



Biosimilars in the US Health Care Landscape

Agenda

- Introduction to Biologics and Biosimilars
- Considering the European Biosimilar Experience
- Summary of FDA Guidance on Establishing Biosimilarity
- Overview of Extrapolation and Interchangeability
- How Biosimilars May Reshape the US Health Care Landscape



Introduction to Biologics and Biosimilars

Biologics and Biosimilars Defined^{1,2}

Biologic

Wide range of products (eg, vaccines, blood and blood components, somatic cells, gene therapy, tissues, therapeutic proteins) derived from genetically engineered living cells or organisms and intended to prevent, treat, or cure a variety of medical conditions¹

Reference biologic

Originally licensed biologic product used for comparison²

Biosimilar

Biologic that is **highly similar** to the reference product with **no clinically meaningful differences** in terms of the **safety profile, purity, and potency**²

1. US Food and Drug Administration. *What Are "Biologics" Questions and Answers*. Rockville, MD: FDA; 2015. <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm>. Accessed December 24, 2015. 2. US Food and Drug Administration. *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*. Rockville, MD: FDA; 2015.

Biologics Have Had a Meaningful Impact on Patient Care^{1,2}

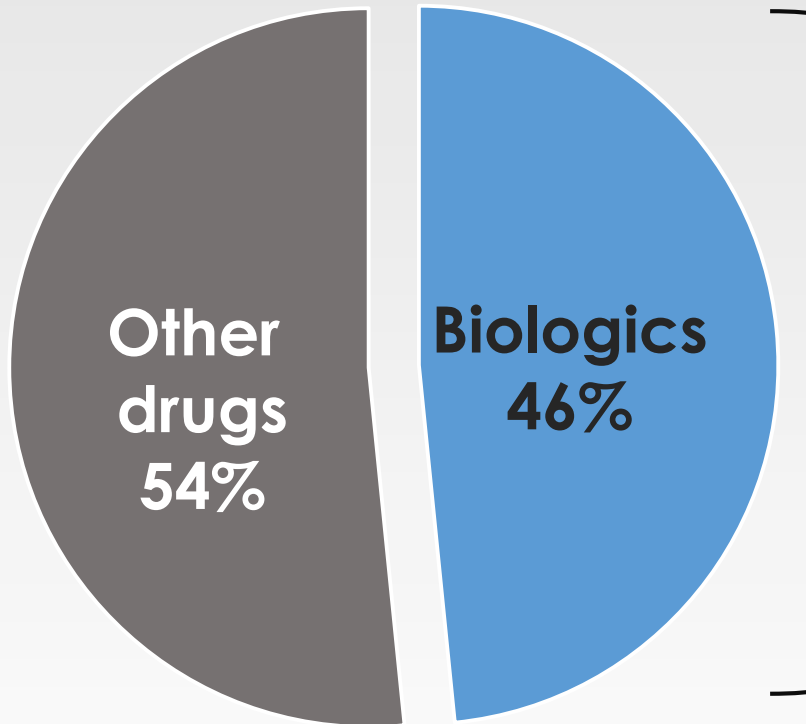
Successfully used to treat many different life-threatening and chronic diseases¹⁻⁵



1. Kozlowski S, et al. *N Engl J Med*. 2011;365(5):385-388. 2. Ryan AM. *Vet Pathol*. 2015;52(2):419-426. 3. Walsh G. *Nat Biotechnol*. 2010;28(9):917-924. 4. Oh DB. *BMB Rep*. 2015;48(8):438-444. 5. Pelaia G, et al. *Ther Clin Risk Manag*. 2016;12:1075-1082.

Biologics in the United States Contribute Significantly to Prescription Drug Spending¹

- Biologics accounted for nearly half of approximately \$85 billion spent on the top 15 drugs in 2015^{1*}



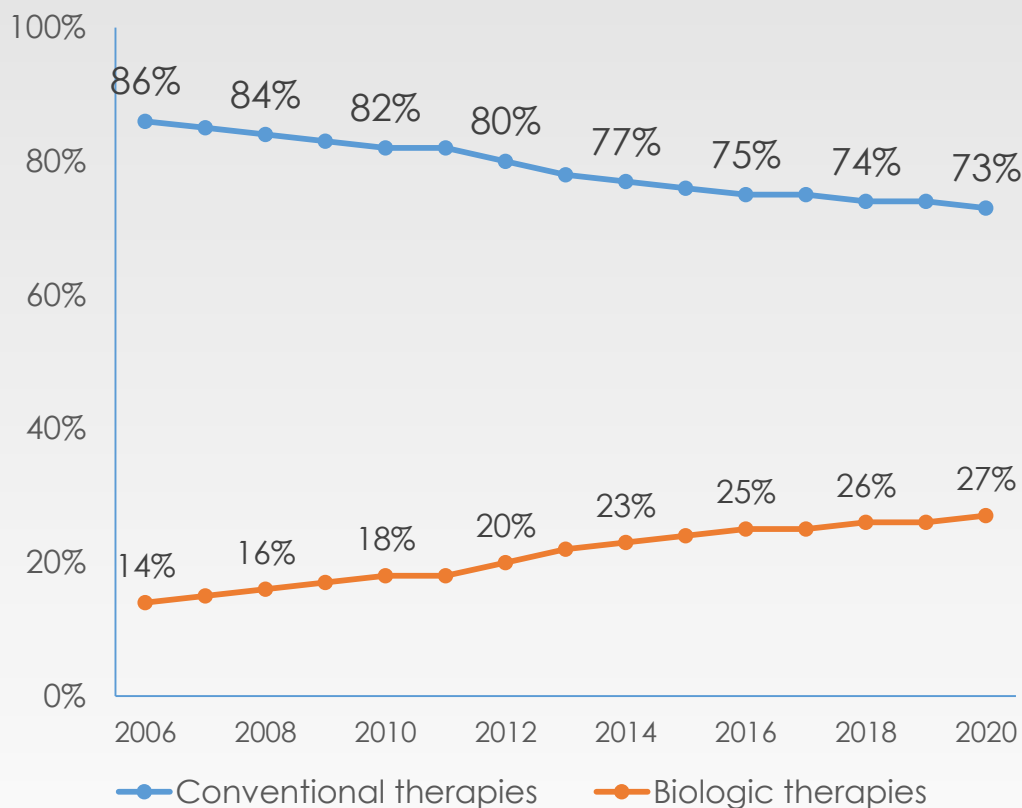
- **7 of the 15** highest expenditure drugs were biologics, **accounting for \$39.5 billion** in spending in 2015¹
- **Nearly \$220 billion** in sales for 8 key biologics could potentially be impacted by biosimilars between 2016 and 2020²

*By non-discounted spending.

1. IMS Institute for Healthcare Informatics. *Medications Use and Spending in the US: A Review of 2015 and Outlook to 2020*. April 2016. Parsippany, NJ: IMS Health Incorporated; 2016. 2. IMS Institute for Healthcare Informatics. *Delivering on the Potential of Biosimilar Medicines: The Role of Functioning Competitive Markets*. April 2016. Parsippany, NJ: IMS Health Incorporated; 2016.

Global Sales of Biologics Continue to Grow¹

**Proportion of Worldwide Pharmaceutical Sales:
Data and Projections Through 2020^{1,a}**



- Biologic sales have grown as a proportion of total pharmaceutical sales¹
- Globally, there is a strong demand for patient access to innovative biologic therapies²

^aIncludes over-the-counter sales.

1. EvaluatePharma. *World Preview 2015, Outlook to 2020*. <http://info.evaluategroup.com/rs/607-YGS-364/images/wp15.pdf>. Accessed October 13, 2016. 2. IMS Institute for Healthcare Informatics. *Global Outlook for Medicines Through 2018*. November 2014. Parsippany, NJ: IMS Health Incorporated; 2014.

Standard and Abbreviated Pathways for Drug Approval in the United States¹⁻⁶

Small molecules

Approved via Food, Drug, and Cosmetic Act (FDCA)

Generics

New drug application (NDA)

Abbreviated new drug application (ANDA), "Hatch-Waxman"

Benefit/risk profile and efficacy must be demonstrated

Bioequivalence must be demonstrated

Biologics

Approved via Public Health Service Act (PHSA)

Biosimilars

Biologics license application (BLA)

Biosimilar biologics license application (BPCI Act)

Benefit/risk profile and efficacy must be demonstrated

Must demonstrate high similarity to reference

No clinically meaningful differences

Higher standards to obtain "Interchangeable" designation

BPCI, Biologics Price Competition and Innovation.

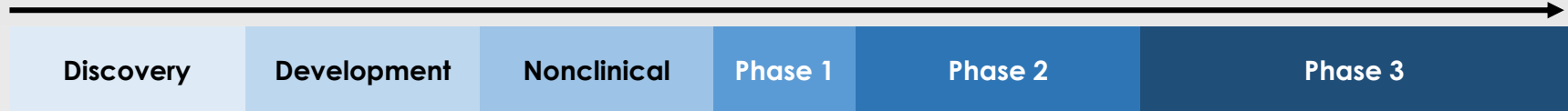
1. US Food and Drug Administration. New Drug Application (NDA). Last updated February 3, 2015. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/>. Accessed December 30, 2015. 2. US Congress. Drug Price Competition and Patent Term Restoration Act of 1984, Title I, 98 Stat 1585 Public Law 98-417. 3. US Food and Drug Administration. *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*. Rockville, MD: FDA; 2015. 4. Patient Protection and Affordable Care Act, March 2010. 5. US Congress. United States Public Health Service Act, Sec. 262 Regulation of Biological Products. 42USC262. <http://www.gpo.gov/fdsys/pkg/USCODE-2010-title42/pdf/USCODE-2010-title42-chap6A-subchapII-partF-subpart1-sec262.pdf>. Accessed December 30, 2015. 6. US Food and Drug Administration. *Guidance for Industry: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*. Rockville, MD: FDA; 2015.

Developing a Biosimilar Requires Investment Compared With a Small Molecule Generic¹⁻⁴

- Despite being rigorous, the development timeline for biosimilars may be shorter than for a new medicine

New medicine¹
(including cost of failures)

Development time: >10 years
Cost: ~\$2.6 billion



Biosimilar²
(cost of failures not available)

Development time: ~5 to 9 years
Cost: Up to \$135 million^a



Comparative evaluations

Small molecule generic^{3,4}

Development time: ~2 years
Cost: ~\$1 to \$4 million



PD, pharmacodynamic; PK, pharmacokinetic.

^aNot including regulatory fees.

1. Pharmaceutical Research and Manufacturers of America. *Drug Discovery and Development: Understanding the R&D Process*. Washington, DC: PhRMA; 2007. 2. Generics and Biosimilars Initiative. GaBI Online. Development of biosimilars. Posted July 1, 2011. <http://www.gabionline.net/Biosimilars/Research/Development-of-biosimilars>. Accessed January 3, 2016. 3. Grabowski H, et al. *Health Aff (Millwood)*. 2006;25(5):1291-1301. 4. IMS Health. Shaping the biosimilars opportunity: a global perspective on the evolving biosimilars landscape. London, UK: IMS Health Incorporated; December 2011.

Biosimilar Development Is More Complex Than Establishing Comparability¹⁻³

- Demonstrating biosimilarity to a reference product requires more data and information than establishing comparability between a post- and premanufacturing change¹
- Although biosimilars are developed against a reference product, they have their own specifications, dependent on²
 - Manufacturing process
 - Industry standards
 - Regulatory expectations
 - Data from comparisons with the reference product
- Rigorous control strategies are necessary to maintain consistency and help ensure biosimilars conform to specifications³

1. US Food and Drug Administration. *Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*. Silver Spring, MD: FDA; 2015. 2. Schiestl M, et al. *Nat Biotechnol*. 2011;29:310-312. 3. US Food and Drug Administration. *Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*. Rockville, MD: FDA; 1997.

Key Points

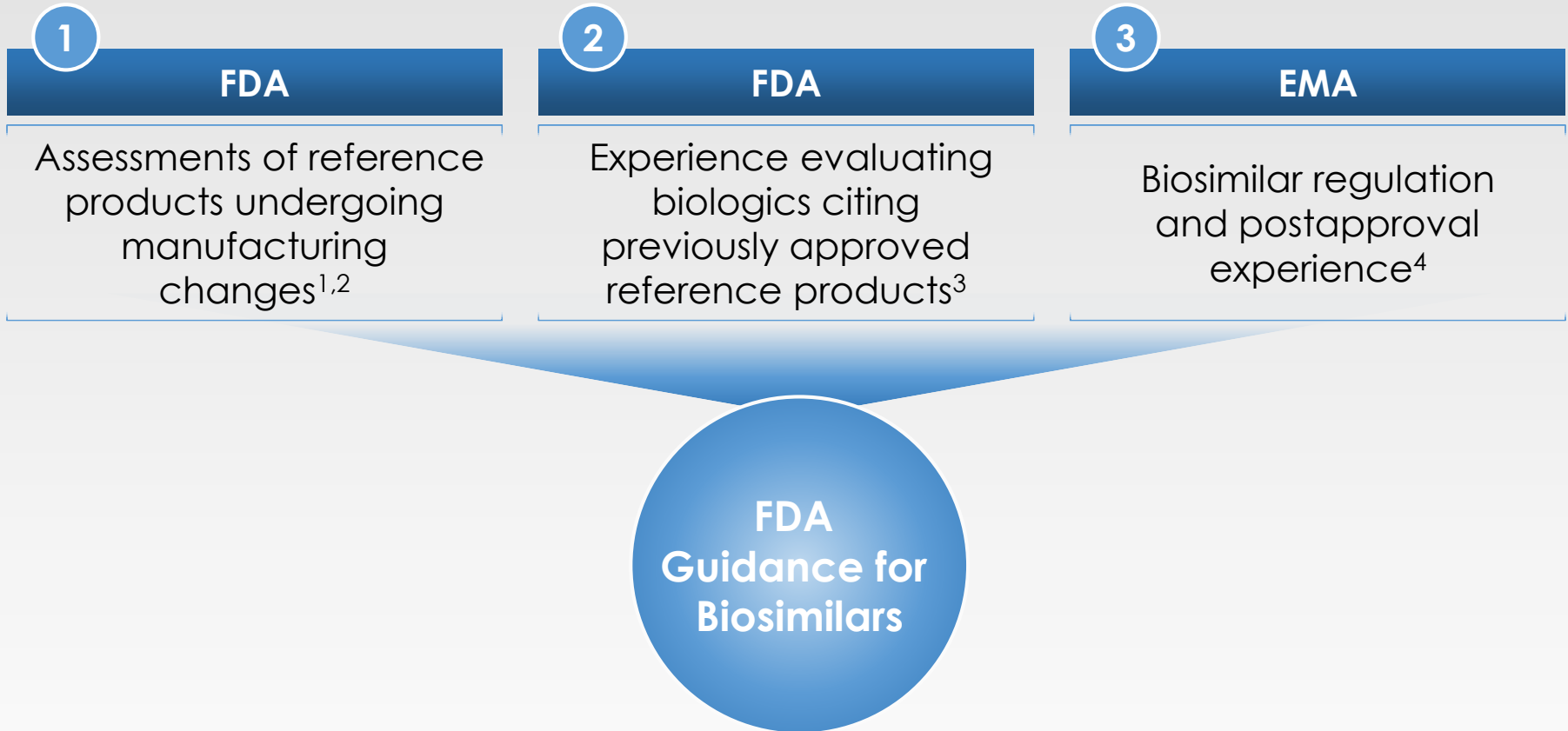
- Global sales of innovative biologics continue to grow and have outpaced total pharmaceutical sales
- A biosimilar is a biologic that is highly similar to a reference product, with no clinically meaningful differences in terms of the safety, purity, and potency
- BPCI Act established an abbreviated pathway for biosimilar approval focusing on similarity to a reference product



Considering the European Biosimilar Experience

FDA Biosimilar Guidelines Developed From Preexisting Guidance, Knowledge, and Experience¹⁻⁴

Some examples of preexisting sources of information



EMA, European Medicines Agency.

1. US Food and Drug Administration. *Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products*. FDA; July 1997. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm124805.pdf>. Accessed January 4, 2016. **2.** US Food and Drug Administration. *Guidance for Industry. ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*. Rockville, MD: FDA; 2005. **3.** Woodcock J, et al. *Nat Rev Drug Discov*. 2007;6:437-442. **4.** Kozlowski S, et al. *N Engl J Med*. 2011;365:385-388.

EMA Guidelines Provide Detailed Requirements for the Approval of Biosimilars^{1,2}

- FDA considered the EMA guidelines as a key source of information in developing US guidelines¹

Defining principles²

Guideline on Similar Biological Medicinal Products^a
(Adopted October 2014)

General comparability guidelines²

Immunogenicity Assessment
(Revision March 2014)

Quality Issues
(Adopted June 2014)

Nonclinical and Clinical Issues
(Adopted December 2014)

Product-specific comparability guidelines²

FSH	IFN-β	IFN-α	mAbs	Insulin	EPO	LMWH	GH	GCSF
Non clinical	Non clinical	Non clinical	Non clinical	Non clinical	Non clinical	Non clinical	Non clinical	Non clinical
Clinical	Clinical	Clinical	Clinical	Clinical	Clinical	Clinical	Clinical	Clinical

EPO, erythropoietin; FSH, follicle-stimulating hormone; GCSF, granulocyte colony-stimulating factor; GH, growth hormone (somatropin); IFN, interferon; LMWH, low-molecular-weight heparin; mAbs, monoclonal antibodies.

^aOriginal guidelines adopted in 2005.

1. Kozlowski S, et al. *N Engl J Med*. 2011;365:385-388. 2. European Medicines Agency. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_00408.jsp&mid=WC0b01ac058002958c. Accessed January 1, 2016.

Cost Savings From Biosimilars to Health Care Systems May Be Significant (Although Estimates Vary)^{1,2}

Source	Examples of Estimated Biosimilar Savings
Express Scripts¹	\$250 billion savings possible during 2014-2024, if 11 likeliest biosimilars enter the market
IMS²	\$54 billion to \$108 billion in cumulative savings in the EU5 and United States combined over the next 5 years

EU5, France, Germany, Italy, Spain, and the United Kingdom. IMS, Intercontinental Marketing Services.

1. Miller S. The \$250 billion potential of biosimilars. St. Louis, MO: Express Scripts; April 23, 2013. [http://lab.express-scripts.com/insights/industry-updates/the-\\$250-billion-potential-of-biosimilars](http://lab.express-scripts.com/insights/industry-updates/the-$250-billion-potential-of-biosimilars). Accessed December 30, 2015. 2. IMS Institute for Healthcare Informatics. Delivering on the Potential of Biosimilar Medicines: The Role of Functioning Competitive Markets. Parsippany, NJ: IMS Institute for Healthcare Informatics; March 2016. https://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Documents/IMS_Institute_Biosimilar_Brief_March_2016.pdf. Accessed April 11, 2016.

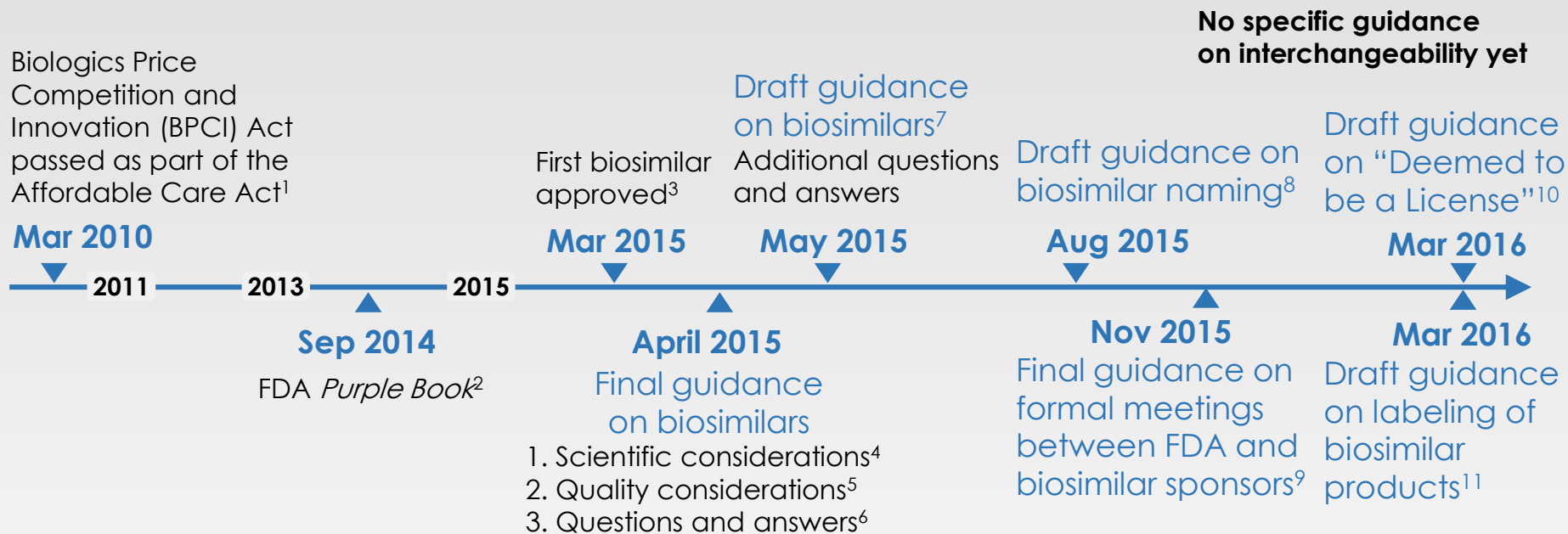
Key Points

- Biosimilars undergo a rigorous but abbreviated development process
 - This abbreviated development process, based on European experience, allows for potentially lower costs compared with reference biologics
- The FDA has adopted biosimilar guidance based on previous US experience with biologics and EMA experience with biosimilars
- Cost savings from biosimilars may be significant, although estimates vary



Summary of FDA Guidance on Establishing Biosimilarity

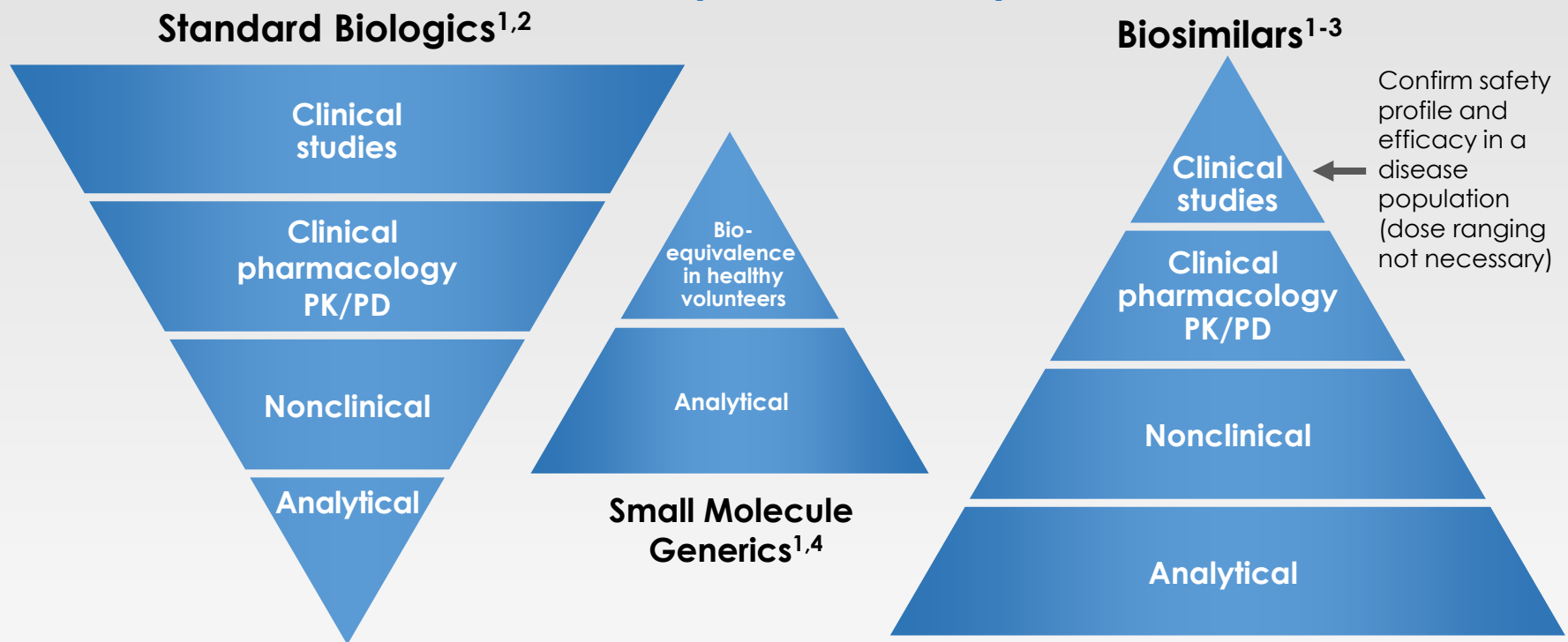
FDA Has Developed Guidance for the Regulatory Approval of Biosimilars¹⁻⁹



1. US House of Representatives. HR 3590 Patient Protection and Affordable Care Act (2010). January 5, 2010. 2. US Food and Drug Administration. *Purple Book*. Last updated March 5, 2015. <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm>. Accessed January 4, 2015. 3. US Food and Drug Administration. FDA approves first biosimilar product Zarxio [news release]. Washington, DC: FDA; 2015. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm>. Accessed March 11, 2015. 4. US Food and Drug Administration. *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*. Silver Spring, MD: FDA; 2015. 5. US Food and Drug Administration. *Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*. Silver Spring, MD: FDA; 2015. 6. US Food and Drug Administration. *Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*. Silver Spring, MD: FDA; 2015. 7. US Food and Drug Administration. *Draft Guidance for Industry: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*. Silver Spring, MD: FDA; 2015. 8. US Food and Drug Administration. *Guidance for Industry: Nonproprietary Naming of Biological Products*. Silver Spring, MD: FDA; 2015. 9. US Food and Drug Administration. *Guidance for Industry: Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*. Silver Spring, MD: FDA; 2015. 10. US Food and Drug Administration. *Guidance for Industry: Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009* [draft guidance]. Silver Spring, MD: FDA; 2016. 11. US Food and Drug Administration. *Guidance for Industry: Labeling for Biosimilar Products*. Silver Spring, MD: FDA; 2016.

The Goal of Biosimilar Development Is to Demonstrate That There Are No Clinically Meaningful Differences Based Upon the **Totality of Evidence**, Not to Reestablish Benefit¹⁻⁴

Development Pathways



- It is not scientifically beneficial to repeat the entire development program of the reference product^{5,6}
- A robust analytical characterization and preclinical foundation reduces the need for extensive animal and clinical testing⁷

1. Schneider CK, et al. *Nat Biotechnol.* 2012;30:1179-1185. 2. McCamish M. Presented at EMA Workshop on Biosimilars; London; October 2013. 3. Berghout A. *Biologicals.* 2011;39:293-296. 4. US Food and Drug Administration. Abbreviated New Drug Applications (ANDA): Generics. Last updated July 14, 2015. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/>. Accessed January 3, 2016. 5. Kozlowski S, et al. *N Engl J Med.* 2011;365:385-388. 6. Noaiseh G, Moreland L. *Biosimilars.* 2013;3:27-33. 7. US Food and Drug Administration. *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.* Silver Spring, MD: FDA; 2015.

Robust Analytical Testing Is Used to Establish High Similarity to the Reference Product

- Analytical testing is a major focus throughout biosimilar development

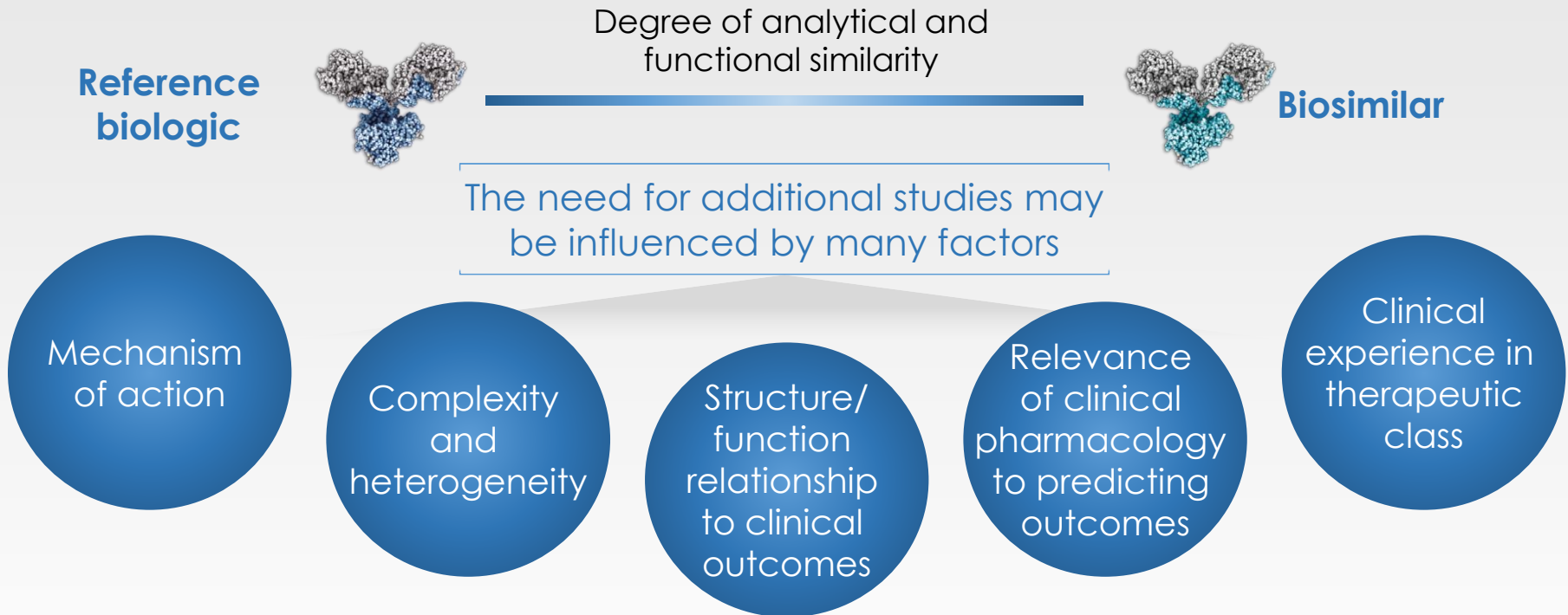


- New techniques and advancements in analytics are available
- More than 1 test method may be used to measure a single quality attribute

Analytical tests maximize the potential for detecting differences between the proposed biosimilar and the reference product

Any Comparative Clinical Evaluation Is Designed on a Case-by-Case Basis

- Comparative safety and effectiveness data are necessary if there are residual uncertainties about the biosimilarity of the 2 products



Key Points

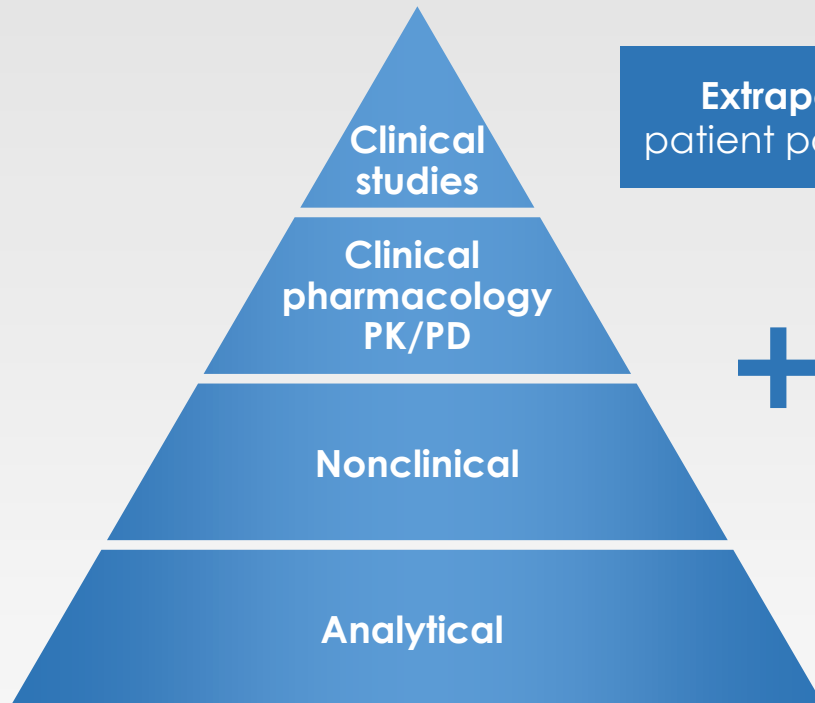
- The FDA will evaluate biosimilars based on a “totality of evidence” approach
- A major focus of biosimilar development is thorough analytical testing used to establish high similarity to the reference product
- Decisions about the approach to comparative clinical analyses are made on a case-by-case basis and are based on the determination of residual uncertainty



An Overview of Extrapolation and Interchangeability

Scientific Justification Is Required to Support Extrapolation to Indications Not Clinically Studied^{1,2}

Biosimilar Pathway



Extrapolation: Extending conclusions from studies in one patient population to make inferences in another population¹



Convincing scientific justification to support extrapolation to a reference biologic's approved indications²



Extrapolated indications

Image adapted from Sherman RE. Biosimilar biological products [biosimilar guidance webinar]. February 15, 2012. <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm292463.pdf>. Accessed January 4, 2016.

1. US Food and Drug Administration. *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*. Silver Spring, MD: FDA; 2015. 2. Weise M, et al. *Blood*. 2012;120(26):5111-5117.

Interchangeability of Biosimilars

- An “interchangeable” biologic product must demonstrate that it can be expected to produce the same clinical result as the reference product in any given patient

The designation of “interchangeability” requires higher standards than “biosimilarity” alone

- In addition, if the biologic product is administered more than once to an individual, the risk in terms of safety profile or diminished efficacy of alternating or switching between the use of the biologic product and the reference product is not greater than the risk of using the reference product without such alternation or switch

Key Points

- The FDA has stated that a biosimilar may be licensed for one or more additional conditions of use for which the reference product is licensed
 - This may occur if the biosimilar has not been directly studied in a comparative clinical trial for that condition
- Extrapolation refers to extending conclusions from studies in one patient population to make inferences in another population
 - Extrapolation will be determined based on “totality of evidence” and is a scientific rationale
 - In order for this determination to be made, there must be convincing evidence to support extrapolation to a reference biologic’s approved indications
- A biosimilar may also be designated as “interchangeable”
 - This means that it can be expected to produce the same clinical effect as the reference product in any given patient
 - It is important that the policy regarding interchangeability be established based on both science and physician supervision
 - To date, the FDA has not issued final guidance regarding interchangeability



How Biosimilars May Reshape the US Health Care Landscape

There Is a Strong Demand for Increased Savings and Efficiencies for Health Care Systems^{1,2}

- According to the Centers for Medicare & Medicaid Services, prescription drug spending growth is projected to average 6.3% annual growth from 2015 through 2024¹

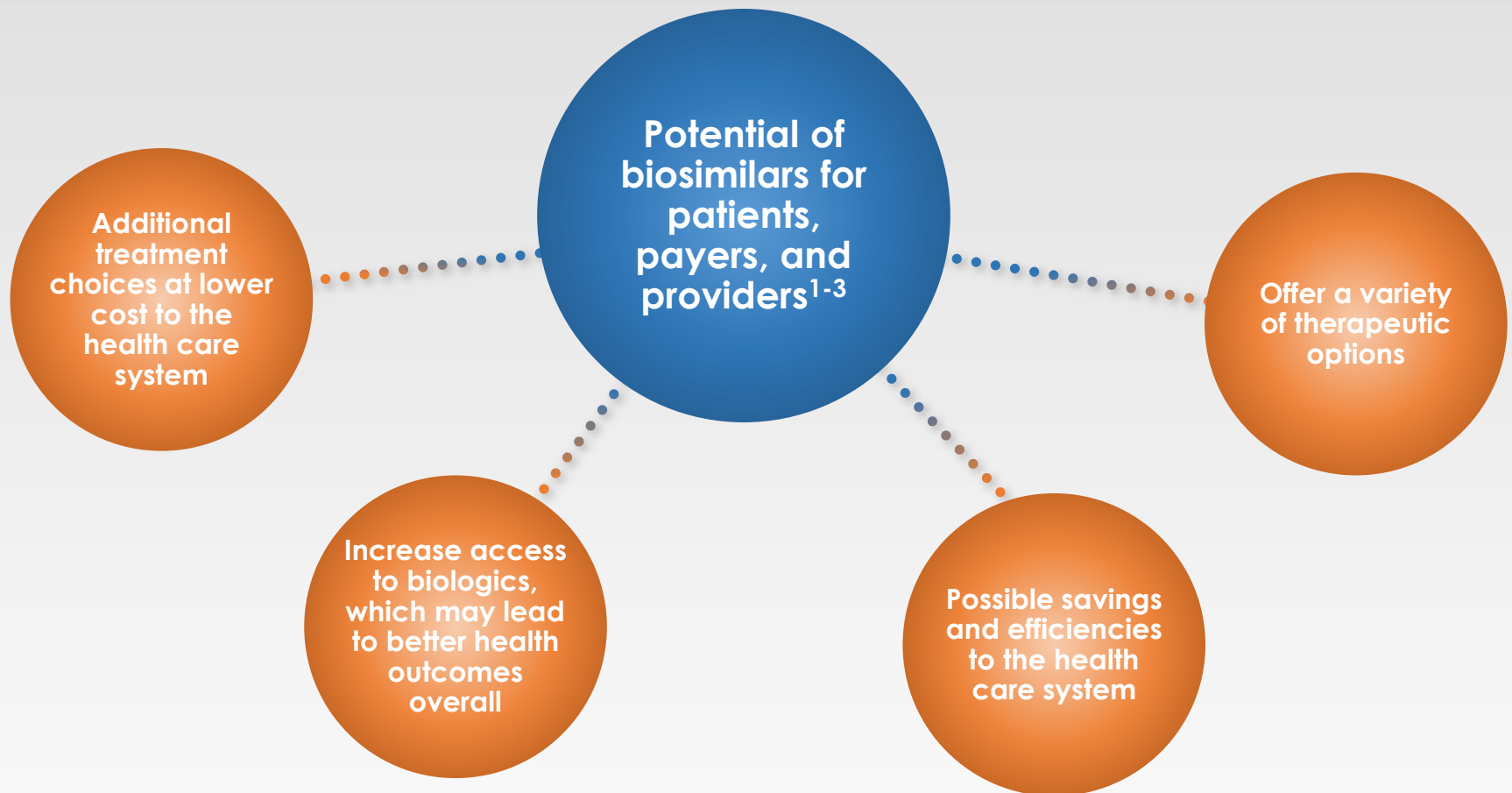
\$ 2014-2024 health care spending projected to grow¹ **1.1% faster than the GDP** → **5.8% on average**

27% of pharmaceutical products approved in 2015 were biologics²

GDP, gross domestic product.

1. Centers for Medicare & Medicaid Services. NHE Projections 2014-2024. <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NationalHealthAccountsProjected.html>. Accessed December 30, 2015. 2. US Food and Drug Administration. *New Molecular Entity and New Therapeutic Biological Product Approvals for 2015*. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm430302.htm>. Accessed December 30, 2015.

Biosimilars May Provide Multiple Benefits to the US Health Care System¹⁻³



1. Strober BE, et al. *J Am Acad Dermatol*. 2012;66(2):317-322. 2. Scheinberg MA, Kay J. *Nat Rev Rheumatol*. 2012;8(7):430-436.
3. Henry D, Taylor C. *Semin Oncol*. 2014;41(suppl 3):S13-S20.

The Future of Biosimilars in the United States Will Require Thoughtful Consideration in Clinical Practice

Will biosimilar approvals face any unique challenges in the United States?

How will the appropriate decision-making groups be educated about biosimilars?

What will the FDA guidance be on interchangeability?

Will extrapolation be sufficient to approve all indications of the reference product?

How will states regulate automatic substitution?

How will reimbursement be managed?

Program Summary

- There is increasing demand for biologics
- The introduction of high-quality biosimilars may
 - Increase access to biologics, which may lead to better health outcomes overall
 - Provide savings and efficiencies to health care systems
 - Provide additional treatment choices at lower cost to the health care system
 - Provide a variety of treatment choices
- The FDA has issued guidance for biosimilars
 - Totality of evidence will be evaluated for each biosimilar on a case-by-case basis
 - Focus is on similarity to a reference biologic
 - Intent is to minimize unnecessary duplication of large clinical studies
 - Scientific justification is required to support extrapolation to indications not clinically studied



For More Information

- To provide clinicians with an in-depth look into the science of biosimilars, Pfizer Biosimilars has established a peer-to-peer professional speakers' bureau
- Topics covered in the program include more information on
 - Establishing and regulating biosimilarity
 - Extrapolation
 - Interchangeability and automatic substitution
- Ask about this opportunity today
- **For more information on biosimilars, you may also visit PfizerBiosimilars.com**





Thank you!

For more information on biosimilars, visit PfizerBiosimilars.com