CTA, the experimental drug then moves into Phase I: human testing.
- **In this phase, the drug is tested in a small number (under 100) of healthy participants.**
- Researchers look to see how well the drug is tolerated, how it is processed by the human body, and what the correct dosing is.

Approval Process: Phase II Human Testing

- Once determined to be tolerated by healthy individuals, the medicine is **tested in (100-300) patients** to determine if it actually works.
- Manufacturer conducts dose range finding studies to estimate patient response for dose given to analyze safety/efficacy.

Approval Process: Phase III Large Scale Human Testing

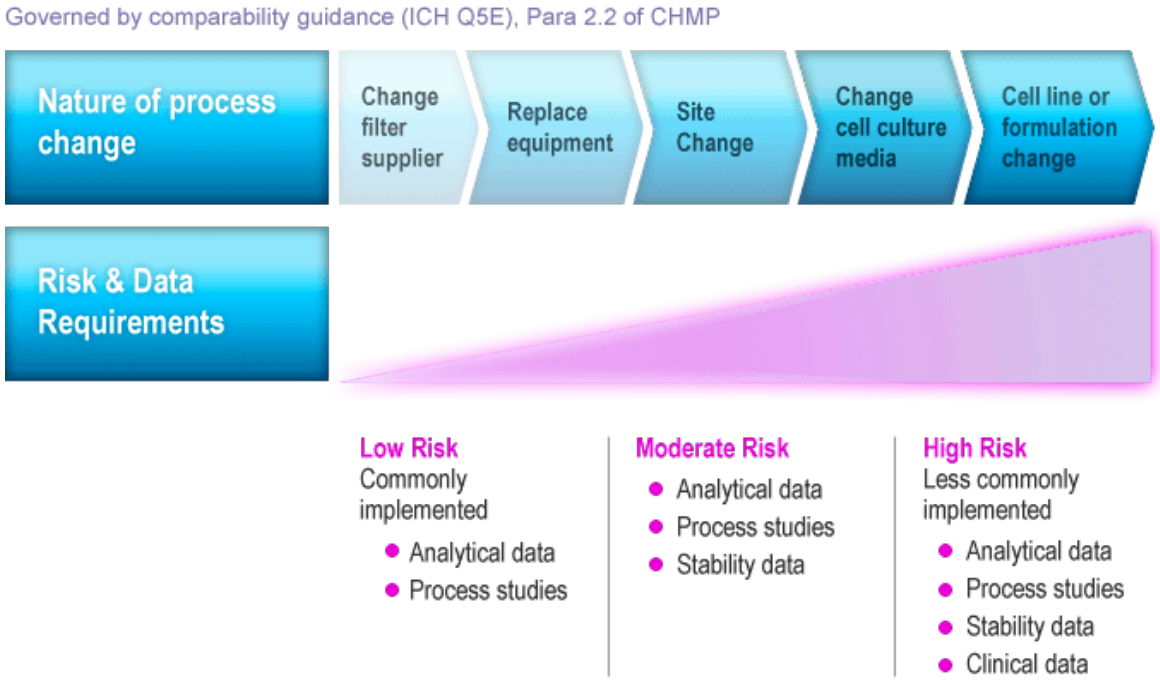
- A large-scale study of effectiveness and side effects is conducted, medicine is **tested in larger population (1000-3000) patients.**
- FDA looks at these data to determine safety and efficacy.
- Manufacturer tests the biologic medicine's viability and determines the logistics of scaling up to a large supply.
- Following Phase III a **Biologics License Application (BLA)** or **Marketing Authorization** are filed with FDA. These are typically 100,000 pages long and contain animal and human trial results and manufacturing data. Approval typically takes 1-2 years.

Approval Process: Phase IV Post-Market Surveillance

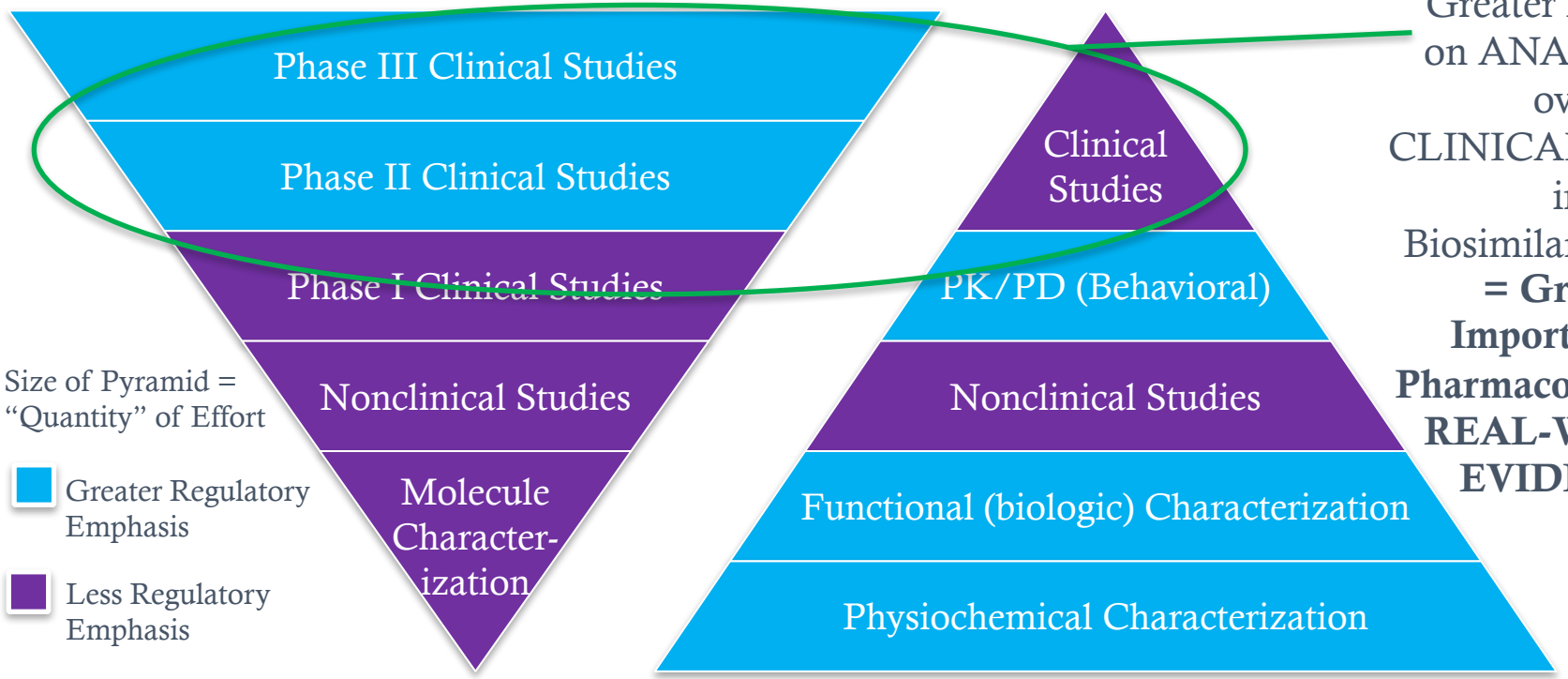
- Once approved, a biologic medicine is then marketed to the general population.
- Short- and long-term side effects are monitored.
- This can result in revision of labeling or manufacturing changes

Approval of Post-Marketing Changes

- Risk to product quality, safety, and efficacy vary based on the nature of the process change.
- Major changes to the process may require additional clinical studies.



Approval Pathway: Originator vs. Biosimilar



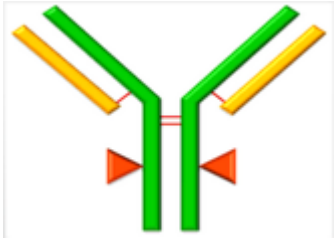
Greater Reliance on ANALYTICS over CLINICAL TRIALS in Biosimilar Pathway **= Greater Importance of Pharmacovigilance, REAL-WORLD EVIDENCE**

Biosimilar Development in the US: The "Patent Dance"

- Biologics Price Competition and Innovation Act of 2009 (BPCIA).
- Law intended to facilitate biosimilar development in the US.
- Patent provisions specify an information exchange between originator and biosimilar developer to encourage efficient resolution of patent conflicts.
- Some parties have declined to "dance"; litigation is common.
- 12 years of data exclusivity is provided for manufacturer of the originator biologic, after which biosimilar manufacturer may rely on the originator data to be approved by FDA.

Sensitivity of Biologics to Structural Modifications can Result in Immunogenicity

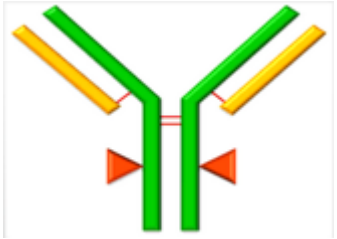
Biologics: Common Structural Modifications



UNALTERED lgG MOLECULE
(simplified model of desired product)

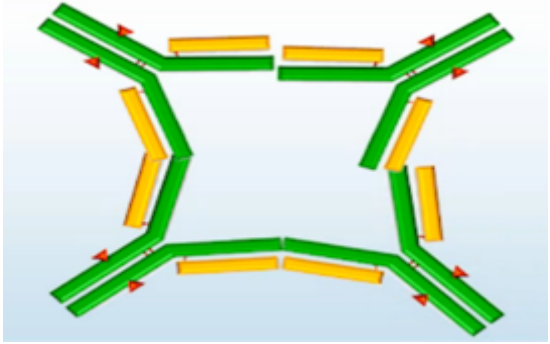
- Several modifications will always occur in production of the protein.
- Manufacturing conditions can have an impact on the molecule's structure.

Structural Modification: Aggregation



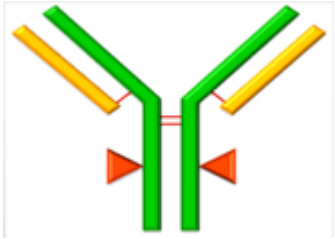
UNALTERED lgG MOLECULE
(simplified model of desired product)

AGGREGATION



- When two or more protein molecules (monomers) bind together.
- Considered undesirable because small aggregates may cause immunogenic reaction, while larger particulates may cause adverse events on administration.

Structural Modification: Fragmentation

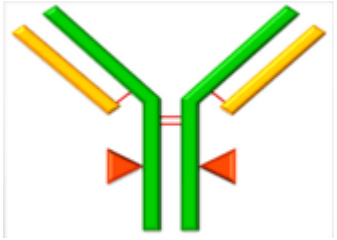


UNALTERED lgG MOLECULE
(simplified model of desired product)

FRAGMENTATION

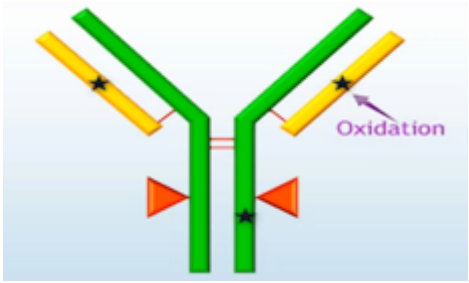
- When an intact protein breaks apart due to manufacturing, processing, or handling conditions.
- Fragments can cause immunogenic reaction since part of protein that is normally unexposed when intact is exposed. Incomplete molecule impacts efficacy.

Structural Modification: Oxidation



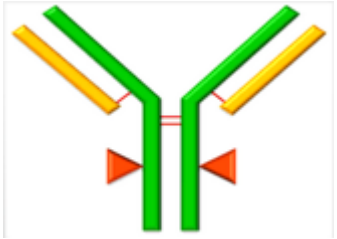
UNALTERED lgG MOLECULE
(simplified model of desired product)

OXIDATION



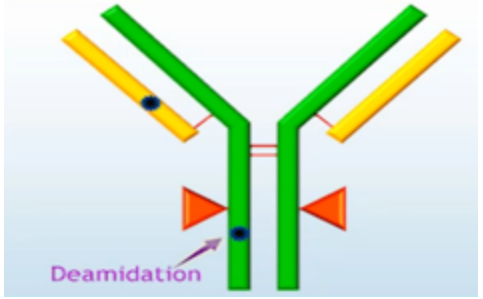
- Specific amino acids in the protein molecule can become oxidized.
- Oxidized products may result in loss of efficacy, or aggregation (which in turn may lead to immunogenic reactions, or adverse events upon administration).

Composition of Biologic Medicine: Structural Modification: Deamidation



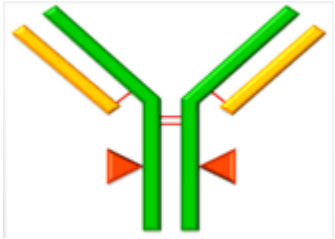
UNALTERED lgG MOLECULE
(simplified model of desired product)

DEAMIDATION



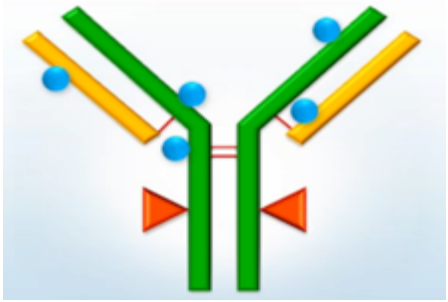
- Protein molecules could lose an amine group ($-NH_3$) due to enzymes or due to manufacturing conditions (such as heat), resulting in a deamidated protein, and reduced efficacy.

Composition of Biologic Medicine: Structural Modification: Glycation



UNALTERED lgG MOLECULE
(simplified model of desired product)

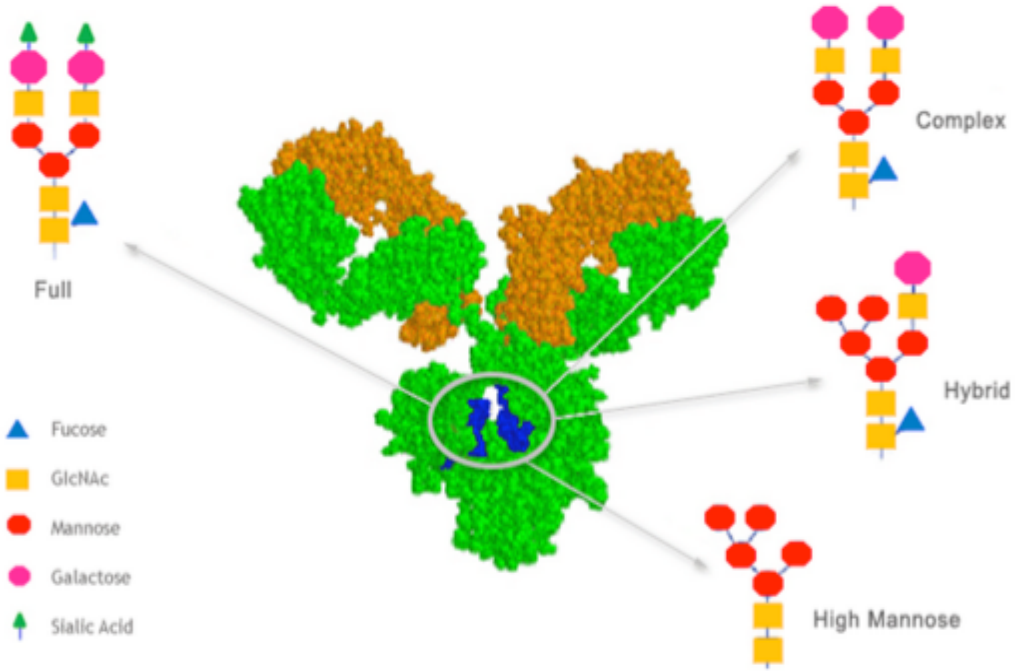
GLYCATION



- Uncontrolled or random addition of sugars (e.g., glucose or fructose) to a protein.
- Can cause aggregation (which in turn may lead to immunogenic reactions, or adverse events upon administration) or reduced efficacy.

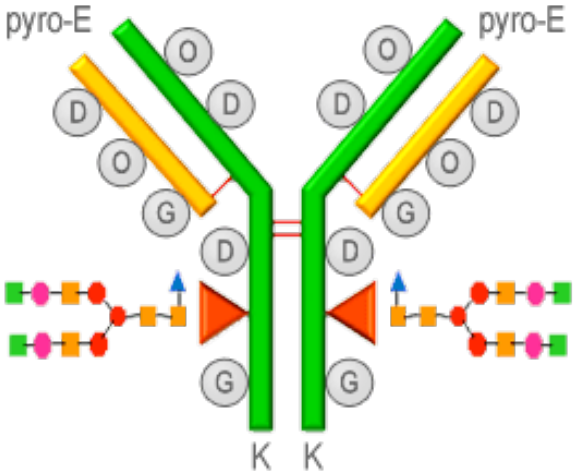
Glycosolation

- Many different types of sugars get linked to a protein during **glycosolation,** a common post-translational modification to improve therapeutic efficacy.
- Even minor changes in these structures can have major impact on safety and efficacy.
- **On occasions, some sugars not natural to humans (e.g., galactose-alpha,1, 3 galactose) that can be found in therapeutic proteins have been reported to cause anaphylaxis.**



Modifications Result in a Heterogenous Product

These modifications (see list below) can occur at multiple sites on protein, for example this **lgG molecule** has 9600 possible variations. **Unlike a chemical drug, a biologic medicine will contain many of these variations.**

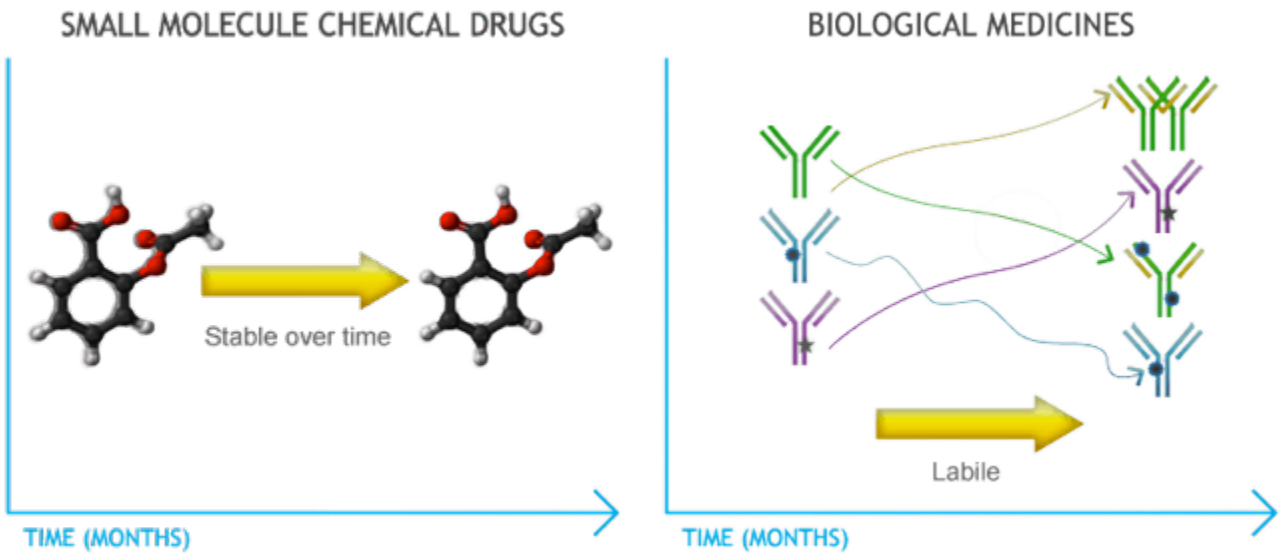


- Pyro-Glu (2)
- Deamidation (3 x 2)
- Methionine oxidation (2 x 2)
- Glycation (2 x 2)
- High mannose G0, G1, G1, G2 (5)
- Sialylation (5)
- C-term Lys (2)

- $(9600)^2 \approx 10^8$
- $2 \times 6 \times 4 \times 4 \times 5 \times 5 \times 2 = 9600$

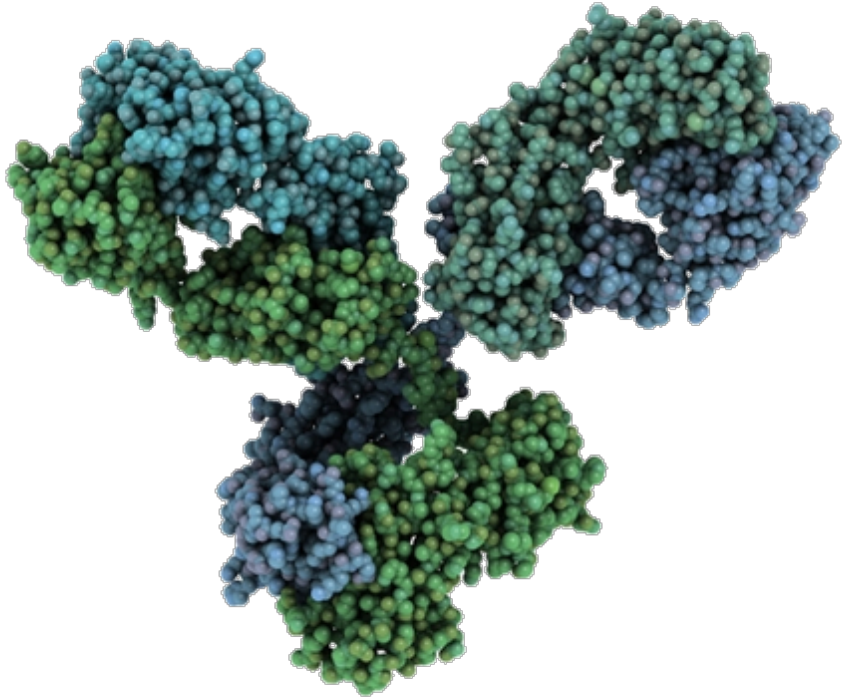
Stability of Biologics

- While chemical medicines are relatively stable, biologics can undergo many modifications during storage, and their composition (which of the molecule's variations are present) will change over time.



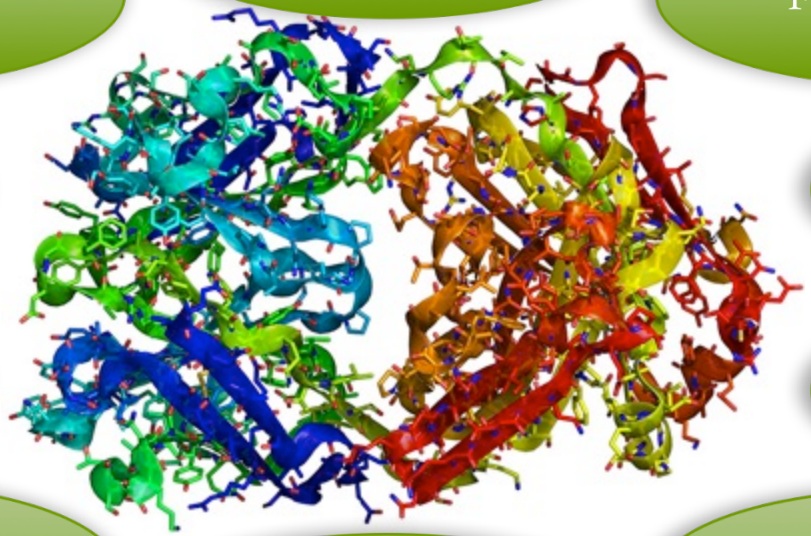
Complete Characterization is Impossible

- The complexity and sensitivity of biologics, their heterogenous nature, and their propensity to change over time, make characterization to the last atom impossible with current scientific knowledge and tools.



Degradation During Storage, Handling, and Preparation of Biologic Medicines

Contributing Factors to Degradation During Storage and Handling of Biologics



- DILUTION
- TEMPERATURE CHANGE
- FILTRATION
- SHAKING
- ADSORPTION
- SHEARING FORCES
- LEACHING
- OXYGEN EXPOSURE
- METAL EXPOSURE
- SILICON EXPOSURE

Potential for Degradation During Preparation

- **TEMPERATURE CHANGE**:
  Removing product from refrigeration can cause aggregation, precipitation.

- **ADDING DILUTENT:**
  Introduction of metal ions, silicon, oxygen can result in oxidation, catalysis, aggregation.

- **RECONSTITUTING:**
  Shaking, interaction with container, shearing forces can result in denaturing, unfolding, aggregation, hydrolysis, deamination.

- **INTRODUCTION TO INFUSION BAG:**
  Absorption, exposure to oxygen, silicon, and metal ions, leaching, shearing forces, etc., can result in denaturing, unfolding, aggregation, hydrolysis, deamination.

Minimizing Degradation of Biologics

- Avoid rapid temperature change- increase temperature gradually.
- Avoid multiple temperature cycles.
- Avoid excess force (shaking, shearing forces).
- Be aware of device composition (needle gauge, potential for contamination).
- Consult manufacturer stability data.

Biosimilars: How Close is “Close Enough”?

All Biologics Contain Minor Differences

- **Biosimilars cannot be, and thus are not expected to be, direct copies of originator (also known as "reference") biologics.**
- FDA defines a biosimilar as **"a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components."**
- Minor differences are expected and permitted but must be demonstrated not to be **"clinically meaningful"** in regards to safety, purity, or potency.

So, Aren't All Biologics Biosimilars, Then?

- No. A biologic will be grown from the same cell line, but will have **a natural range of variability** from lot to lot.

- By contrast, a biosimilar to that reference product is a **new molecule, made from a different cell line**, grown through different processes, that has **a starting point well outside this range.**

So, Aren't All Biologics Biosimilars, Then?

- How close it can get to the range- and performance- of the reference product will determine whether it is a different biologic, a biosimilar (highly similar), or an interchangeable (same results expected, no additional risks if switched).

- In 2009, a manufacturer scaled up production of a biologic, Myozyme, and though it was grown from the same cell line, the differences took it outside its expected range**. It was required to file a Biologics License Application as a new product,** and was only approved for same indications as Myozyme in 2014.

Myozyme becomes Lumizyme after biologics scale-up

By Nick Taylor, 16-Feb-2009

Related tags: Genzyme, Myozyme, FDA

Genzyme will launch the same biologic under two different names in the US after the FDA decided the drug produced at 2000L was considerably different to the 160L version.

US Food and Drug Administration (FDA) approval is now imminent, according to Genzyme, which would draw a line under a challenging 10 months for the company's Myozyme.

In an effort to scale up production of Myozyme Genzyme built a facility housing a 2000L bioreactor, which offered considerably more capacity than the 160L site.

However, the FDA ruled that in the process of scaling up from 160L to 2000L the product had changed sufficiently to require a new Biologics License Application (BLA).

Of the 12 Biosimilars Currently Approved in U.S., None are "Interchangeable"

Amjevita (adalimumab-atto)
Cyltezo (adalimumab-adbm)
Erelzi (etanercept-szzs)
Fulphilia (pegfilgrastim-jmdb)
Inflectra (infliximab- dyyb)
Ixifi (infliximab-qbtx)
Mvasi (bevacizumab-awwb)
Nivestym (filgrastim-aafi)
Ogivri (trastuzumab-dkst)
Renflexis (infliximab-abda)
Retacrit (epoetin alfa-epbx)
Zarxio (filgrastim-sndz)

What Does "Interchangeable" Mean?

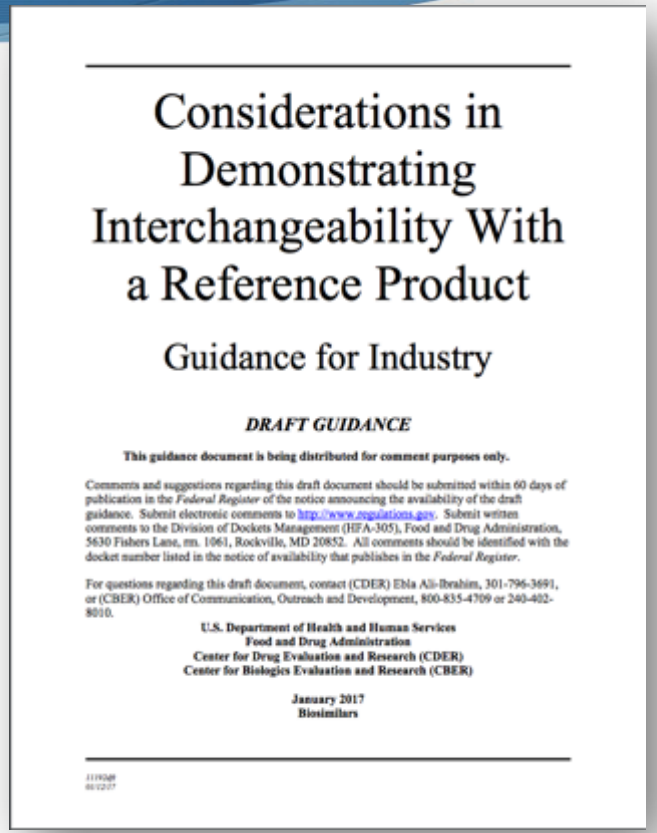
A higher regulatory standard to meet. More data is required.

An "INTERCHANGEABLE" :

1) Must be **biosimilar** ("highly similar" to reference product).
2) Must have **same clinical result expected** as with reference product.
3) Must create **no additional risk** to patient when switching back and forth between itself and reference product.
4) **May be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.**

FDA Draft Interchangeability Guidance

- On January 12th, 2017, FDA released its Draft Guidance on Interchangeability.
- Dr. Partha Roy of PAREXEL will discuss this Guidance and the biosimilar approval process in more detail today.



Considerations in Demonstrating Interchangeability With a Reference Product

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ebla Ali-Ibrahim, 301-796-3691, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2017
Biosimilars

Thank You For Your Attention