BIOSIMILARS 101:

What are biosimilars and why should you care?

Richard Dolinar, MD
Chairman, Alliance for Safe Biologic Medicines

June 4, 2012

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About the Alliance for Safe Biologic Medicines

The new voice for biologic safety has diverse representation

- ✓ Patients
- ✓ Physicians
- ✓ Scientists
- ✓ CROs
- ✓ Innovator industry

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General Members

Steering Committee

Mission of the Alliance

- Serve as an authoritative resource providing access to information about issues related to ensuring the safety and quality of biologics.
- Advocate for policies that allow for doctors and patients to choose the best course of treatment.
- Seek solutions that ensure affordability and accessibility of biologic medications while never compromising on patient safety.

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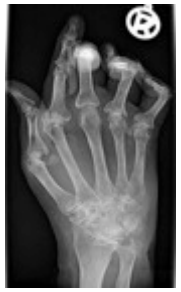
Role of Biotechnology in Medicine

Advancements in science have increased the number of biotechnology products, revolutionizing the diagnosis, prevention, cure and management of many serious diseases.



X-Ray of rheumatoid arthritis affected hand

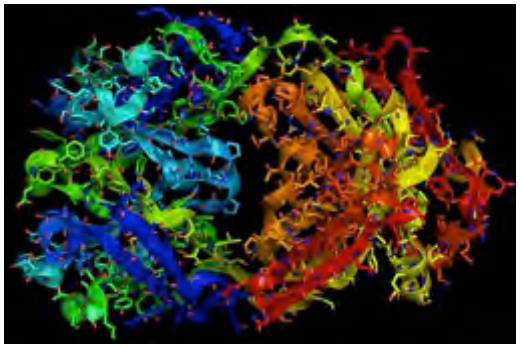
RHEUMATOID ARTHRITIS
This disorder attacks healthy parts of the body, including its own joints, causing swelling, pain and even disfigurement. New biotech drugs target the affected area without suppressing the entire immune system.

30th Anniversary of AIDS Badge, AIDS.gov

HIV/AIDS
Some antiretroviral therapies like Infuvirtide (Fuzeon) stop the HIV virus from infecting cells while others treat HIV-related anemia and other complications.

Humalog Insulin

DIABETES
Synthetically made Human insulin was made available in the 1980's. Before then, it was made from cows and pigs.



Trastuzumab (monoclonal antibody)

CANCER
Several biologics including this image of Trastuzumab (a monoclonal antibody) treat cancers.

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Examples of Biologic Medicines

Product	Manufacturer	Condition
HumulinR *Insulin Injection (Human Recombinant)*	Eli Lilly	Diabetes
Betaseron *Interferon beta-1b*	Bayer	Multiple Sclerosis
Genotropic *Somatropin*	Pfizer	Children with growth hormone deficiency; Prader-Willi syndrome, girls with Turner syndrome
Follistim *Follitropin Beta*	Organon	Infertility
NovSeven *Coagulation Factor VIIa*	Novo Nordisk	Hemophilia
Enbrel *Etanercept*	Amgen	Rheumatoid Arthritis, Psoriasis
Epogen *Epeotin alfa*	Amgen	Anemia caused by chronic kidney disease
Rituxan *Rituximab*	Genentech	Non-Hodgkin's lymphoma, Rheumatoid Arthritis
Humira *Adalimumab injection*	Abbot Labs	Rheumatoid Arthritis, Crone's disease, ankylosing spondylitis, psoriatic arthritis
Erbitux *Cetuximab injection*	Bristol-Meyers Squibb	Head & Neck Cancer, Colorectal Cancer
Pegasys *Peginterferon alfa-2a*	Roche	Hepatitis C, Hepatitis B
Herceptin *Trastuzumab injection*	Genentech	Metastatic Breast Cancer
Avastin *Bevacizumab*	Genentech	Colorectal Cancer, Lung Cancer, Metastatic Breast Cancer, Gliobastoma, Metastatic Kidney Cancer

"By 2014, it is projected that six out of the 10 top-selling drugs in the U.S. will be biologics, some of which may face biosimilar entry."

Analysis Group Health Care Consulting Bulletin (Fall/Winter 2010)

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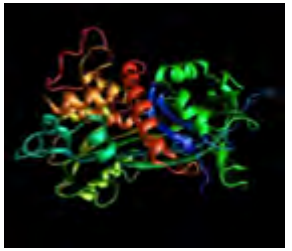
The differences between Chemical Drugs and Biotech Medicines you can see



Chemical drugs	Biotech medicines
Made by chemical synthesis	Made by living cells – Unique cell lines, from bacteria, yeast or mammals – Recombinant proteins
Defined structure, Easy to characterize	Heterogeneous structure, Difficult to characterize.
Usually taken by mouth and prescribed by a general practitioner	Usually injected and prescribed by specialists

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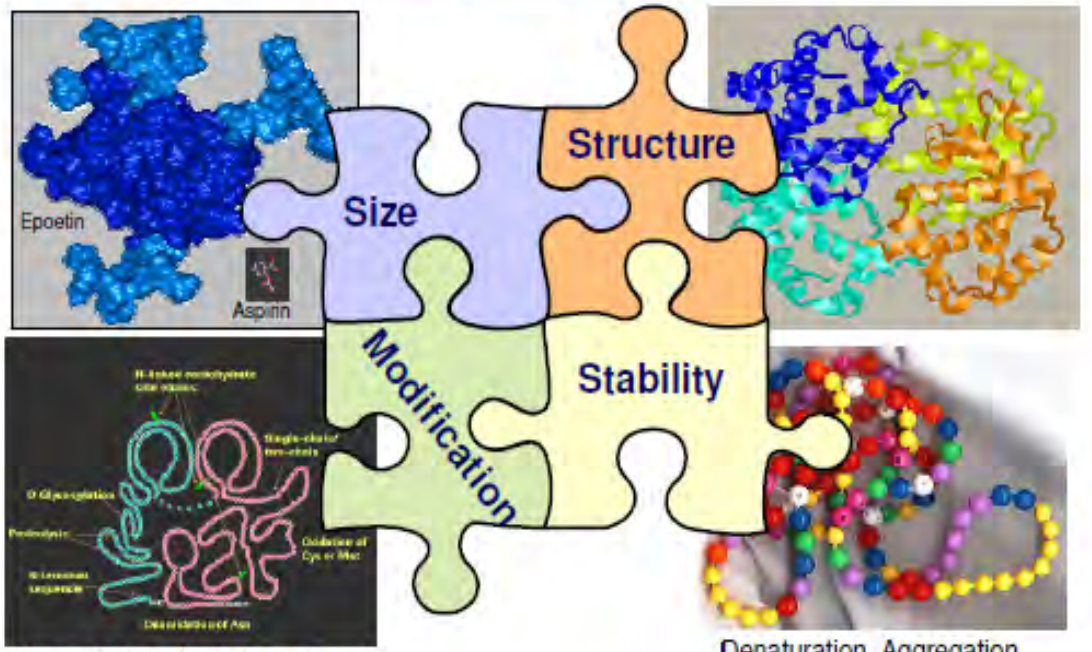
Types of Variation

Biotech and Chemical Molecules: Differences that Matter



Source: World Health Organization

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What are Biosimilars?

- Biosimilars are often referred to as follow-on biologics, generic biologics or follow-on proteins.
- Biosimilars are new versions of existing trade-name biological products whose patents have expired.
- While “highly similar” biosimilars are not “identical” to the reference product.
- They do not utilize the same living cell line, production process, or raw material as the innovator drug.

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Why are biosimilars not generics?

Chemical Drug

- Few atoms
- Easily characterized
- Relatively Simple

Generic

- Same active ingredient
- Identical strength, dosage form, and route of administration as the reference drug

Biologic Medicine

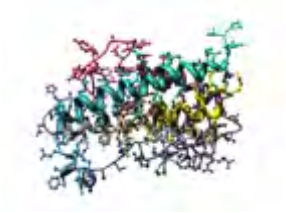
- Made from living cells
- Difficult to characterize
- Very Complex

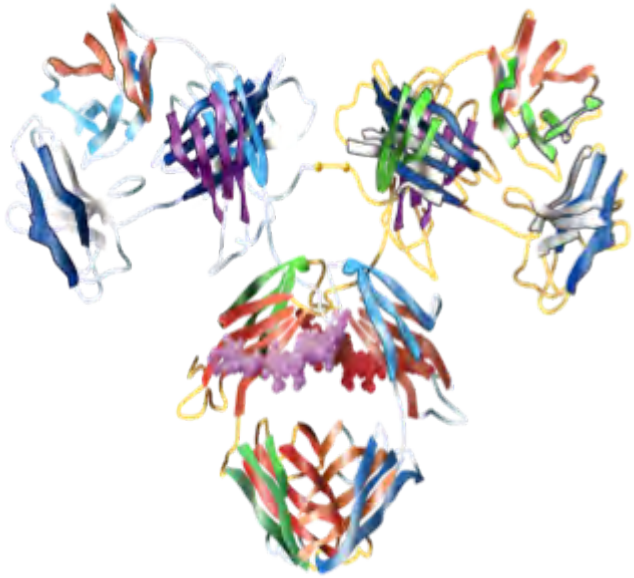
Biosimilar

- Never identical
- Uses unique cell lines which cannot be replicated

Key differences between chemical drugs and biologics

Size





Aspirin
~180 daltons
21 atoms

Human Growth Hormone
191 amino acids
~22,000 daltons
3091 atoms

IgG1 antibody
>1000 amino acids
~150,000 daltons
>20,000 atoms

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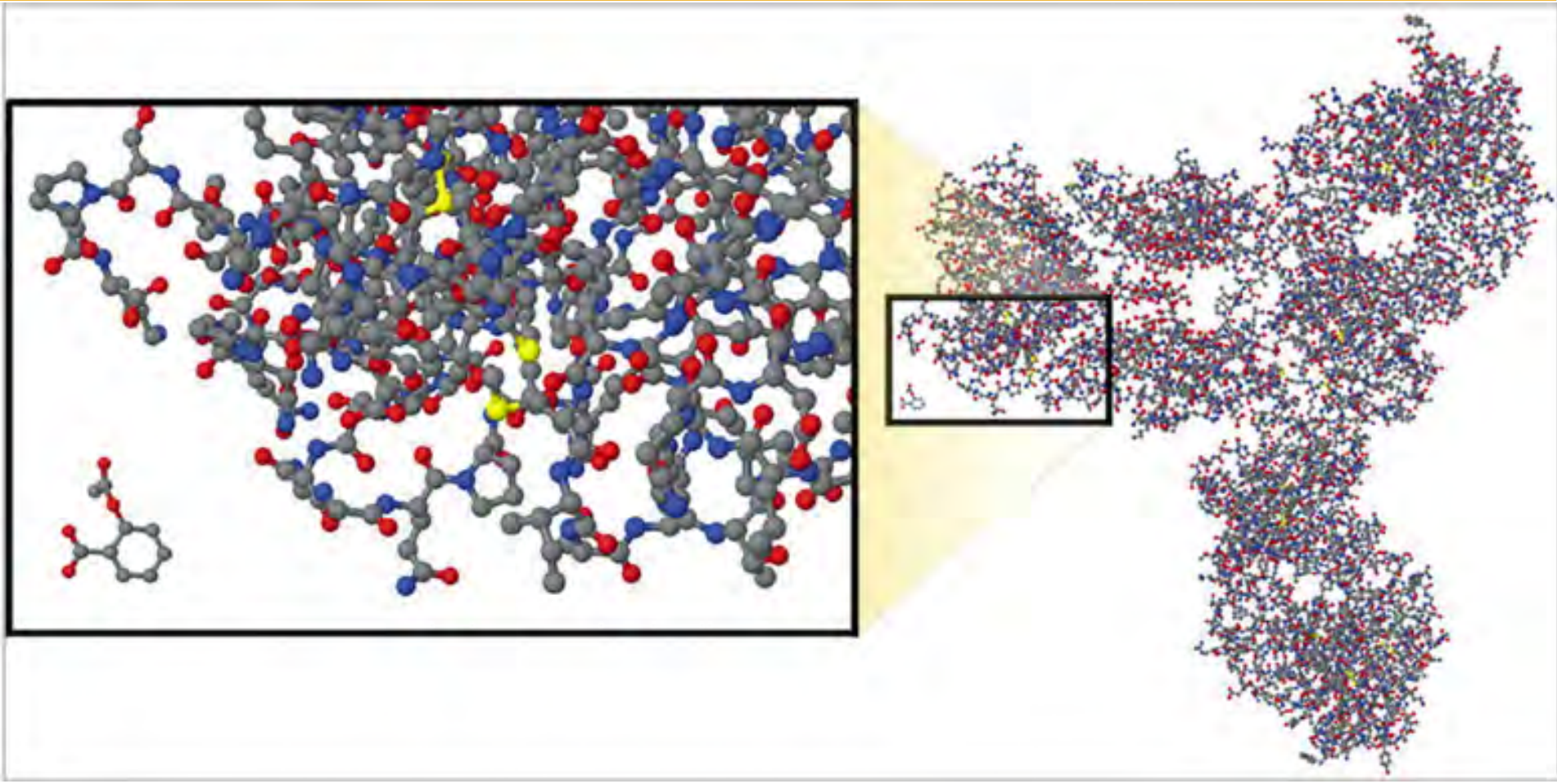
Genentech

Molecular Comparison:
Aspirin vs. Biologic Monoclonal Antibody



Source: New England Journal of Medicines, “Developing the Nation’s Biosimilars Program,” August 4, 2011

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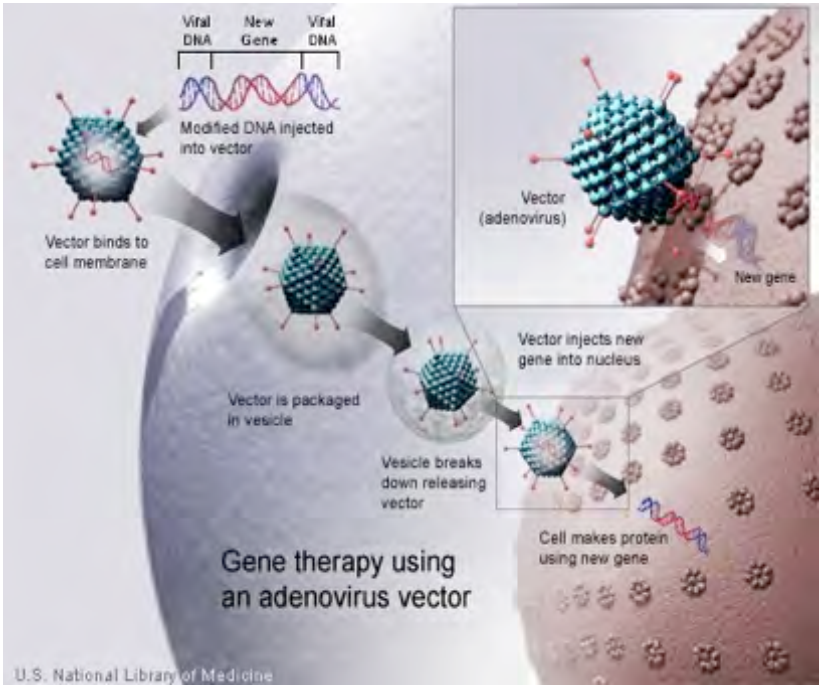
Highly Complex Manufacturing Process



Design the gene sequence

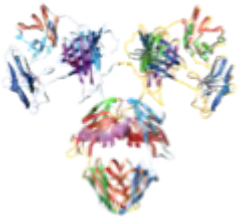
Place gene sequence inside a vector

Place vector inside a specific cell

Fermentation – cells produce the protein defined by the vector

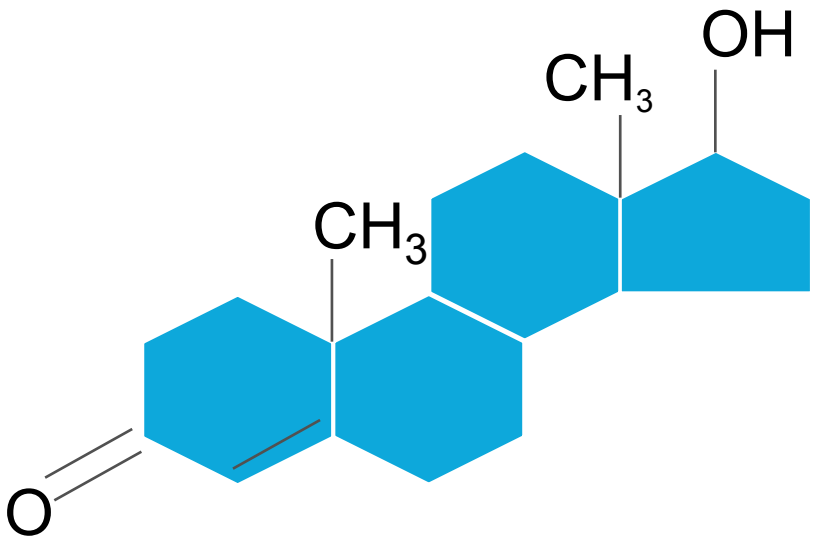
Purification – removing the impurities

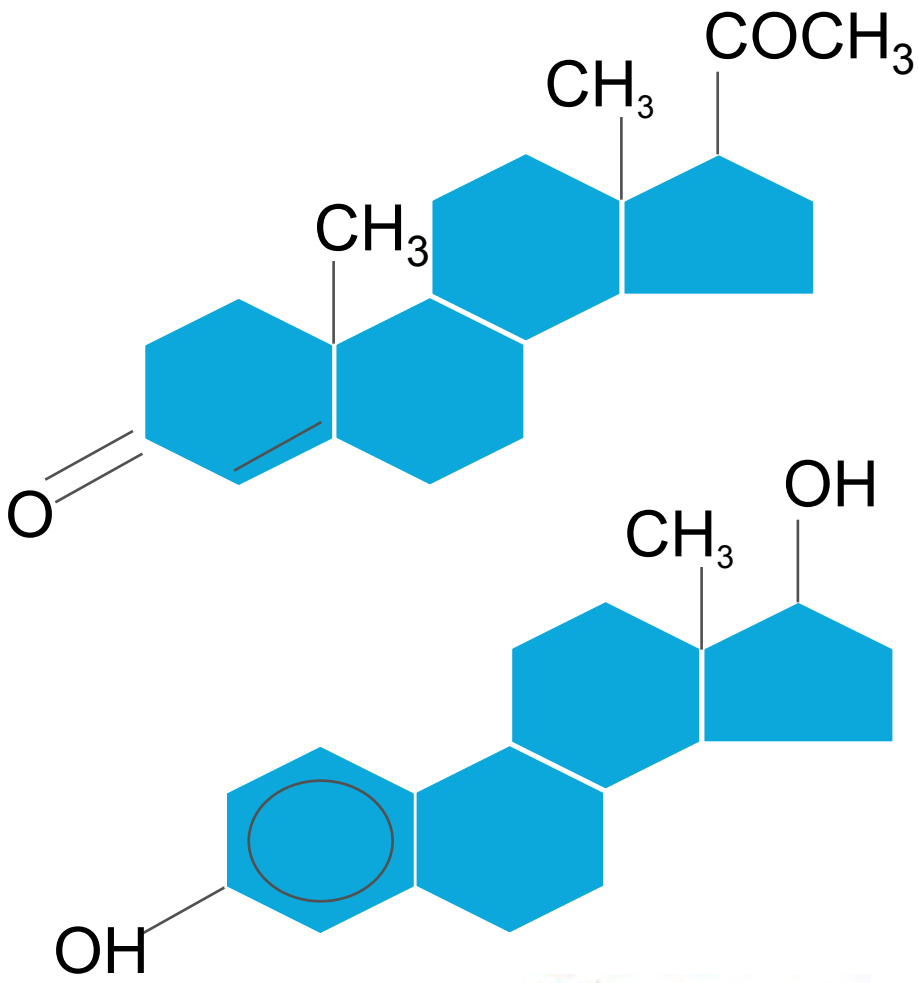
Highly complex protein with 3 or 4 levels of structure



IgG1 antibody
>1000 amino acids
~150,000 daltons
>20,000 atoms

Small Differences = Large Impact





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Source: Bilao LLC, 2008

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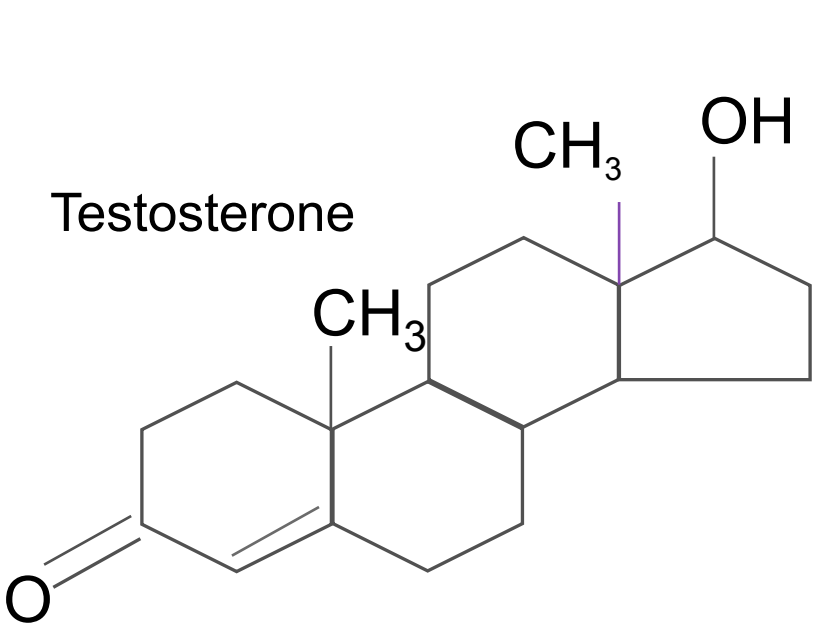

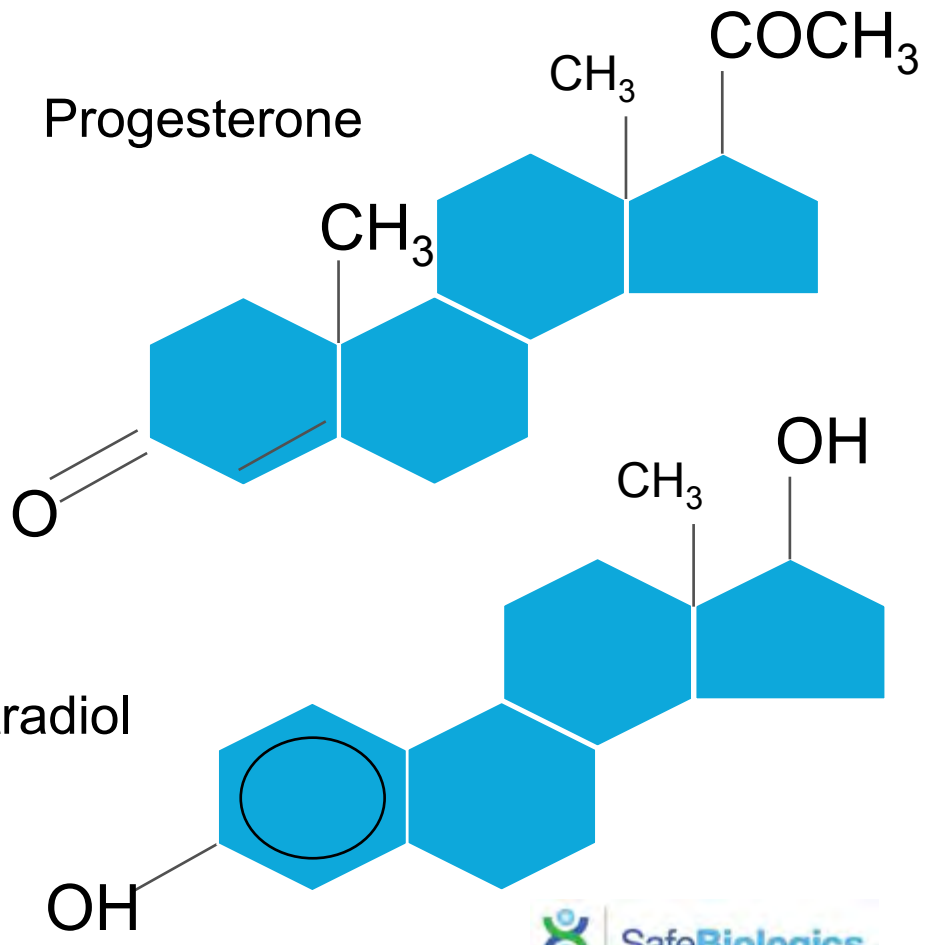

Source: Bilao LLC, 2008

Degree of Manufacturing Change

The degree of change determines the level of risk and thus the data required to demonstrate the product remains equally safe and effective

Supplier for tubing changed

Relocate equipment within same facility

Relocate to new facility

Manufacturing scaled up to production level

New cell line New process

Low risk and common change = Minimal data required

Higher risk / less common changes = Maximal Data Required *(Clinical Testing, Analytical and Process)*

**Biotech medicines cannot be fully copied*

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Current Examples of a Biosimilar Pathway

- The European Union authorized the first formal regulatory pathway for biosimilars in 2004
- Currently the European Medicines Agency (EMA) regulates biosimilars.
- Others that have developed a pathway are Japan (2009), Canada (2010), South Africa, (2010), and the World Health Organization (2009).

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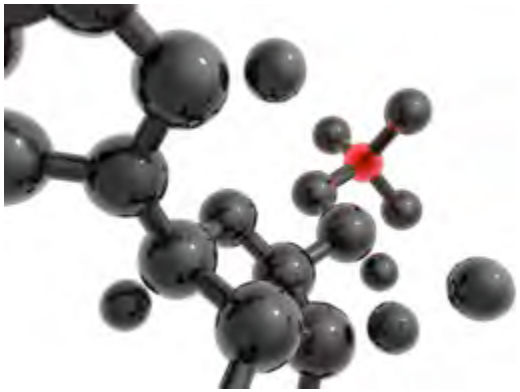
Biosimilars Pathway

- Biologics are not covered under the 1984 Hatch-Waxman Act for generic versions of conventional drugs.
- On March 23, 2010 President Obama signed into law the Patient Protection and Affordable Care Act that included a pathway for the approval of biosimilars (also referred to as the Biologics Price Competition and Innovation Act (BPCIA).
- In November 2010, the Food and Drug Administration began consulting with patient groups, physicians and industry on how to approve the first copies of biologics, known as follow-on biologics or biosimilars.
- On February 9, 2012 the FDA issued a draft guidance seeking public input.
- On May 11, the FDA held its first public hearing on the draft guidance.



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ASBM Testimony at May 11 Public Hearing

Stressed the need for the FDA to make patient safety the cornerstone of the biosimilars pathway, calling for:

1. robust clinical testing;
2. the establishment of steps to monitor the global supply chain and manufacturing process;
3. the creation of track, trace and naming provisions;
4. the development of clear packaging, labeling and prescribing information; and
5. very close and deliberate scrutiny of a biosimilar before it is deemed interchangeable.

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Biosimilar Policy Considerations

Patient safety is the priority

- Biologics are complex compounds made from living cells and have highly intricate structures that are not easily understood, characterized or replicated.
- Patient safety must preeminently guide regulatory decisions.

Doctors must make medical decisions

- Patients and doctors together should carefully decide the best course of treatment.
- Medical decisions should be made in doctors' offices and not by legislators and regulators.

Leveraging what we know

- A science-based approach must be used to establish the pathway for biosimilars.
- Biosimilars are more complex than generics, and therefore Hatch/Waxman does not apply.
- Learn lessons from Canadian and European experiences

Pharmacovigilance is essential

- There must be a robust traceability system for biosimilars once approved.
- A common-sense approach to tracking biosimilars must be used to ensure patient safety.

Conclusion

- Biosimilars are not generics.
- The FDA released a ‘biosimilars pathway’ earlier this year.
- The FDA will decide what analytical, preclinical and clinical data will be needed for approval.
- Prior to biosimilars’ market entry, key policy questions must be addressed with a science-based, transparent approach that seeks the input of major stakeholders and puts patients first.

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