Biosimilars & Interchangeable Biologic Products

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What is a Biologic Product?

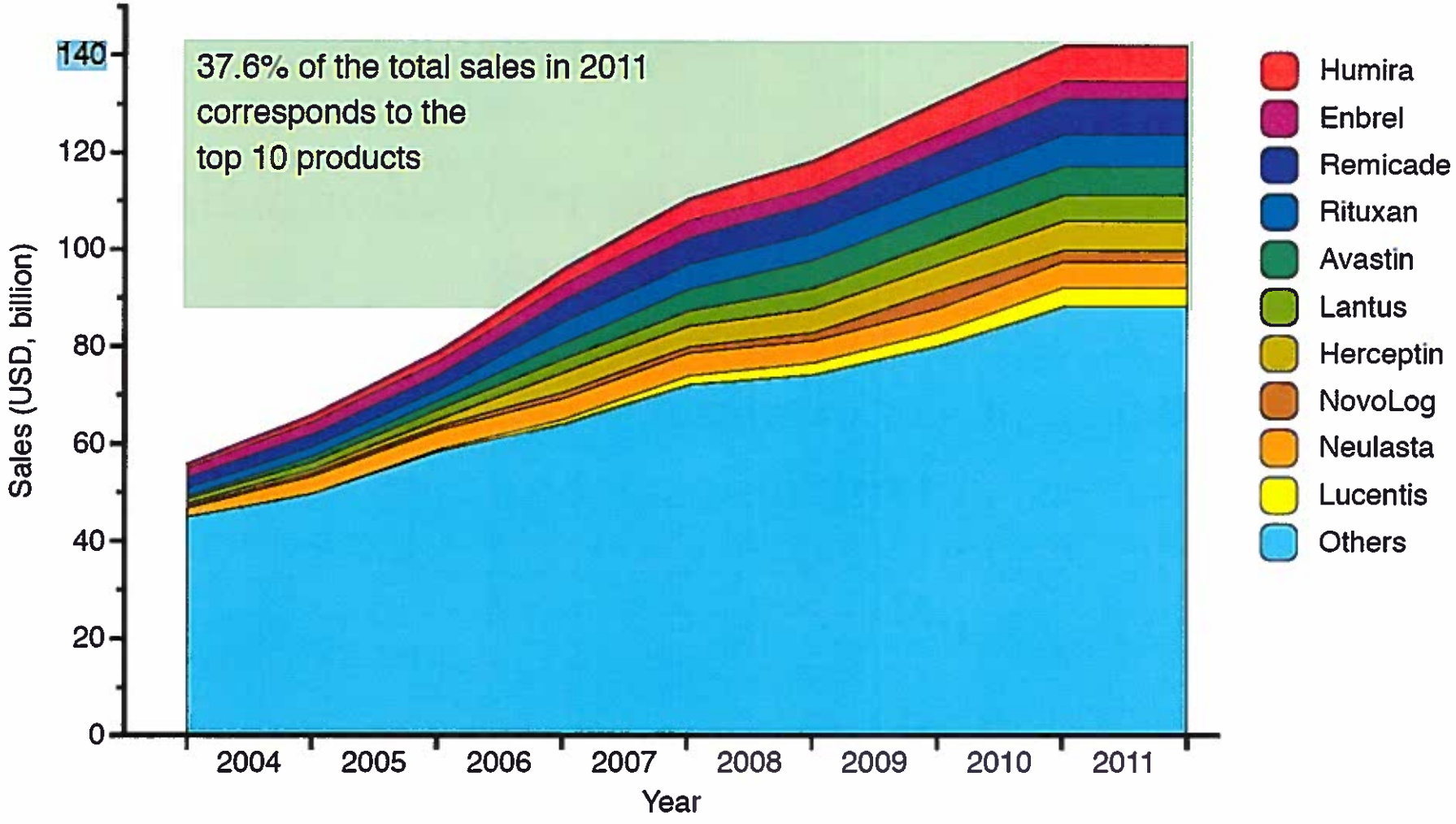
"Biological products, or biologics, are medical products. **Many biologics are made from a variety of natural sources** (human, animal or microorganism). Like drugs, some biologics are intended to treat diseases and medical conditions. Other biologics are used to prevent or diagnose diseases."

What is a Biologic Product?

Examples of biological products include:

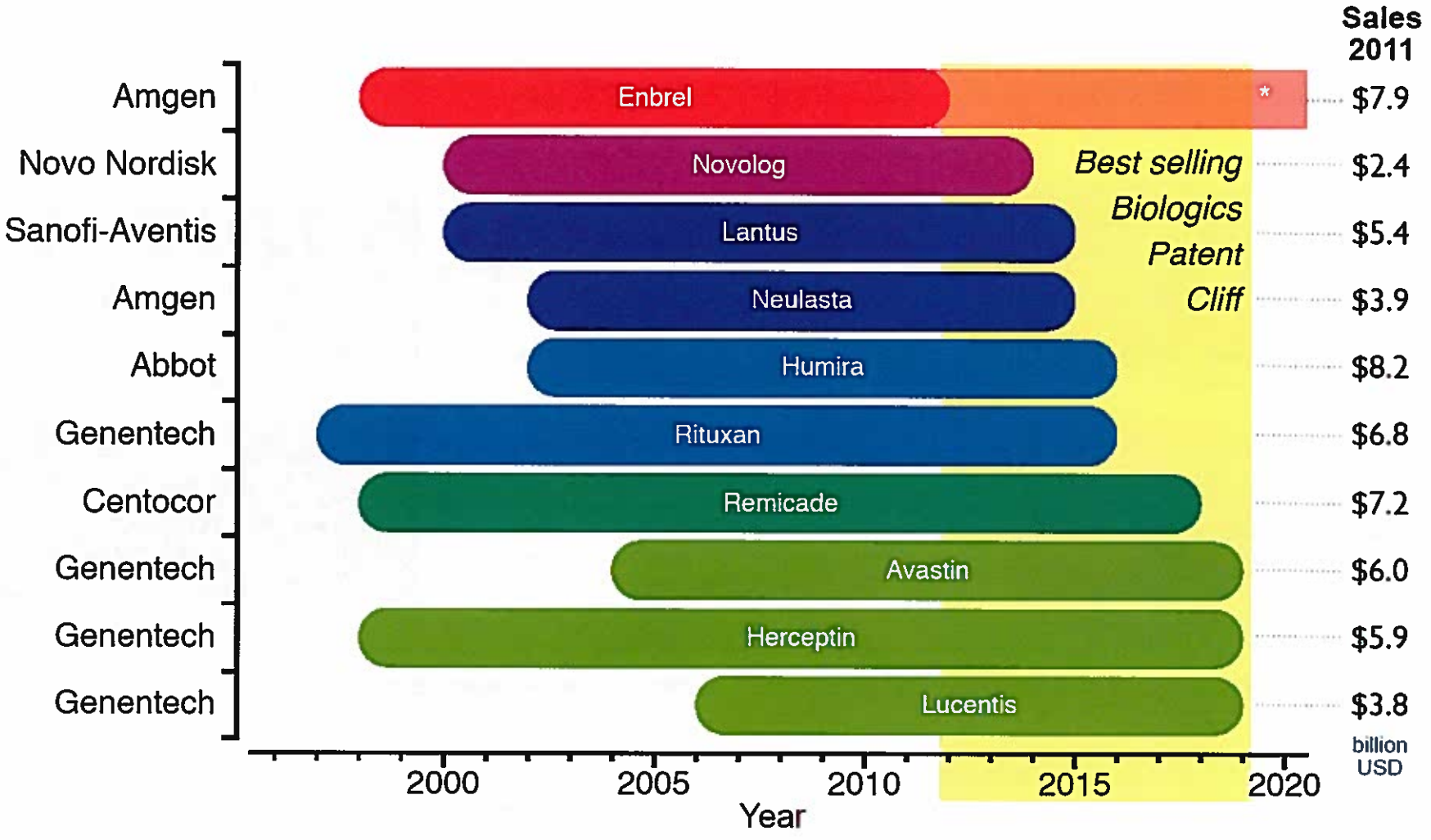
- **Vaccines**
- **Blood and blood products** for transfusion and/or manufacturing into other products
- **Allergenic extracts**, which are used for both diagnosis and treatment (for example, allergy shots)
- **Human cells and tissues** used for transplantation (for example, tendons, ligaments and bone)
- **Gene therapies**
- **Cellular therapies**
- Tests to screen potential blood donors for infectious agents such as HIV

Estimated Biologic Drug Spend



Calo Fernandez, Bruno and Martinez-Hurtadeo, Juan; Biosimilars: Company Strategies to Captrue Value from the Biologics Market. Pharmaceuticals 2012, 5, 1393-1408; doi:10.3390/ph5121393

Biologic Product Patent Cliff



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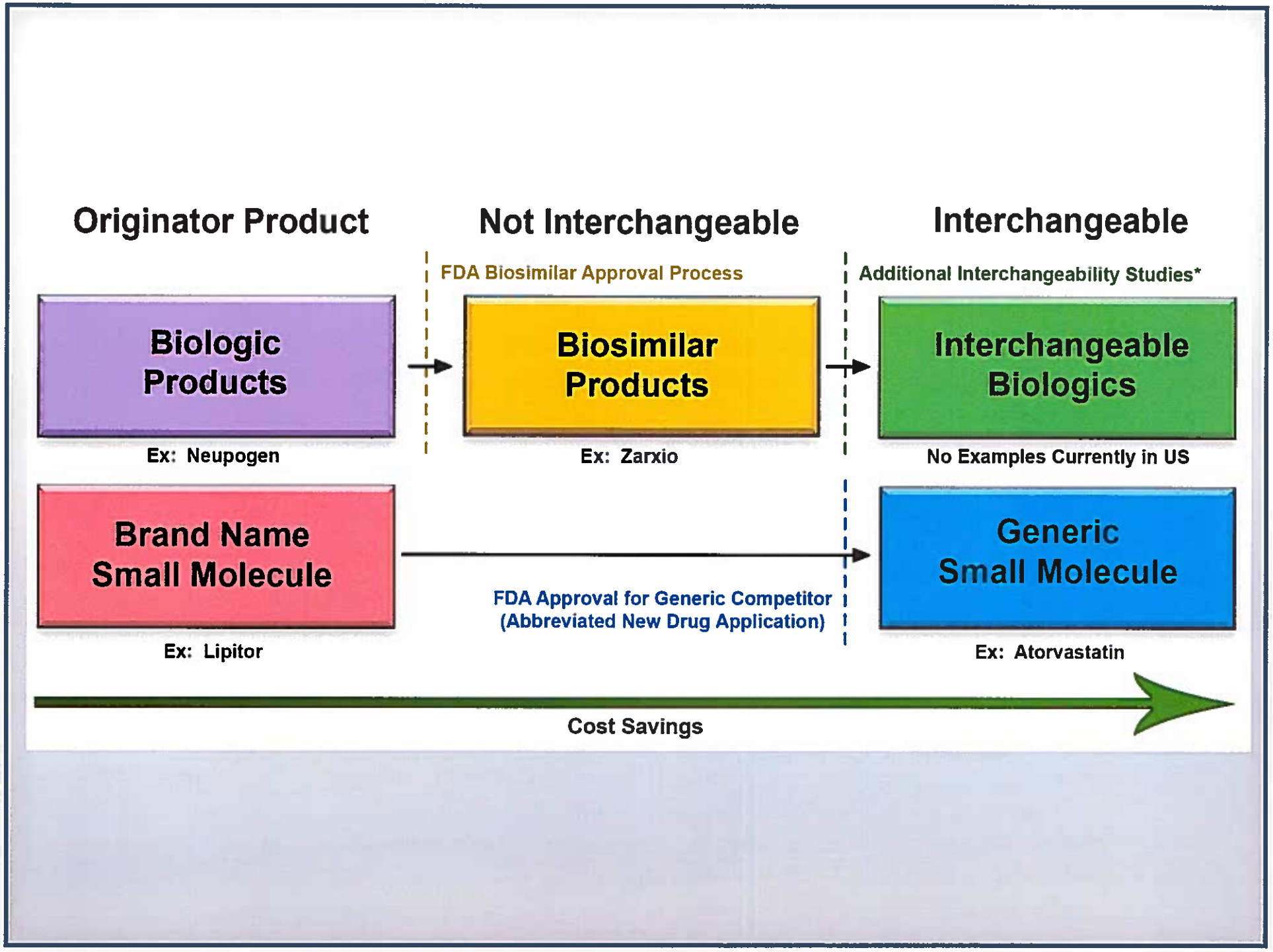
Originator Product
Not Interchangeable
Interchangeable
FDA Biosimilar Approval Process
Additional Interchangeability Studies*
Biologic Products
Biosimilar Products
Interchangeable Biologics
Ex: Neupogen
Ex: Zarxio
No Examples Currently in US
Brand Name Small Molecule
Generic Small Molecule
FDA Approval for Generic Competitor (Abbreviated New Drug Application)
Ex: Lipitor
Ex: Atorvastatin
Cost Savings

The Generic Substitution Process

- Pharmacists may substitute a generic equivalent of a brand named drug product at the point of sale.
- Product must be **lower cost.**
- **Purchaser must be notified** if a substitution is made, and the name of both the brand prescribed and the product dispensed shall appear on the label.
- Prescribers who do not wish to have a product substituted may indicated "**dispense as written**" or **DAW** on the prescription.

Immunogenicity

- "**Immunogenicity** is the ability of a particular substance… to provoke an immune response in the body of a human or animal. "
- "In other words, **immunogenicity** is the ability to induce a humoral and/or cell mediated immune response."
- As it relates to pharmaceuticals… this is better known as a "**drug allergy**."

Drug Allergies

- **Immunogenicity** and **drug allergies** are not a problem exclusive to biologics and large, complex molecules.
  - Example: Penicillin and Sulfa Allergies
- Drug allergies and other drug related safety concerns are detected and evaluated in the clinical trial process.
- Due to theoretical concerns related to issues of immunogenicity and biosimilars the **FDA** has implemented a **more stringent standard of evidence for products seeking interchangeable status.**

Excerpt from FDA Guidance to Industry

Section 351(i) defines biosimilarity to mean "that the biological product is **highly similar** to the reference product **not withstanding minor differences in clinically inactive components**" and that "there are **no clinically meaningful differences** between the biological product and the reference product in terms of the **safety**, **purity**, and **potency** of the product"

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf

Excerpt from FDA Guidance to Industry

Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an **application for a proposed biosimilar product** and **an application or a supplement for a proposed interchangeable product**.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf

Excerpt from FDA Guidance to Industry

- To meet the higher standard of "interchangeability," an applicant must provide sufficient information to demonstrate:
  - **Biosimilarity**
  - That the biological product can be expected to **produce the same clinical result as the reference product in any given patient**
  - If the biological product is administered more than once to an individual, **the risk in terms of safety or diminished efficacy from alternating or switching** between the use of the biological product and the reference product **is not greater** than the risk of using the reference product without such alternation or switch.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf

42 U.S. Code § 262 - Regulation of biological products

(i) "Biological product" defined In this section:

(1) The term "**biological product**" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

(2) The term "**biosimilar**" or "**biosimilarity**", in reference to a biological product that is the subject of an application under subsection (k), means—

(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and

(B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

(3) The term "**interchangeable**" or "interchangeability", in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that **the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.**

(4) The term "reference product" means the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k).

42 U.S. Code § 262 - Regulation of biological products

(4) Safety standards for determining interchangeability Upon review of an application submitted under this subsection or any supplement to such application, the Secretary shall determine the biological product to be interchangeable with the reference product if the Secretary determines that the information submitted in the application (**or a supplement to such application**) is sufficient to show that—

(A) the biological product—

(i) is **biosimilar** to the reference product; and

(ii) can be expected to produce the same clinical result as the reference product in any given patient; and

(B) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of **alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.**

The Importance of Substitution

Attempts to undermine trust in biosimilars are:

"...worrisome and represent a disservice to patients who could benefit from these lower cost treatments."

- Margaret Hamburg

Former FDA Commissioner (2009-2015)

The Importance of Substitution

"**Substitutability** helped spur the growth of the generic[s] industry and is similarly **essential to help foster competition in the biological drug market.** Ultimately, such competition will **spur innovation, improve consumer choice and drive down medical costs**."

- Margaret Hamburg

Former FDA Commissioner (2009-2015)

Summary

- Biosimilar and interchangeable biologic products are essential for **improving access** and **reducing costs** for the most cutting edge medical and pharmaceutical technologies.
- The **FDA** has put in place a system to evaluate the **safety** and **efficacy** of these classes of products.
- The FDA continues to refine the guidelines for clinical evidence for **safe interchangeability** to insure the **highest degree of safety** for our patients who use these products.

Conclusion

- The Michigan Pharmacists Association urges the legislature to adopt policies that is **consistent with currently implemented federal regulations**.
- The FDA's rigorous approval process **negates the clinical necessity of additional notification requirements**.
- Additional requirements related to notification will only work to:
  - Undermine **prescriber** and **consumer confidence**.
  - Create **additional administrative burden** on the part of **all providers**.

References

1. FDA Biosimilars page: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm.
2. Excerpts from US Code: https://www.law.cornell.edu/uscode/text/42/262.
3. Statements from former FDA commissioner: http://gabi-journal.net/news/us-fda-defends-biosimilar-substitution.