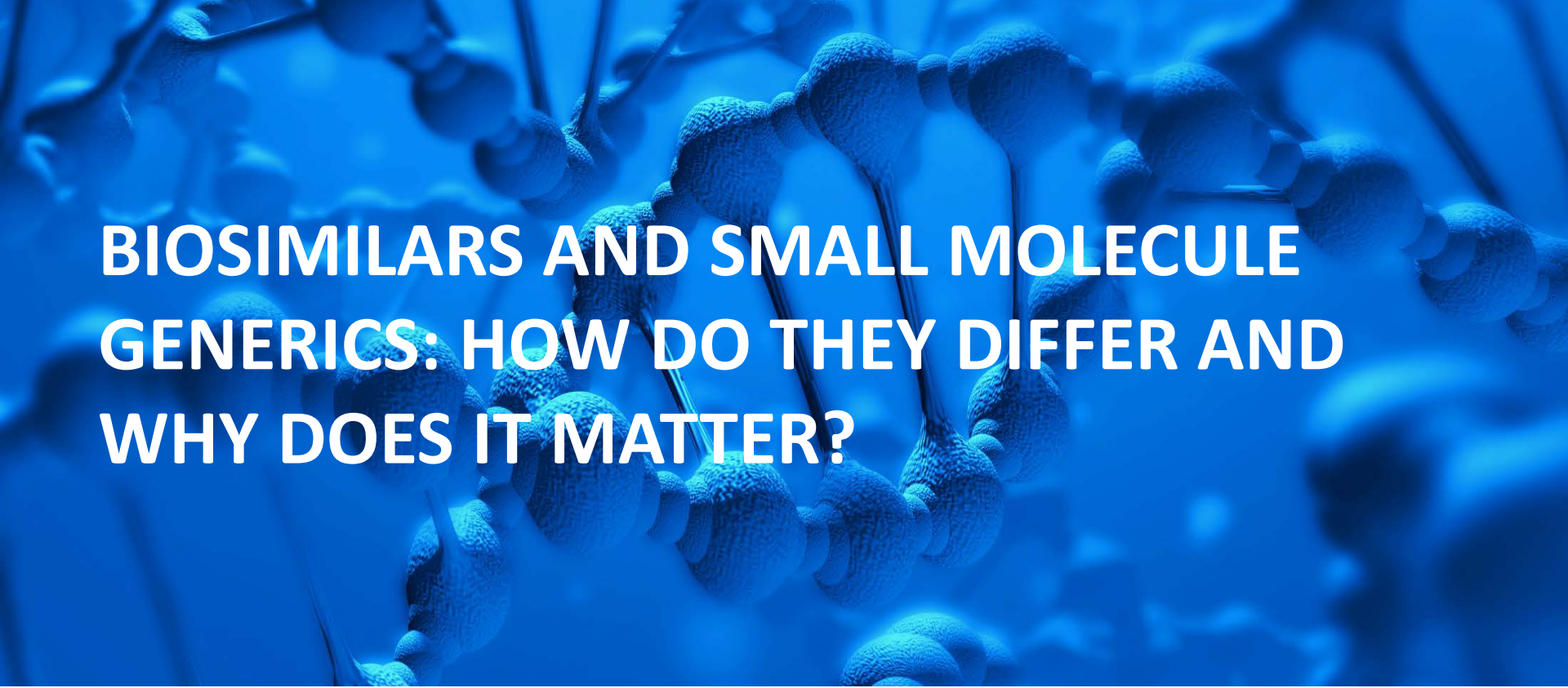

BIOSIMILARS AND SMALL MOLECULE GENERICS: HOW DO THEY DIFFER AND WHY DOES IT MATTER?

THOMAS FELIX, MD
MEDICAL DIRECTOR, R&D POLICY

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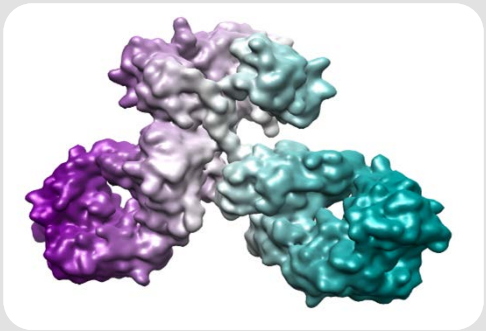
WHAT IS A BIOLOGIC MEDICINE?

- A biologic is a substance that is made from a living organism or its products.[1]
- Biologics are developed in living systems, including bacterial[2], yeast[3,4], and mammalian[5,6] cells.



1. National Cancer Institute: Dictionary of Cancer Terms. Available at: http://www.cancer.gov/dictionary?cdrid=426407. Accessed January, 18, 2013. 2. Baneyx F, *Curr Opin Biotechnol*. 1999;10:411-421. 3. Cregg JM, et al. *Mol Biotechnol*. 2000;16:23-52. 4. Malys N, et al. *Methods in Enzymology*. 2011;500:197-212. 5. Lackner A, et al. *Anal Biochem*. 2008;380:146-148. 6. Rosser MP, et al. *Protein Expr Purif.* 2005;40:237-243.

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BIOLOGIC THERAPIES HAVE TRANSFORMED HEALTHCARE

Worldwide, nearly 200 biologics have transformed the lives of over 800 million patients with serious illnesses[1]

1. Essential Action: Saving Billions: The Case for Effective Biogenerics Legislation. Available at: http://www.essentialaction.org/access/uploads/BiogenericsGeneralFactSheetFinal.pdf Last accessed March 17, 2014.

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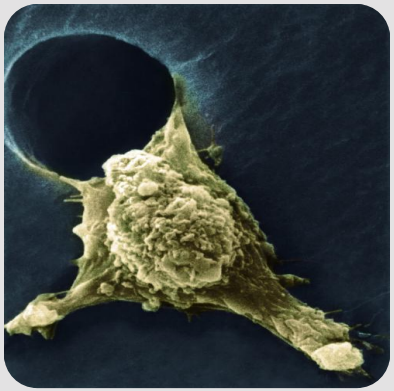
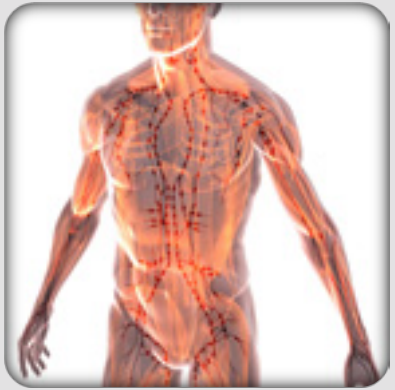
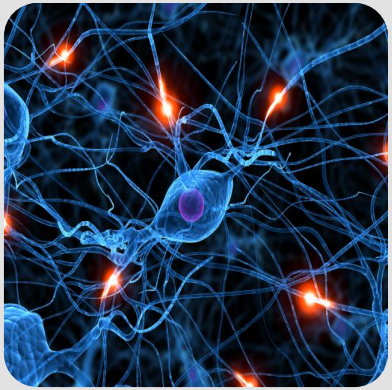
BIOLOGICS ARE APPROVED TO TREAT VARIOUS CONDITIONS



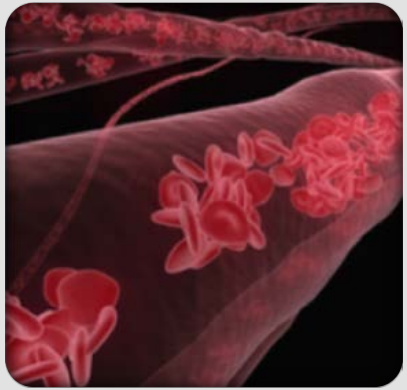
Cancers[1]



Immune system disorders[1,2]



Neurological disorders[1]



Hematologic conditions[1,2]

1. Biotechnology Industry Organization. Guilford-Blake R, Strickland D, eds. Guide to Biotechnology. 2008. www.bio.org/sites/default/files/BiotechGuide2008.pdf. Accessed February 2, 2012; 2. Kozlowski S, et al. *N Engl J Med.* 2011:365:385-388.

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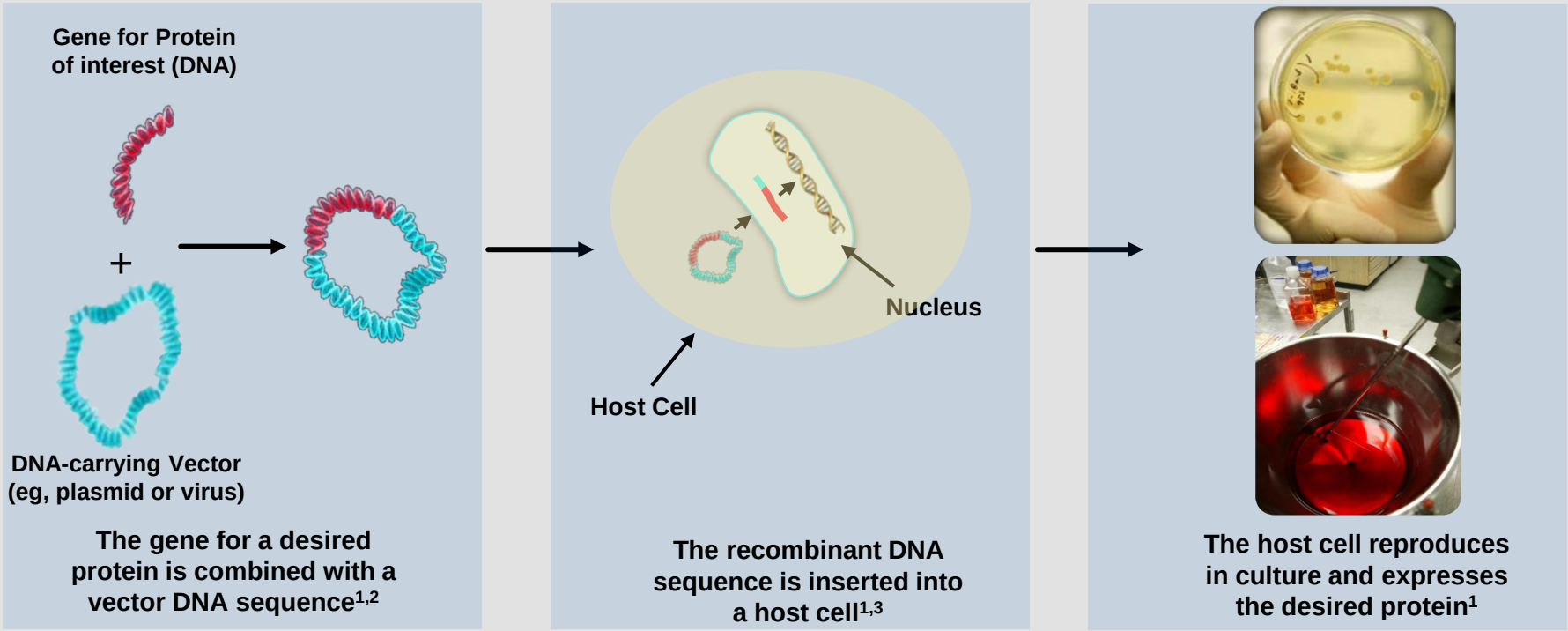
RECOMBINANT DNA TECHNOLOGY TO PRODUCE BIOLOGICS



1. Gottlieb S. *Am J Health Syst Pharm.* 2008;65(suppl 6):S2-S8. 2. Sharma BG. *EJHP Practice.* 2007;13:54-56. 3. Kresse GB, et al. *Eur J Pharm Biopharm*. 2009;72:479-486.

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A HOST CELL IS CHOSEN TO MASS PRODUCE THE PROTEIN

Cells that most effectively produce the protein are replicated[1,2]

A cell bank of master cells are isolated and stored[1,2]

Some cells are used to create a working cell bank and are used to make the protein of interest[1,2]

Each biologic starts with a cell bank designed to produce that specific protein

1.Kresse GB, et al. *Eur J Pharm Biopharm*. 2009;72:479-486. 2. Amgen Inc. An Introduction to Biotechnology. Available at: http://wwwext.amgen.com/pdfs/misc/An_Introduction_Biotechnology.pdf. Accessed January, 2013. 3. Chuck AS, et al. In: Elliot SG, et al, eds. *Erythropoietins, erythropoietic factors, and erythropoiesis: molecular, cellular, preclinical, and clinical biology*. 2nd ed. Basel, Switzerland: Birkhäuser Basel; 2009:87-104

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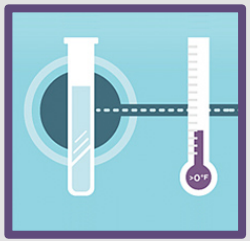
COMMERCIAL SCALE BIOLOGICS ARE MADE IN LIVING CELLS USING COMPLEX AND WELL CONTROLLED PROCESSES

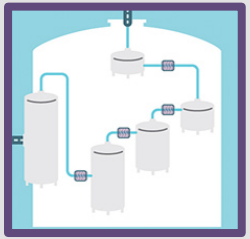
1



Cell Culture[1]

Cells from the working cell bank are thawed

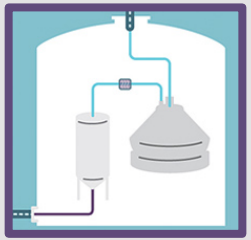
2



Scale-Up[1]

Cells are cultured in large vessels. Bioreactors can hold up to 10,000-20,000L

3



Recovery and Purification[1]

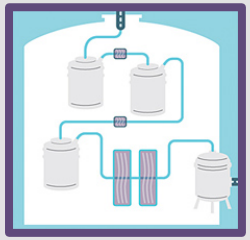
Protein product is extracted and purified

4

Quality Assurance[1,2]

Tests and controls are performed to demonstrate identity, strength, quality, potency, and purity

5



Fill and Finish[1]

The product is purified and the final product is packaged

6

Refrigerate, Store, Transport[3]

Tightly controlled environmental conditions are required for transportation and storage

1.Amgen Inc. An Introduction to Biotechnology. 2009. Available at: http://wwwext.amgen.com/pdfs/misc/An_Introduction_Biotechnology.pdf. Accessed January, 2013 2. Food and Drug Administration. Guidance for industry: potency tests for cellular and gene therapy products. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM243392.pdf. Accessed June 1, 2013. 3. Sharma BG. *EJHP Pract.* 2007;13:54-56.

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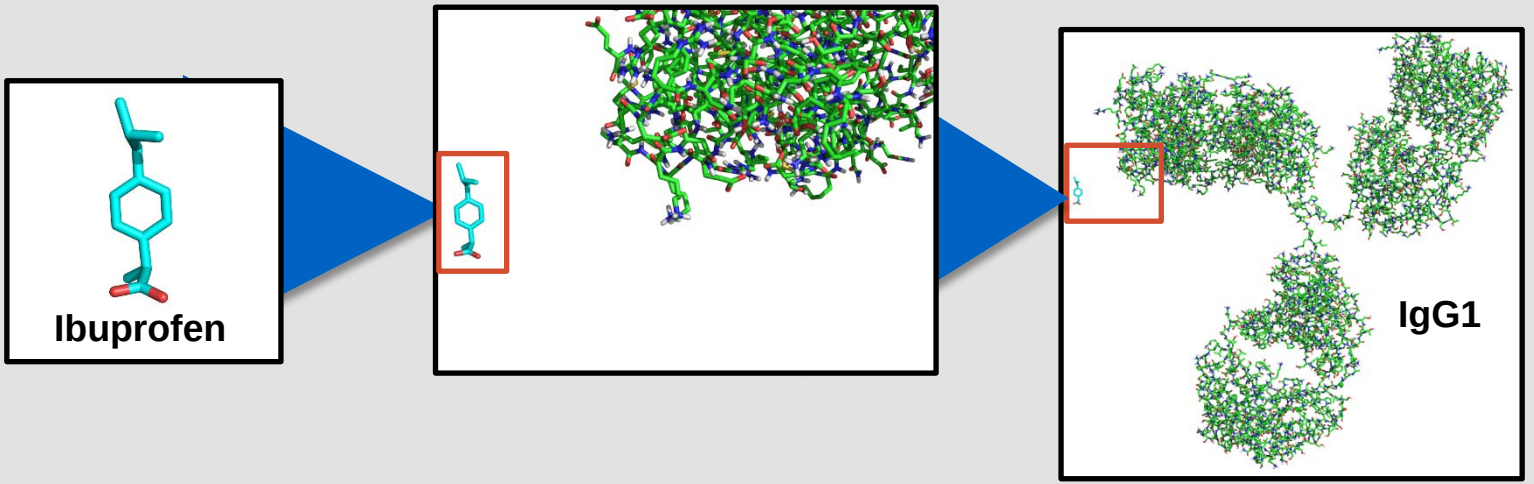
SMALL MOLECULES AND BIOLOGICS DIFFER SUBSTANTIALLY

Small molecules (chemically based drugs)[1]

Biologics (protein-based drugs)[1]



Example	Ibuprofen[2] 29 atoms	Biologic (monoclonal antibody)[3] ~ 25,000 atoms

1. Kozlowski S, et al. *N Engl J Med.* 2011;365:385-388; 2. Motrin® comprehensive prescribing information, http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/017463s105lbl.pdf. Accessed September 9, 2016; 3. Davies DR, et al. *Ann Rev Biochem*. 1975;44:639-667.

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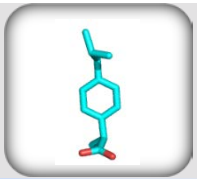
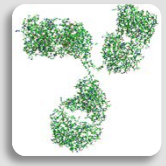
DIFFERENCES BETWEEN SMALL MOLECULES AND BIOLOGICS





Properties		
Example	Ibuprofen[1] 29 atoms	Biologic - monoclonal antibody ~25,000 atoms[6]
Size	Small[2]	Large[2] – ~600x larger
Structure	Simple[3] and well defined[2,4]	Complex with many options for post-translational modification[7]
Manufacturing	Predictable chemical process; Identical copy can be made[2]	Each manufactured in a unique living cell line[2] Similar but not identical copy can be made[2]
Characterizations	Easy to fully characterize[5]	Difficult to characterize fully due to a mixture of related molecules[2]
Stability	Relatively stable[2]	Sensitive to storage and handling conditions[2]
Immunogenicity	Lower potential[2]	Higher potential[2]

Images are for illustrative purposes and are not to scale.

1. Motrin® comprehensive prescribing information, http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/017463s105lbl.pdf. Accessed September 9, 2016;
2. Genazzani AA, et al. *Biodrugs*. 2007;21:351-356; 3. Prugnaud JL. *Br J Clin Pharmacol*. 2007;65:619-620; 4. Crommelin DJ, Storm G, Verrijk R, et al. *Int J Pharm*. 2003;266:3-16; 5. Gottlieb S. *Am J Health Syst Pharm*. 2008;65(suppl 6):S2-S8; 6. Davies DR, et al. *Ann Rev Biochem*. 1975;44:639-667;
7. Roger SD. *Nephrology*. 2006;11:341-346.

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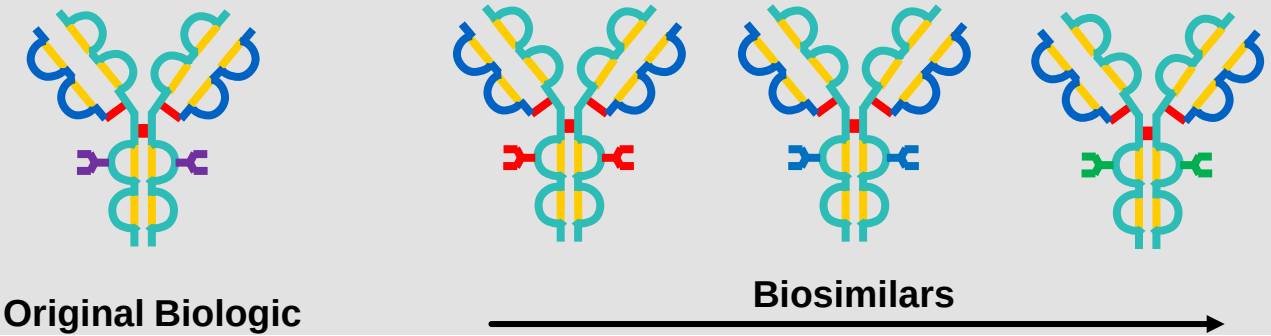
WHAT ARE BIOSIMILARS?

- Biosimilars highly similar, but not identical to, existing biological products.[1]
- The Public Health Service Act defines biosimilar or biosimilarity as:
  - "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,"[2] and
  - "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."[2]



1. Mellstedt H, et al. *Ann Oncol.* 2008;19:411-419
2. Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act.

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FDA PERSPECTIVE: A "TOTALITY OF THE EVIDENCE" APPROACH WILL BE APPLIED TO ASSESS BIOSIMILARITY

Generics

- Establish same active ingredient
- Demonstration of bioequivalence

Biosimilars

- Extensive structural and functional characterization
- Consider need for animal data to assess toxicity
- Clinical studies to compare PK/PD, safety/efficacy, and immunogenicity

→

- Sufficient to demonstrate that the product is "highly similar" to the reference product and safe, pure, and potent for one or more approved conditions of use
- FDA has discretion to determine that certain studies not required

Food and Drug Administration. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed September 13, 2016.

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INTERCHANGEABILITY DESIGNATION REQUIRES EVIDENCE BEYOND THAT NEEDED TO DEMONSTRATE BIOSIMILARITY

Biosimilarity

- **Highly similar** notwithstanding minor differences in clinically inactive components
- No clinically meaningful differences in **safety, purity, and potency**

Interchangeability

Approved as a biosimilar **AND**:

- Expectation of **same clinical result** in any given patient and…
- For a product that is administered more than once, **no additional risk to safety or efficacy** as a result of alternating or switching

Patient Protection and Affordable Care Act. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_bills&docid=f:h3590pp.txt.pdf
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241720.htm. **Last accessed September 13, 2016.**

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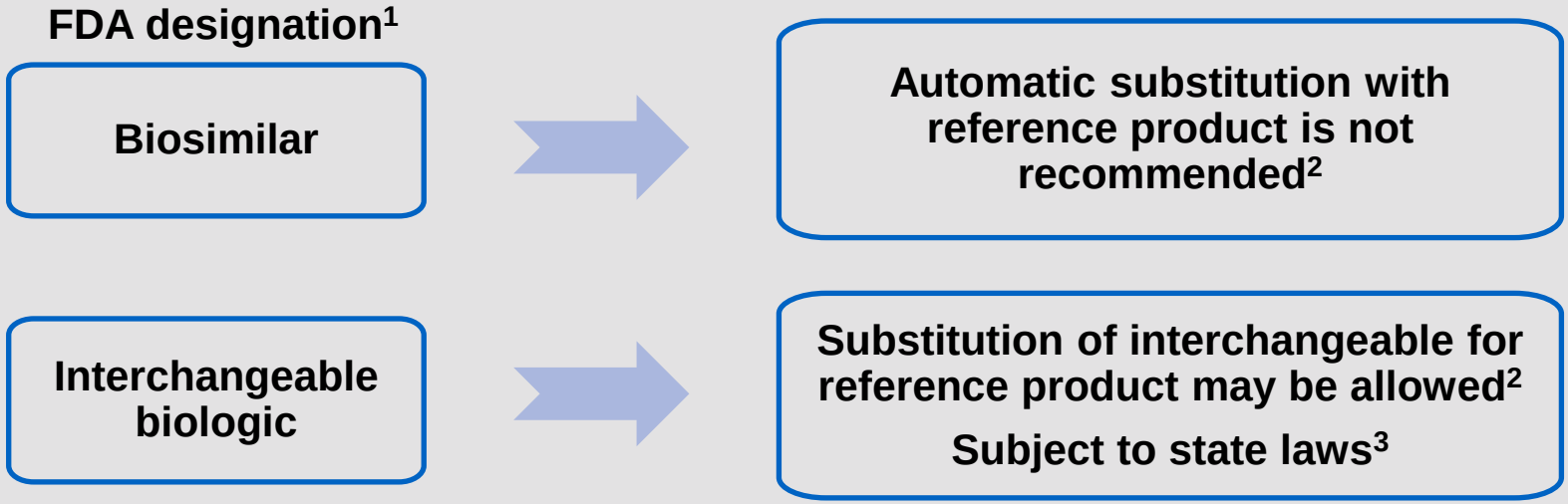
FDA DETERMINES INTERCHANGEABILITY, WHILE AUTOMATIC SUBSTITUTION IS GOVERNED BY STATES



- FDA policy on approval standards for biosimilars does not address automatic substitution
- There is ongoing legislative activity in multiple states with regard to automatic substitution of interchangeable biologics for the reference product[3]

1. Patient Protection and Affordable Care Act. 2009. http://www.gpo.gov/fdsys/pkg/BILLS-111hr3590pp/pdf/BILLS-111hr3590pp.pdf. Accessed April 30, 2015. 2. FDA. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm. Accessed February 18, 2015. 3. NCSL. *State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars.* 2014. http://www.ncsl.org/documents/health/Biologics_BiosimilarsNCSLReport_July_2014.pdf. Accessed April 4, 2015.

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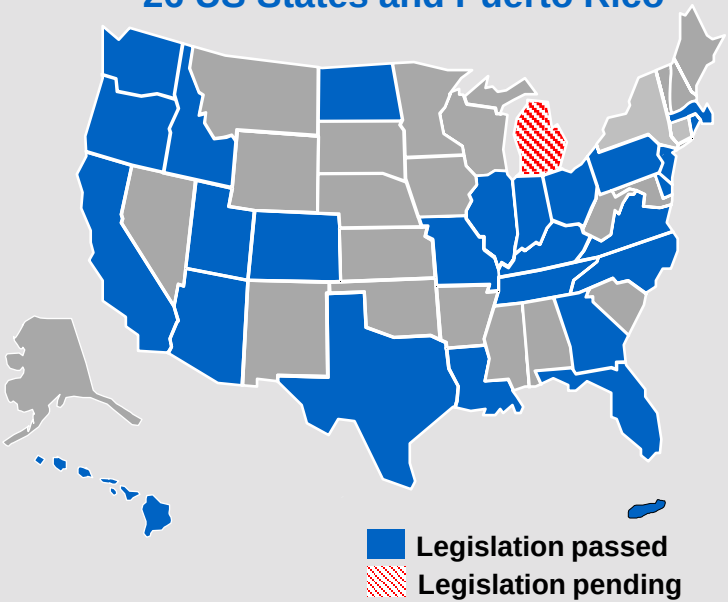
26 STATES HAVE ENACTED PHARMACY PRACTICE ACTS RELATED TO BIOLOGICS AND BIOSIMILAR SUBSTITUTION

26 US States and Puerto Rico



- Indiana
- Delaware
- Massachusetts
- North Dakota
- Florida
- Virginia
- Oregon
- California
- Colorado
- Illinois
- Idaho
- Louisiana
- New Jersey
- North Carolina
- Tennessee
- Texas
- Utah
- Kentucky
- Arizona
- Missouri
- Rhode Island
- Hawaii
- Pennsylvania
- Washington
- Georgia
- Puerto Rico
- Ohio

1. http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx. Last accessed September 13, 2016.

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PROTECTING PATIENTS WITH SCIENCE-BASED POLICY

Principle	Prevailing Generic Requirements	Suggested Biosimilar Requirements
Substitution based on an FDA determination	Yes-therapeutic equivalence	Yes-interchangeable
The prescribing physician should be able to specify ‘dispense as written’	Yes	Yes
The patient should be informed of the substitution	Yes	Yes
Pharmacy records should be maintained	Yes	Yes
Only after dispensing, the patient’s medical record should be updated with HCP (e.g., through direct entry into a shared electronic record, communication via fax)	No	Yes

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SUMMARY

- Biologics are developed in living cells[1,2], using complex processes involving many highly regulated and unique steps[3-6]
- Biosimilars are highly similar, but not identical to the innovator biologic[2]
- The US pathway for approval of biosimilars was signed into law as part of the Patient Protection and Affordable Care Act[7]
  - A totality of evidence will be considered when evaluating a biosimilar product for approval[8]
  - Determination of interchangeability requires a higher standard of evidence[7,9]
- Patient care is advanced when physicians and pharmacists communicate after the dispensing of a biologic.

1. Biotechnology Industry Organization. Guilford-Blake R, Strickland D, eds. Guide to Biotechnology. 2008. www.bio.org/sites/default/files/ BiotechGuide2008.pdf. Accessed January 24, 2013; 2. Mellstedt H, et al. *Ann Oncol.* 2008;19:411-419; 3. Amgen Inc. An Introduction to Biotechnology. 2009. www.amgen.com/pdfs/misc/An_Introduction_Biotechnology.pdf. Accessed January 24, 2013; 4. Kresse GB, et al. *Eur J Pharm Biopharm.* 2009;72:479-486; 5. Sharma BG. *EJHP Practice.* 2007;13:54-56; 6. Roger SD. *Nephrology.* 2006;11:341-346; 7. Patient Protection and Affordable Care Act. frwebgate.access.gpo.gov/cgibin/getdoc.cgi?dbname=111_cong_bills&docid=f:h3590pp.txt. pdf. Accessed January 24, 2013; 8. Food and Drug Administration. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm259797.htm. Accessed January 24, 2013; 9. Kozlowski S, et al. *N Engl J Med.* 2011:365:385-388;

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