Biosimilars
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Disclosures
I have no actual or potential conflicts of interest in relation to this presentation

Objectives for Learning:
By the end of this presentation, attendees will be able to:
1. Describe what biosimilars are
2. Explain the current approval process in the US for developing Biosimilars
3. Discuss some regulatory concerns regarding biosimilar development
4. Name some biosimilars currently on the market

Overview
What are Biologics, What are Biosimilars, Are they the same?
Why do we care about making Biosimilars?
How are they made?
What is the FDA approval process?
What are some areas of concern?
How will pharmacists be involved?
What is currently on the market?

Pre-Quiz:

ARE BIOSIMILARS GENERIC VERSIONS OF BIOLOGIC MEDICATIONS?
What Is A Biologic Medication?

“Any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries.”

- Hormones (insulin, growth hormone)
- Blood and Blood Products
- Vaccines
- Interleukins
- Antibodies (bevacizumab, trastuzumab)

How Is A Biosimilar Different?

- Biologic Products are structurally complex, 200-1000x bigger than chemical products

Proteins: Size, Structure & Complexity

Two Sources of Biologics

Natural:
- Eggs
- Pigs
- Cows
- Humans

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

How Do You Make A Biologic?
How Do You Make A Biologic?
Modification of any of the steps may alter the product’s effectiveness and safety
- Different vector
- System for screening and selection to establish a master cell bank
- Culture medium
- Method of protein production or purification
- Excipients
Manufacturer may be required by FDA to assess the effects of changes to its processes

Can You Make A Generic Biologic?
Requires reverse-engineering the “innovator” biologic
- Unlike generic copies of chemical medicines
  - Made using living cells
  - Cannot be copied exactly
  - Items can only ever be “similar” or “interchangeable”
These items are NOT truly generics

What Is A Biosimilar?
A biologic product that is “highly similar” or interchangeable with a biologic product
- Established in US by the Biologics Price Competition and Innovation Act of 2009
- No clinically meaningful differences in terms of safety, purity, and potency
- Available in same dosage strength and form
- Manufactured according to current Good Manufacturing Practice (cGMP) regulations,
- Synonyms: follow-on biologic, follow-on protein, generic biopharmaceutical, biogeneric, comparable biologic, subsequent-entry biologic

Why Do We Care About Biosimilars?
Biologic medications:
- Very commonly used
- Very expensive
- Use is rapidly increasing: Nearly 200 biologic and recombinant biotechnology medicines helping 800 million patients worldwide
- Patents are expiring

Pharmacists will play a key role in future utilization
Europe As A Model

- Regulatory framework for approval established in 2005 (European Medicines Agency)
- First biosimilar approved in 2006 (somatropin)
- EU: “a copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy, and safety based on a comprehensive comparability exercise.”
- Biosimilars must be shown to be of a “similar nature in terms of quality, safety, and efficacy” compared with the innovator.
- 10–11 years of exclusivity provided to innovators
- Routine post-marketing monitoring required
- EMA-FDA biosimilar “cluster” to communicate regarding biosimilars

FDA Process for Approval

Two separate standards for biosimilarity and interchangeability
- Must prove that the product is “highly similar,” notwithstanding minor differences in clinically-inactive ingredients
- No clinically-meaningful differences between the biological product and the reference product in safety, purity, or potency
- The risk of switching between the biosimilar product and reference product must not be greater than the risk of using only the reference product consistently
FDA Oversight

FDA has discretion to determine what is needed in each case
- Requirements vary by drug and class
- Totality-of-the-evidence approach
- No defined threshold for the scope or amount of data required

Patents/Exclusivity to encourage innovation:
- 12yrs of exclusivity for innovator product
- Additional 6months for pediatric studies
- Biosimilar application cannot be submitted for first 4years

Three Pathways:

Acceptable Differences

- Impurity profiles
- Excipients and formulation of the finished product
- Container/closure and delivery system
- Differences in the active substance can be permissible
- Expression system need not be the same

Naming

- Like other medications, International Noproprietary Name (INN) designated by WHO
- In US given a USAN, US Assigned Name, often the same
- Since innovator biologic and biosimilars are DIFFERENT:
  - Must have distinguishable nonproprietary names
  - Allows accurate, unambiguous patient record
- FDA: Draft Guidance only
  - Core name + designated suffix
  - Ex: putonastim alfa-jnzt
  - putonastim alfa-kgnx

Are There Concerns About Biosimilars?

There is MUCH to care about
They AREN'T the same
They AREN'T generics
As in life, there is much more complexity than we would like
The more we know, the less we understand

-Harry L Gewanter, MD, FAAP, FACR, Chairman of the Alliance for Safe Biological Medicines
Areas of Concern

Prescriber Confidence
Interchangability/Substitution
Immunogenicity
Pharmacovigilence
Naming
Education

Prescriber Confidence
As with anything new, much we still do not know
- Provider’s ultimately want to Do No Harm
- What Medication is pt actually receiving?
- If a substitution occurs, when, by whom, to what, consistently or inconsistently?
- Are they really the same?
- Who is going to have oversight and monitor for issues?

Interchangability/Substitution
- Do not rush biosimilars, don’t undermine acceptance
- “Dispense As Written”
- More data and slow introduction into clinical practice will allow monitoring
- Above all:
  GOOD COMMUNICATION between Provider, Patient, and Pharmacy

Immunogenicity
All biologics have potential to contribute to an immune response
- Various product and patient related factors
  - Product: structural, processing, formulation, storage, handling, presence of impurities
  - Patient: genetic background, immune status, route of administration
- Adverse events unique to biosimilars may be found due to slight differences
- Reactions can take up to several months to manifest

Pharmacovigilence
- Potential for immunogenicity when switching between innovator and biosimilar products
- Data on switching is important
- Post-marketing pharmacovigilence is needed to detect and assess
- Rare but serious events unlikely to be detected prior to marketing

Naming
Importance of sorting out Naming:
- >30 biosimilars to stimulate red blood cell production stimulating agents on market in Thailand
- One (or more) caused a deadly condition known as Pure Red Cell Aplasia (PRCA)
- Since all share the same INN, difficult to determine which products contributed to this issue
PRACTICAL APPLICATION: HOW DOES THIS AFFECT US AS PHARMACISTS?

Pharmacists Will Be Involved
- Substituting products at the dispensing level
- Developing P&T policies regarding use
- Understanding cost/coverage
- Input on laws and regulations regarding use
- Educating other healthcare providers
- Educating patients
- Ongoing surveillance/pharmacovigilance

Substitution Policy in the US
CONGRESS: Sets the legal definition of Interchangeable: substitution without physician intervention
FDA: Makes scientific decisions and sets interchangeability criteria
STATES: Decides what pharmacists are allowed to do

What Biosimilars Are Already On The Market?
**EU:**
- Insulin Glargine (Abasaglar)
- Epoetin alfa (Absaamed, Birecrt, Epoetin alfa Hexal)
- Epoetin Zeta (Retacrit, Silapo)
- Etanercept (Benept)
- Filgrastim (Accofil, Biofrastim, Filgrastim Hexal, Filgrastim Ratiopharm, Grastofil, Nivestim, Ratiograstim, Tevagras, Zanco)
- Folitropin alfa (Semifina, Ovulate)
- Infliximab (Inflectra, Remsima)
- Somatotropin (Omnitrope, Valtropin)

**USA:**
- Filgrastim-sdx (Zarzio)
- Recently rejected several products
Practical Application: Coverage
Managed Care projects massive savings
Is this panning out?
Who is covering?

Assessment:

Please:
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Questions:

Thank You!