# Biologic and Biosimilar Medicines

## Their Purpose, Development, Structure, and Effects

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- Previously directed the Pharmacy Residency program at Ohio State University where he also led an inter-professional program to improve the medication use system to reduce adverse drug events.
- Past president of the American Society of Health System Pharmacists (ASHP).
- Former Chairman of the Board of Pharmaceutical Practice of the International Pharmaceutical Federation (FIP), current Vice President and Fellow of FIP.
- Published more than 180 articles and abstracts in professional and scientific journals, 38 book chapters, edited seven books and given more than 500 contributed or invited presentations in 22 countries and the U.S.
- Recipient of Donald E. Francke Medal for significant international contributions to health-system pharmacy (2006); Harvey A.K. Whitney Award, known as health-system pharmacy's highest honor (2008).
- 2012 recognized as a Fellow of the American Society for Parenteral and Enteral Nutrition (FASPEN).
- 2014 Advisory Board Chair of the Alliance for Safe Biologic Medicines, a group of physicians, pharmacists, patient advocates and others, which educates and advises policymakers working on biosimilar policy.

THE UNIVERSITY OF ARIZONA College of Pharmacy

ashp

fip international pharmaceutical federation

# 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 200–1,000 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 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.**
- FDA is in the process of drafting 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.**
- **"Interchangeable" biosimilars are those which pharmacists will potentially be able to substitute.** Biosimilar substitution will be discussed in more detail later today.

# 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).

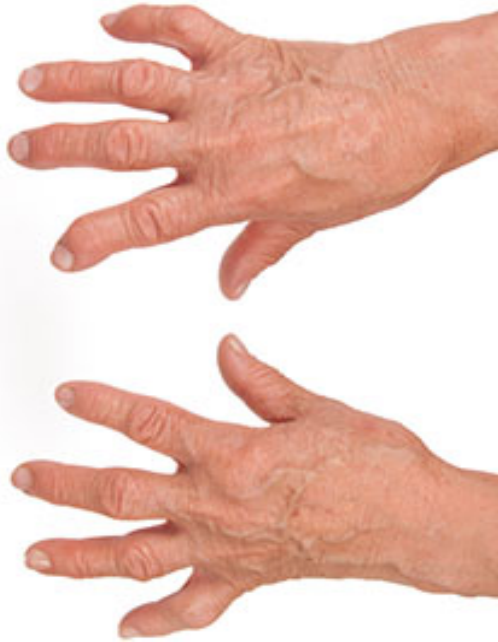
- By understanding the mechanisms of diseases, companies have developed biologic medicines to target and modify the underlying causes of disease, potentially altering the course of the disease rather than simply treating symptoms.

- 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.

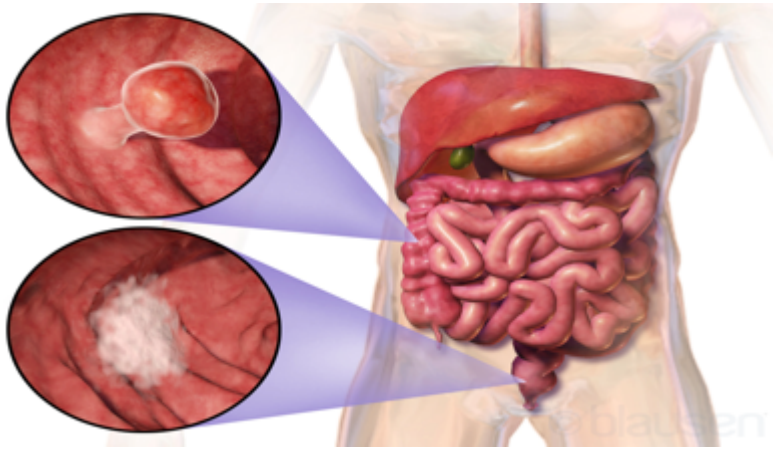
- Dr. Harry Gewanter, chairman of the Alliance for Safe Biologic Medicines, and a practicing pediatric rheumatologist, will explain this later in more detail.



# 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 over-expression of epidermal growth factor receptors (EGFR), resulting in the overly rapid cell growth associated with most cancers. There are several EGFR inhibitors available to patients.



# Two Sources of Biologic Medicines

**NATURAL:**

- Eggs
- Pigs
- Cows
- Humans

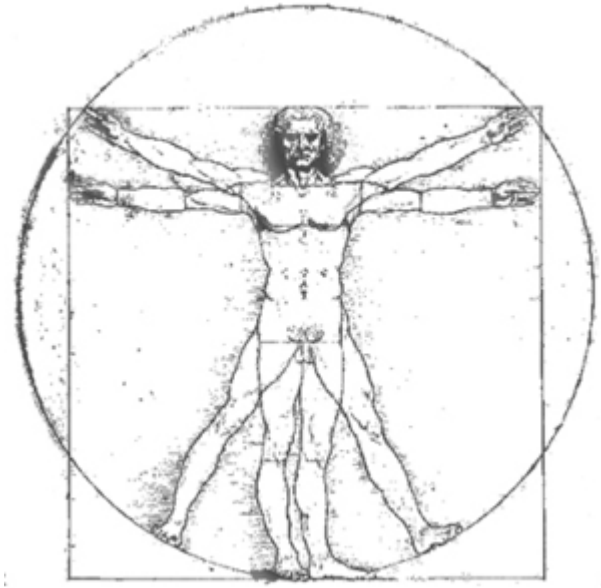
**RECOMBINANT:**

- 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<br><br>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).<br>Yeast has also become a source of recombinant forms of insulin and human growth hormone (HGH).<br><br>Factor VIII (used in the treatment of blood-clotting disorder Hemophilia A)<br><br>Erythropoietins (used to treat anemia due to cancer or kidney disease).<br><br>"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<br><br>Treatment of multiple sclerosis or Hepatitis C using interferons<br><br>Treatment of cancer (trastuzumab, panitumumab, etc.)<br><br>Treatment of rheumatoid arthritis (etanercept, adalimumab) |

# Biologic Medicines Today

- 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.

# Education on Biosimilars is a Top Priority for Pharmacist Organizations

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## Pharmacists and health systems prepare to add biosimilars to formularies

January 01, 2015

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*Pharmacists can help address many unknowns among health systems, prescribers*

Prescription drug spending is increasing while most other areas of health care spending are slowing down.[1] In 2013, the most recent year for which CMS data are available, prescription drug spending increased by 2.5%—a staggering leap from the 0.5% increase in 2012.[2] Many in health care are pinning their hopes on biosimilars to help slow the quick clip of rising drug costs.

The first two biosimilars, versions of filgrastim (Neupogen—Amgen) and infliximab (Remicade—Janseen), could hit the U.S. market in the first or second quarter of 2015. Because biosimilars are not identical copies of their biologic counterparts to the degree that generics are copies of small-molecule drugs, there are many unknowns among health systems and prescribers. Pharmacists can help address these issues as health systems add the new drugs to their formularies.

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## Biosimilars: Implications for health-system pharmacists

Minimize

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**Abstract**

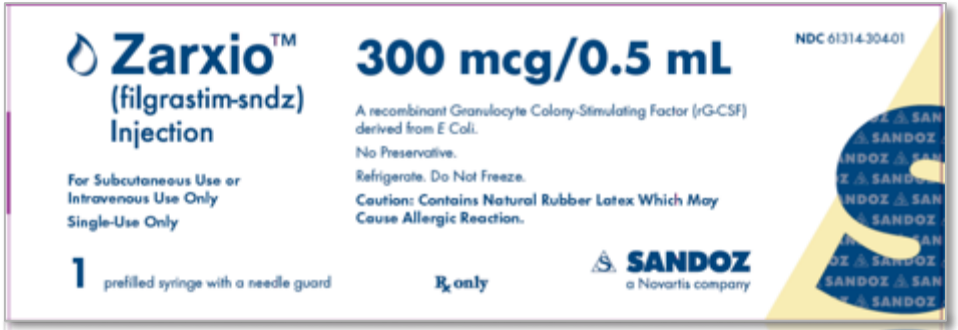
Purpose An update on scientific and regulatory challenges in the rapidly evolving field of biosimilar product development is presented.

Summary The U.S. market for biosimilar products (i.e., highly similar "follow-on" versions of approved biological drugs) is expected to expand with establishment of an expedited-approval pathway for biosimilars similar to that implemented in European Union countries eight years ago. In 2012, the Food and Drug Administration (FDA) published draft guidance clarifying the requirements of the biosimilars approval pathway; although no biosimilar has yet been approved via that pathway, FDA is engaged in ongoing meetings with a number of potential applicants. Due to molecular differences between innovator products and biosimilar versions, biosimilars are highly sensitive to manufacturing changes that can potentially have important safety and efficacy implications. Establishing the interchangeability of biosimilar and innovator drugs may be difficult at first, and it is possible that some biosimilars might not carry all the same indications for which the reference drug is approved. Pharmaceutical cost savings attained through the use of biosimilars are expected to average 20–30%. With several top-selling biologicals likely to lose patent exclusivity by 2020, health systems should prepare for the availability of new biosimilars by addressing formulary management and therapeutic interchange issues, pharmacovigilance and patient safety concerns, and related financial and operational issues.

Conclusion Over the coming years, biosimilars will present opportunities for health care organizations to manage the growth of pharmaceutical

# First U.S. Biosimilar Approved: Zarxio (filgrastim-sndz)

- Approved March 6, 2015
- Treats lack of white blood cells due to cancer or bone marrow transplant.
- Name is clearly distinguishable from reference product (filgrastim) but this may not be continued in official FDA policy due later this year.



# FDA Approval of More Biosimilars is Expected Shortly

- On March 17th, FDA's Arthritis Advisory Committee was scheduled to review Remsima, a biosimilar to Remicade (infliximab)—used to treat rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis. Meeting was postponed.
- This is the first monoclonal antibody (MaB) to seek approval from FDA under its approval pathway. Approved in EU and Canada, although for different indications.
- FDA approval is sought for all indications for which the innovator product has approval.

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**FDA sets date for Celltrion biosimilar of Remicade**

DAILY NEWS | FEBRUARY 10, 2015

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Advisors to the US Food and Drug Administration will meet next month to review Celltrion's biosimilar of Johnson & Johnson and Merck & Co's anti-inflammatory blockbuster Remicade.

The FDA's Arthritis Advisory Committee will gather on March 17 to discuss the South Korean-based group's Remsima, its version of Remicade (infliximab). The filing, in August, was the first for a monoclonal antibody using the agency's new biosimilar pathway.

FDA

Celltrion is seeking to get approval for Remsima in the

# 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, it is not possible to create an identical copy of a biologic medicine using a different cell line and/or different manufacturing process.**

- **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.**

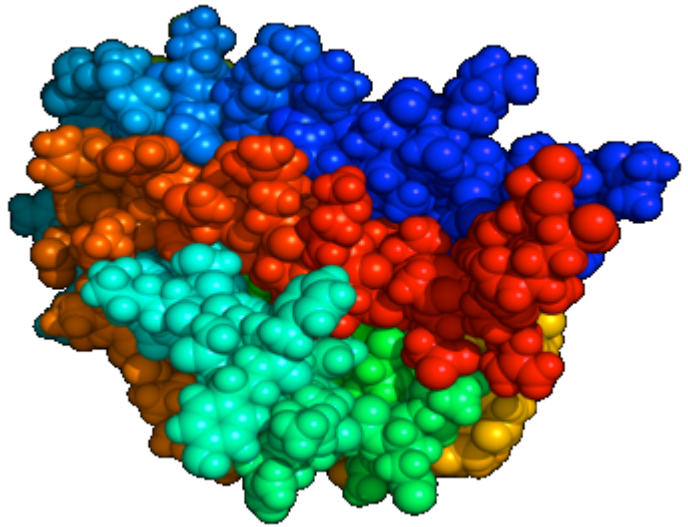
# Proteins: Size, Structure & Complexity

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

Source: Genentech

# Advantages of Large Size/Complexity of Biologic Medicines

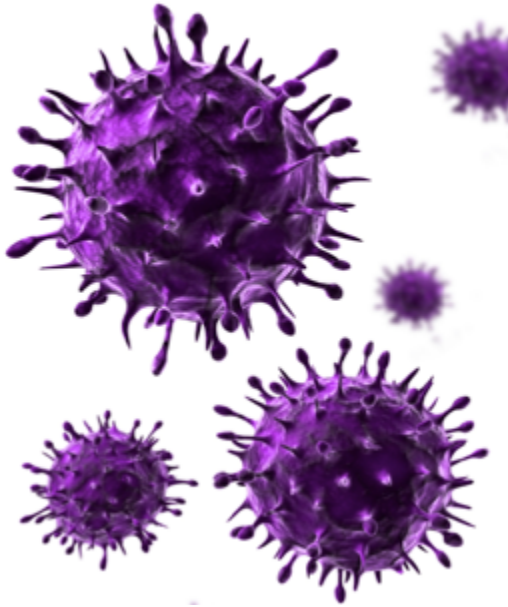
- **More precise fit to a large target (disease)**
- Can interact with multiple targets (such as binding to two receptors) simultaneously
- Large molecule can stay in body longer



# 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.**



# 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 an 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 production 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.**

# 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 FDA 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 determine the correct dosing.

# 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

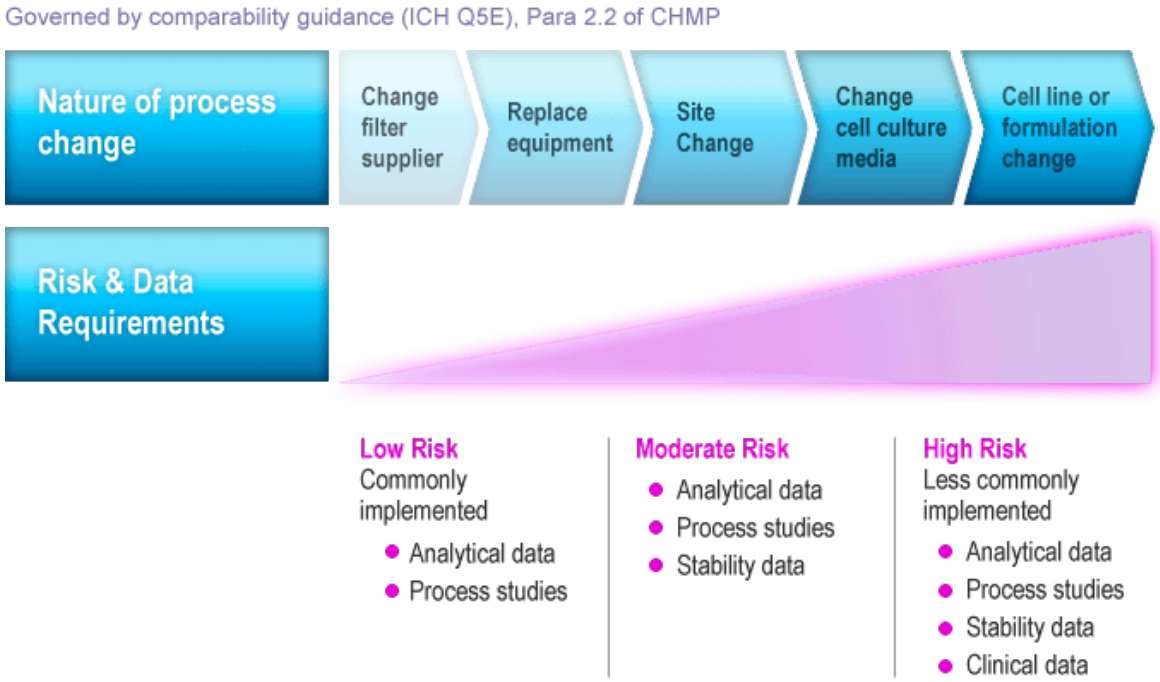
- A large-scale study of effectiveness and side effects is conducted; medicine is **tested in larger population (1,000-3,000) of patients.**
- FDA looks at these data to determine safety and efficacy.
- Manufacturer tests the biologic medicine's viability and determines the logistics of scaling up to 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

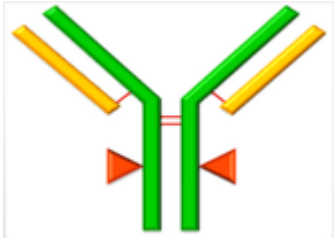
# Approval of Post-Marketing Changes

- 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.



# Sensitivity of Biologics to Structural Modifications can Result in Immunogenicity

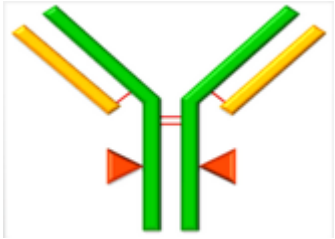
# Biologics: Common Structural Modifications



**UNALTERED lgG MOLECULE**
(simplified model of desired product)

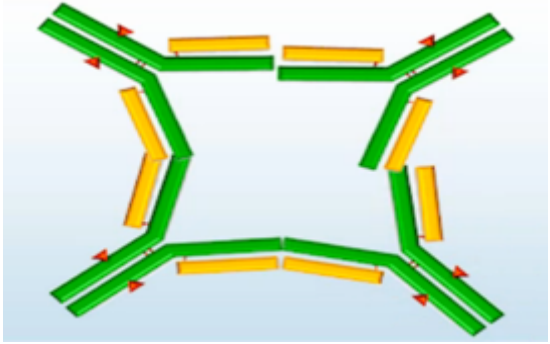
- Several modifications will always occur in production of the protein.
- Manufacturing conditions can have an impact on the molecule's structure.

# Structural Modification: Aggregation



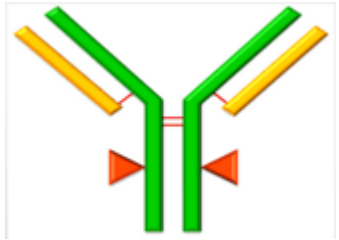
**UNALTERED lgG MOLECULE**
(simplified model of desired product)

**AGGREGATION**

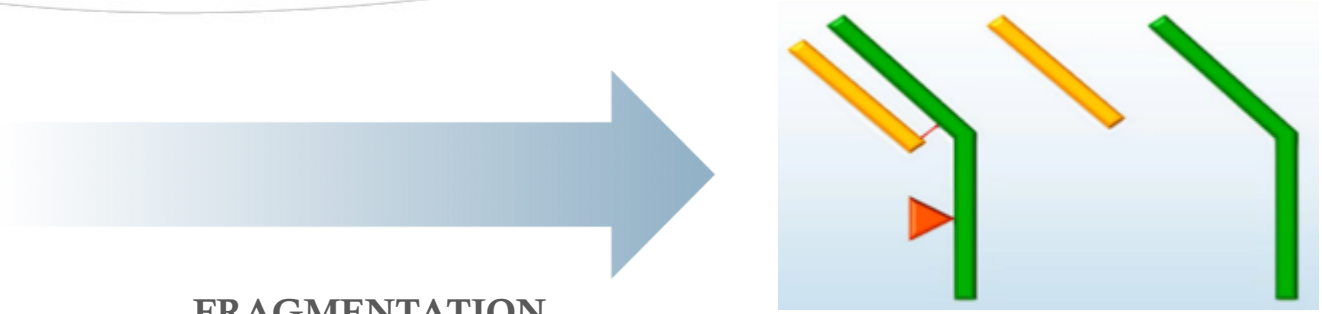


- When two or more protein molecules (monomers) bind together.
- Considered undesirable because small aggregates may cause immunogenic reaction, while larger particulates may cause adverse events on administration.

# Structural Modification: Fragmentation



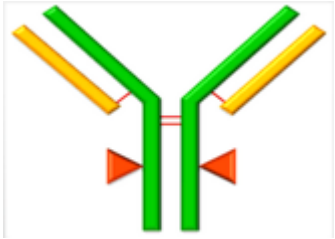
**UNALTERED IgG MOLECULE**
(simplified model of desired product)



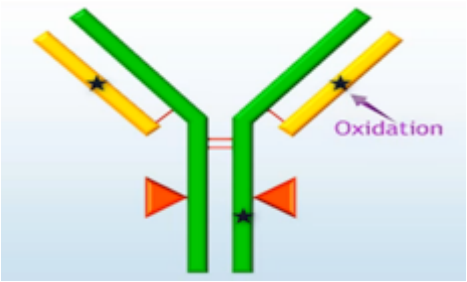
**FRAGMENTATION**

- 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



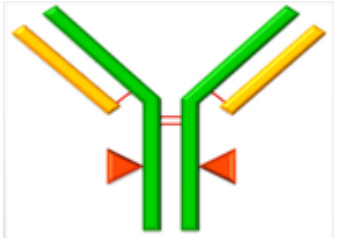
**OXIDATION**



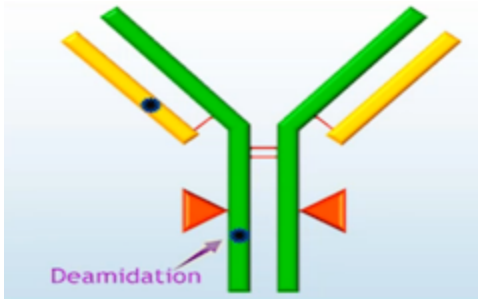

**UNALTERED IgG MOLECULE**
(simplified model of desired product)

- 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



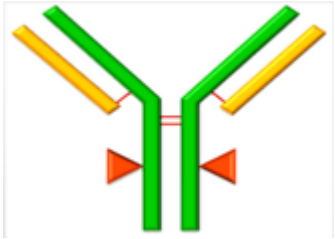
**UNALTERED lgG MOLECULE**
(simplified model of desired product)




**DEAMIDATION**

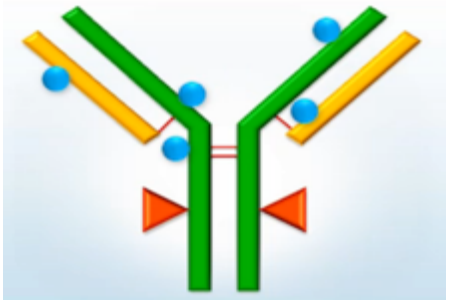
- Protein molecules could lose an amine group ($-NH_3$) due to enzymes or due to manufacturing conditions (such as heat), resulting in a deamidated protein, and reduced efficacy.

# Composition of Biologic Medicine: Structural Modification: Glycation



**UNALTERED lgG MOLECULE**
(simplified model of desired product)

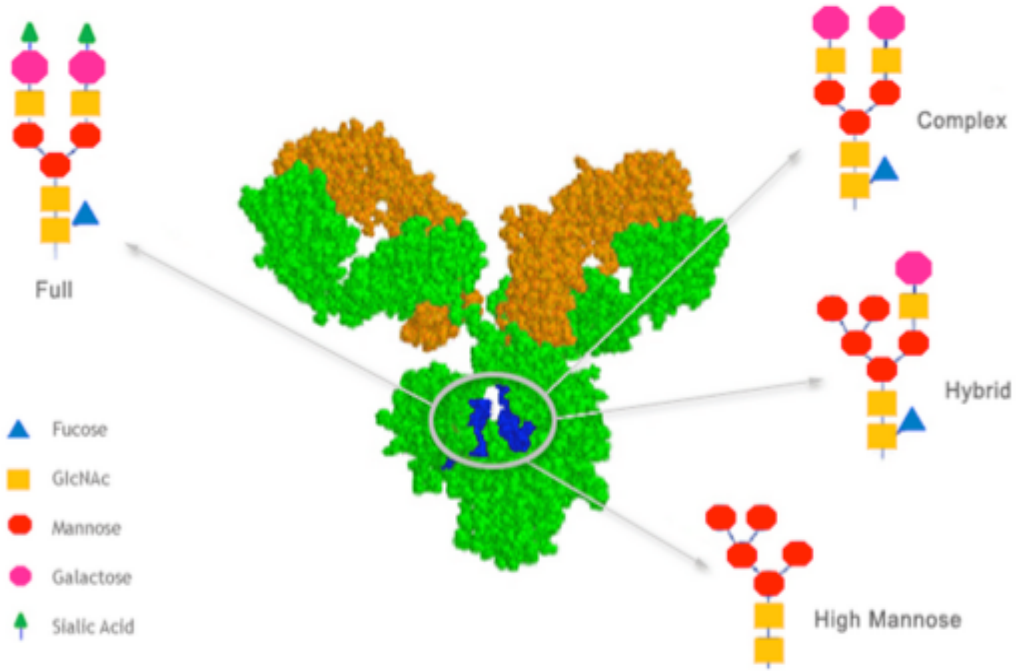
**GLYCATION**



- 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.

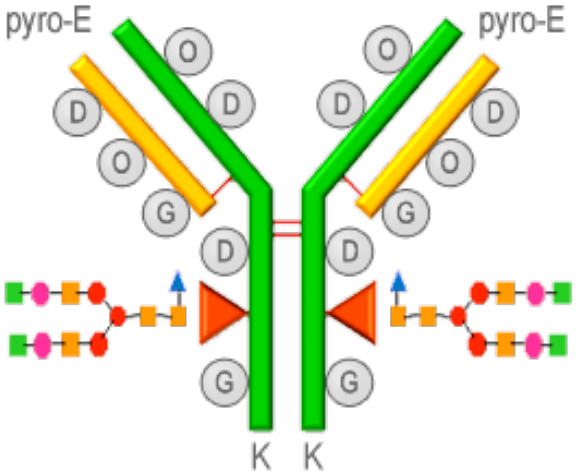
# Glycosolation

- 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 9,600 possible variations. **Unlike a chemical drug, a biologic medicine will contain many of these variations.**

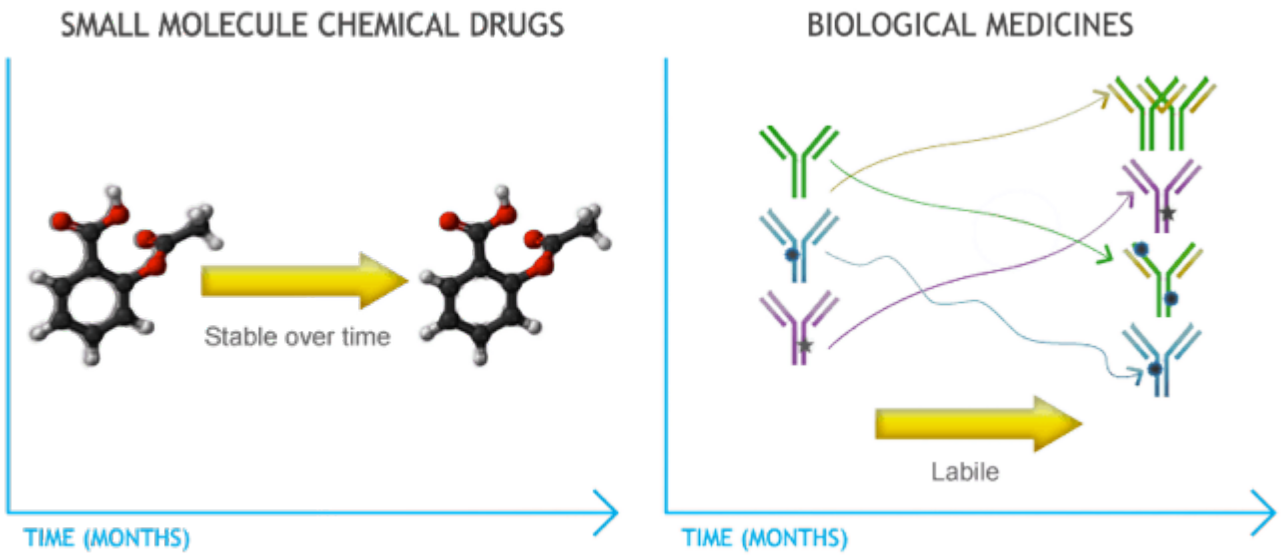



- Pyro-Glu (2)
- Deamidation (3 x 2)
- Methionine oxidation (2 x 2)
- Glycation (2 x 2)
- High mannose G0, G1, G1, G2 (5)
- Sialylation (5)
- C-term Lys (2)

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

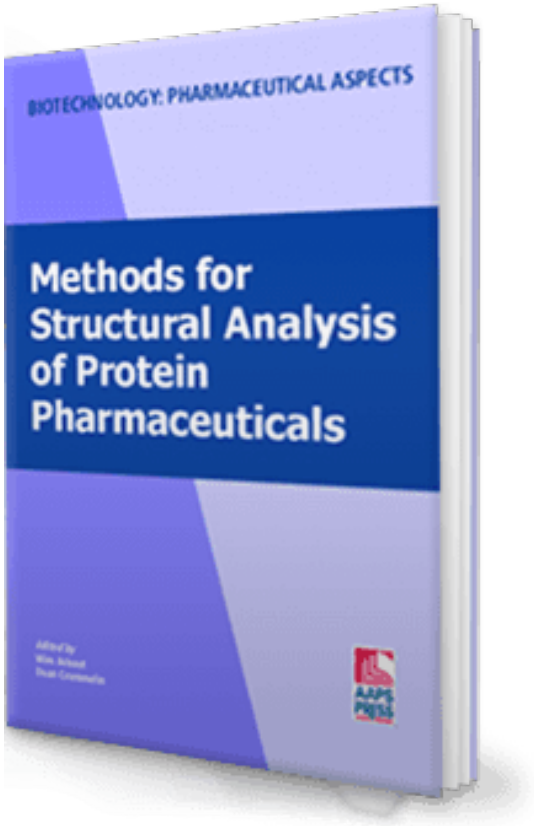
# Stability of Biologics

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



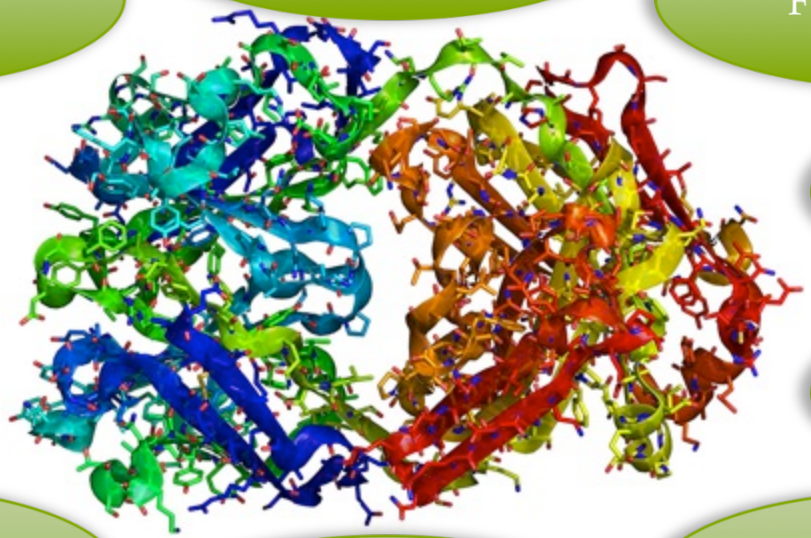
# Complete Characterization is Impossible

- 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.
- To learn more about characterization of biologics, please consult ***International Journal of Pharmaceuticals, 2003, November, 266, 3-16***



# 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.

# Significant Differences = Different Product

- GenZyme, a biologic manufacturer, made a manufacturing process change when scaling up production of its FDA-approved biologic.
- **Even though made from the same cell line, the resulting molecule was different enough that new clinical trials were required and a new International Nonproprietary Name (INN) was assigned to it**—which was in effect a new product—a biosimilar to its reference molecule.

# Example: How will Biosimilars be Labeled?

- Some concerns surrounding insufficient transparency in Zarxio's labeling:
- It is not identified as a biosimilar;
- No data used to demonstrate biosimilarity is included;
- Not specified for which indications approval was based on trial data, or extrapolation;
- Data provided is from innovator product but not identified as such.

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use ZARXIO safely and effectively. See full prescribing information for ZARXIO.**

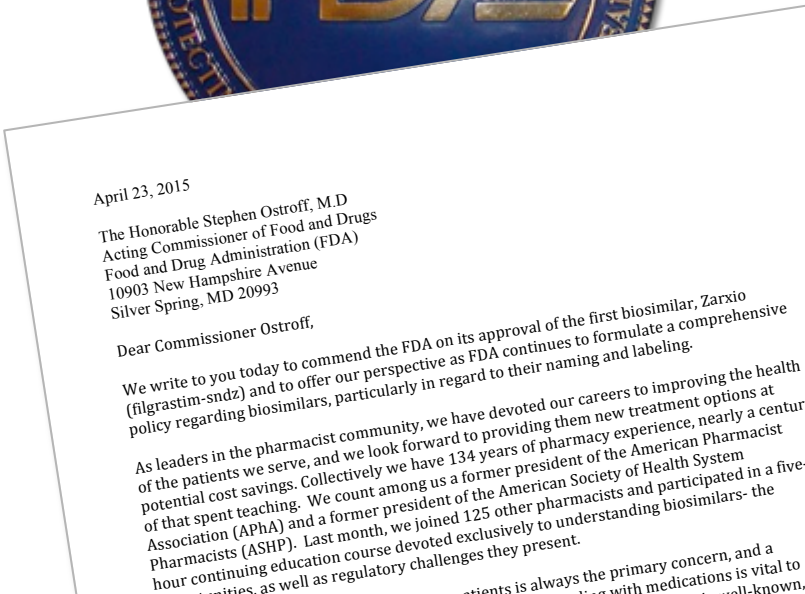
**ZARXIO™ (filgrastim-sndz) injection, for subcutaneous or intravenous use**
**Initial U.S. Approval: 2015**

----------**INDICATIONS AND USAGE**----------
ZARXIO is a leukocyte growth factor indicated to:

- Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever (1.1)
- Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML) (1.2)
- Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT) (1.3)
- Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (1.4)
- Reduce the incidence and duration of sequelae of severe neutropenia (e.g.,fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia (1.5)

# Prominent Pharmacists Write Letter to FDA on Labeling Concerns

- Philip Schneider,
  Professor, University of Arizona College of Pharmacy
  Former President, AHSP
- Ronald P. Jordan,
  Dean, Chapman University School of Pharmacy
  Former President, APhA
- Joseph J. Bova,
  Director of Continuing Education,
  Long Island University College of Pharmac

April 23, 2015

The Honorable Stephen Ostroff, M.D
Acting Commissioner of Food and Drugs
Food and Drug Administration (FDA)
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Ostroff,

We write to you today to commend the FDA on its approval of the first biosimilar, Zarxio (filgrastim-sndz) and to offer our perspective as FDA continues to formulate a comprehensive policy regarding biosimilars, particularly in regard to their naming and labeling.

As leaders in the pharmacist community, we have devoted our careers to improving the health of the patients we serve, and we look forward to providing them new treatment options at potential cost savings. Collectively we have 134 years of pharmacy experience, nearly a centur of that spent teaching. We count among us a former president of the American Pharmacist Association (APhA) and a former president of the American Society of Health System Pharmacists (ASHP). Last month, we joined 125 other pharmacists and participated in a five- hour continuing education course devoted exclusively to understanding biosimilars- the

# Example: How Will Biosimilars be Named?

- Biologic medicines, like other medicines, are assigned an **International Nonproprietary Name (INN)** by the World Health Organization.
- In the U.S., the nonproprietary name is the "USAN" United States Assigned Name. It is often, but not always, the same as the INN.
- Since an innovator biologic and its biosimilar are different medicines, and minor differences may cause adverse effects in patients, **nonproprietary names must be distinguishable from one another.**
- **Distinguishable naming** allows an accurate, unambiguous patient record, and correct attribution of adverse events to the precise product, not a general category of similar medicines.

World Health Organization

# Pharmacists and Distinguishable Naming

- Pharmacists have traditionally avoided look-alike, sound-alike drug names.
- Even if a drug is considered similar, it should be easily identified.
- Industry has been asked in the past to change drug names to avoid confusion and errors.

**SOME SUGGESTED WAYS OF DISTINGUISHING BIOSIMILARS:**

Unique USAN?

Same USAN + Suffix?

Same USAN + NDC Code

Prefix + Same USAN?

# Distinguishable Naming: ASHP Position

- The American Society of Health-System Pharmacists (ASHP) **is not opposed to the addition of a suffix, but opposes use of prefixes that it feels can lead to medication error.**

- Breast cancer medication KADCYLA® (ado-trastuzumab) is **dosed differently from its reference biologic** HERCEPTIN® (trastuzumab). Cases have occurred wherein a prescribing **physician has mistakenly omitted the distinguishing prefix**, resulting in a patient receiving the **wrong medication at the wrong dose**.

- ASHP is **not opposed to adding the National Drug Code (NDC) to the USAN as a suffix**, but the NDC not being used to track a product in all settings, reuse of NDCs by manufacturers, and other concerns may make this approach problematic.

ashp
pharmacists advancing healthcare

"…**We do not oppose the addition of suffixes** to the INN name if experts believe this approach is needed to facilitate pharmacovigilance,"

*- Christopher Topoleski, ASHP Director of Federal Regulatory Affairs.*

# Distinguishable Naming: APhA Position

- **APhA does not support unique nonproprietary names on the grounds** that it may interfere with current pharmacy safety alert systems and complicate the collection of global safety information.
- As with Human Growth Hormone and Insulin, the same nonproprietary name will not necessarily denote interchangeability, but rather be used to categorize a similar therapeutic drug.
- **APhA supports using a unique identifier, such as an NDC code** that pharmacies already use to track products, for identifying or tracking the specific drug that a patient is prescribed.

APhA

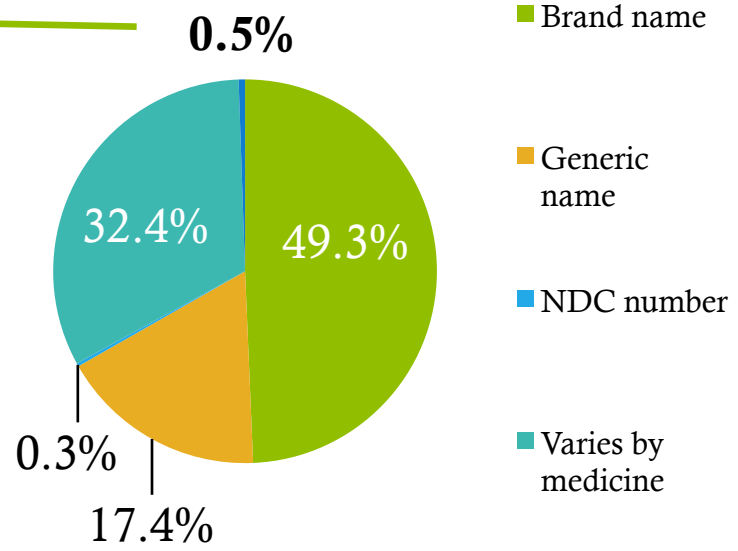
"**…a unique identifier, such as an NDC code that pharmacies already use to track products, can be used to track the specific drug that a patient is prescribed.** We recognize that non-pharmacy dispensing settings may not currently track by NDC number. "

*-APhA Letter to FDA, May 2012.*

# Is the NDC Code an Adequate Solution?

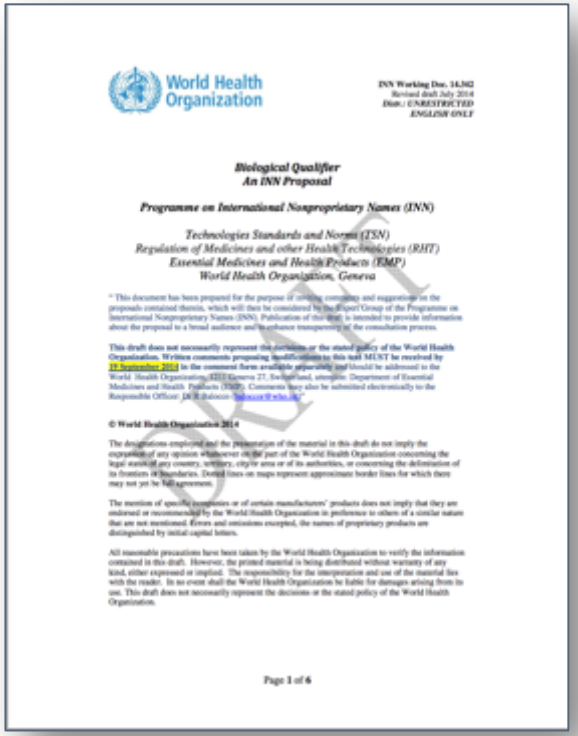
- ASBM 2012 Survey of 376 U.S. physicians who prescribe biologics showed that NDC codes were **not used by physicians to identify medicines in a patient record (0.5%).**
- NDC codes are not routinely used in billing systems. Thus, the identifier is missing in many circumstances where product-specific identification is important.
- Additionally, NDC code is fundamentally an attempt at **a LOCAL solution to what is essentially a GLOBAL problem.**

*When you identify a medicine for prescription or recording in a patient record, are you more likely to identify the medicine by brand name, non-proprietary / generic name, or NDC number?*



# Distinguishable Naming: WHO Proposal

- The WHO has proposed adding **a unique, random 4-letter code called a Biological Qualifier (BQ) to the INN of all biologics, including biosimilars,** to differentiate them.
- Adherence to the BQ System is voluntary. A similar system is already in place in Japan. **FDA has not yet weighed in.**
- **ASBM chairman Dr. Harry Gewanter and I presented our perspectives at a meeting of the WHO's Consultation on International Nonproprietary Names in April and are attending the next INN meeting in June.**
- Dr. Gewanter will discuss in more detail ASBM's work with the WHO in developing international naming standards.



World Health Organization

INN Working Doc. 14.302
Revised draft July 2014
Distr.: UNRESTRICTED
ENGLISH ONLY

***Biological Qualifier***
***An INN Proposal***

***Programme on International Nonproprietary Names (INN)***

*Technologies Standards and Norms (TSN)*
*Regulation of Medicines and other Health Technologies (RHT)*
*Essential Medicines and Health Products (EMP)*
*World Health Organization, Geneva*

* This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Group of the Programme on International Nonproprietary Names (INN). Publication of this draft is intended to provide information about the proposal to a broad audience and to enhance transparency of the consultation process.

This draft does not necessarily represent the decisions or the stated policy of the World Health Organization. Written comments proposing modifications to this text MUST be received by 15 September 2014 in the comment form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: Dr R Johnson: johnsonr@who.int

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Page 1 of 6

# Thank You
# For Your Attention