Biosimilars in the US Health Care Landscape

April 2016
PP-BIO-USA-0093

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 conditions[1]

Reference Biologic

Originally licensed biologic product used for comparison[2]

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]

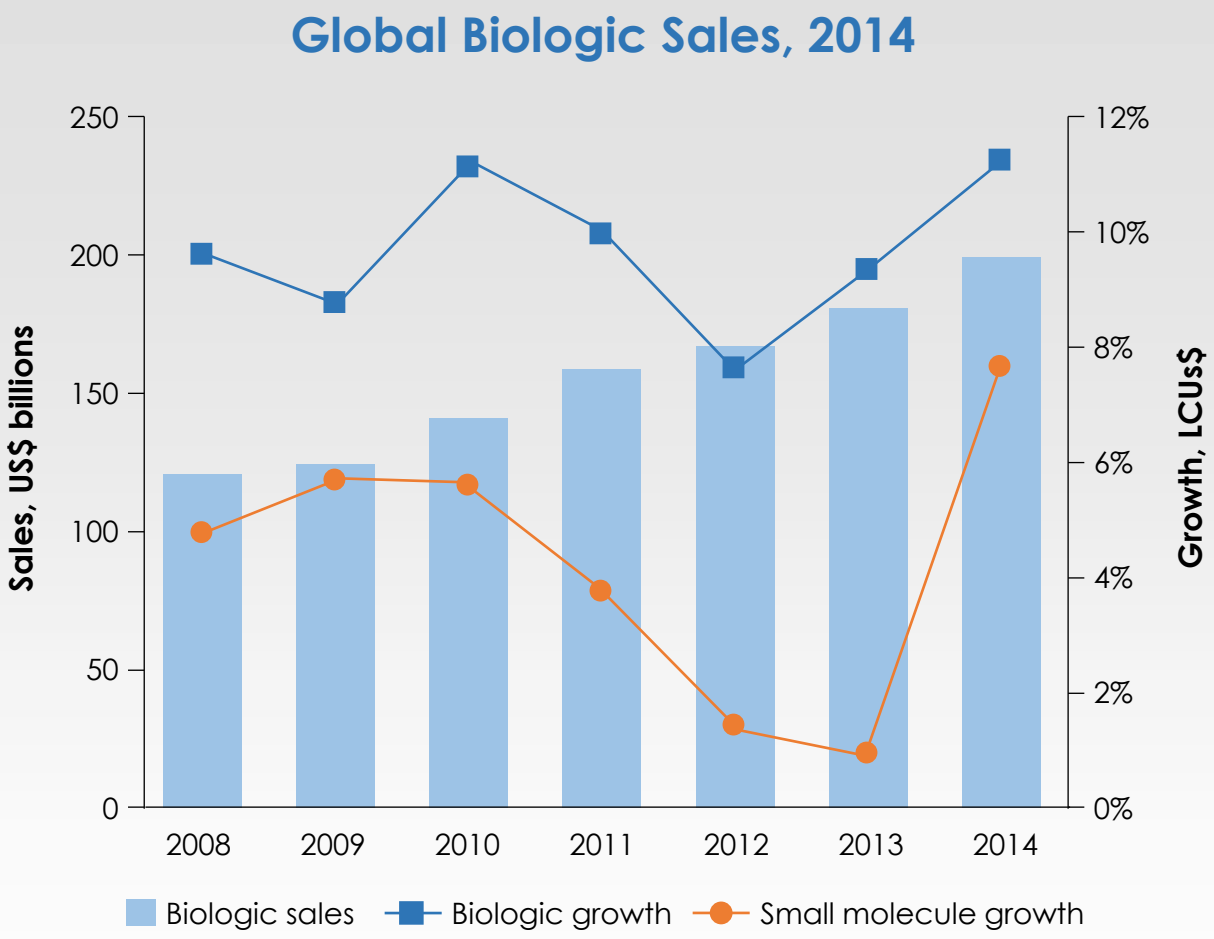
1. US Food and Drug Administration. *What Are "Biologics" Questions and Answers*. Rockville, MD: FDA; 2015. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/ CBER/ucm133077.htm. Accessed December 24, 2015. **2.** US Food and Drug Administration. *Guidance for Industry: Scientific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

Biologics Have Had a Meaningful Impact on Patient Care[1-3]

Successfully used to treat many different life-threatening and chronic diseases

1. Walsh G. *Nat Biotechnol*. 2010;28(9):917-924. **2.** Stockwin LH, Holmes S. *Expert Opin Biol Ther*. 2003;3(7):1133-1152.
3. Chan IS, Ginsburg GS. *Annu Rev Genomics Hum Genet*. 2011;12:217-244.

Global Sales of Innovative Biologics Continue to Grow[1,2]

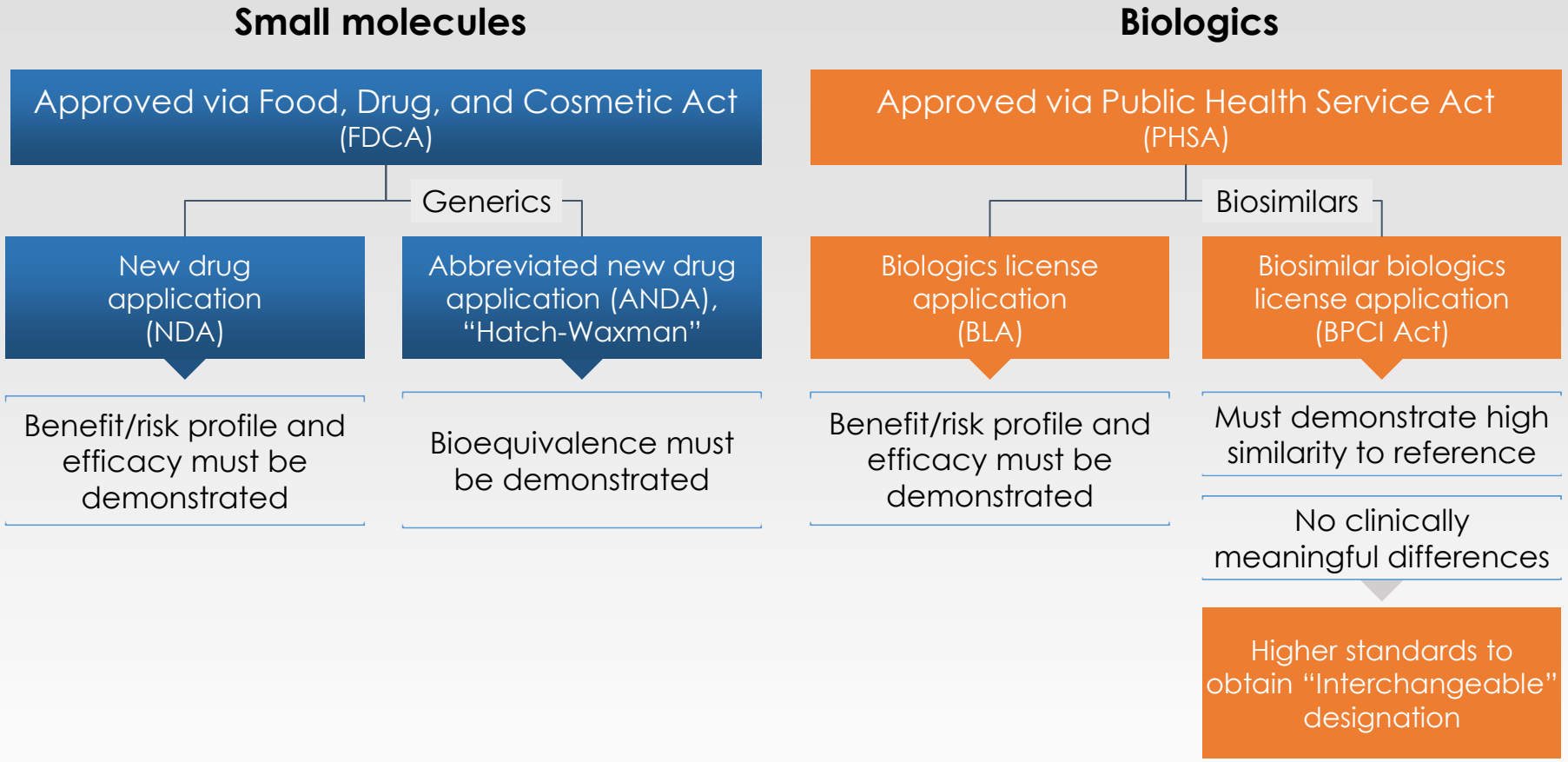


- Biologic sales have increased in recent years[1,2]
- Globally, there is a strong demand for patient access to innovative biologic therapies[2]

LCU, local currency unit.

1. Long D. IMS Health. Perspectives on the evolving biosimilars landscape. Presented at: HDMA Distribution Management Conference and Expo; Orlando, FL; March 8-11, 2015. **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 States[1-6]

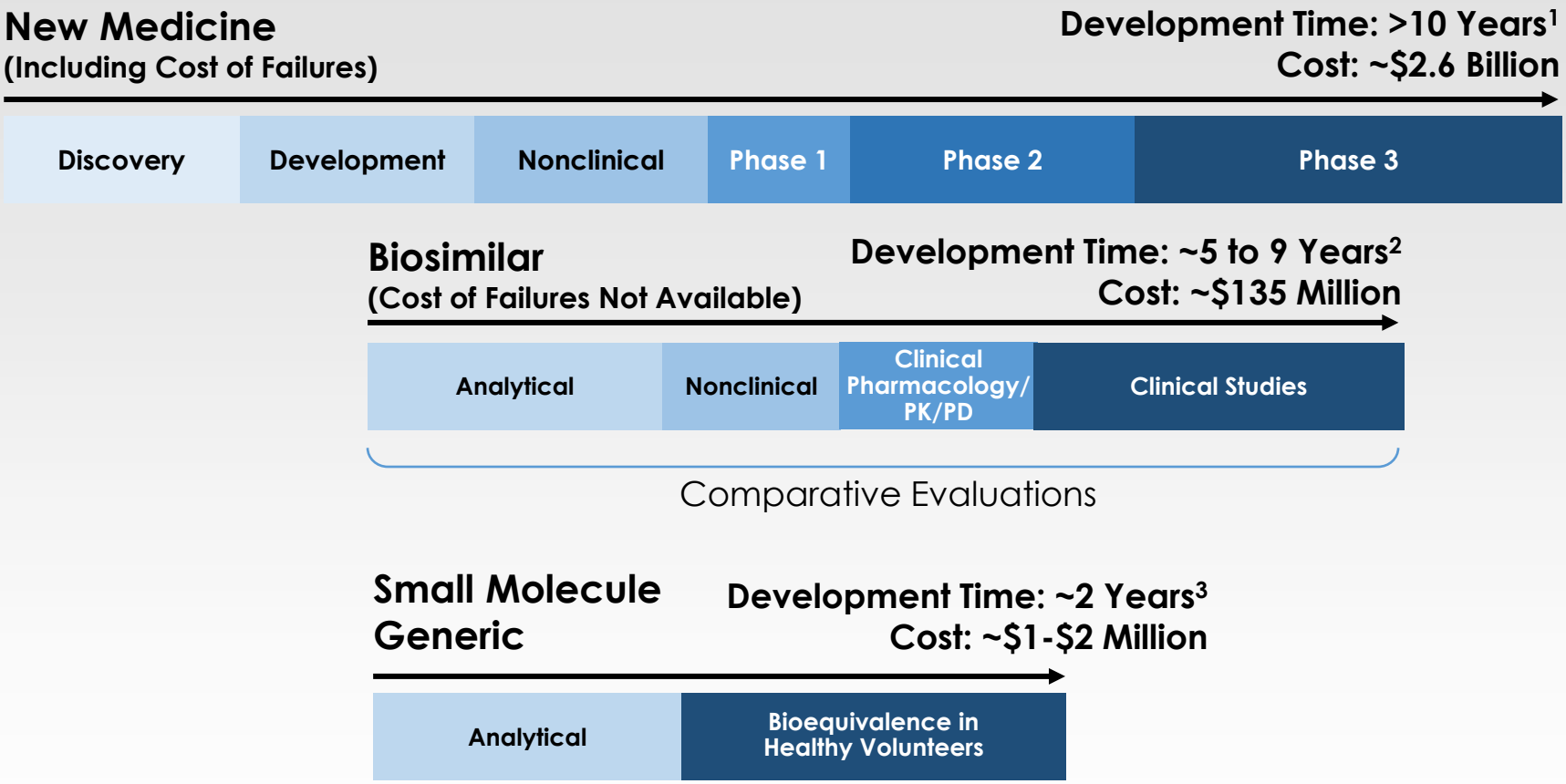


BPCI, Biologics Price Competition and Innovation.

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 Generic[1-3]

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



PD, pharmacodynamic; PK, pharmacokinetic.

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.

Biosimilar Development Is More Complex Than Establishing Comparability[1-3]

- Demonstrating biosimilarity to a reference product requires more data and information than establishing comparability between a post- and premanufacturing change[1]
- Although biosimilars are developed against a reference product, they have their own specifications, dependent on[2]
  - Manufacturing process
  - Industry standards
  - Regulatory expectations
  - Data from comparisons with the reference product
- Rigorous control strategies are necessary to maintain consistency and ensure biosimilars conform to specifications[3]

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*. 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 Experience[1-4]

Some examples of preexisting sources of information

1 — FDA

Assessments of reference products undergoing manufacturing changes[1,2]

2 — FDA

Experience evaluating biologics citing previously approved reference products[3]

3 — EMA

Biosimilar regulation and postapproval experience[4]

FDA Guidance for Biosimilars

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 guidelines[1]

Defining Principles[2]

- Guideline on Similar Biological Medicinal Products[a] (Adopted October 2014)

General Comparability Guidelines[2]

- Immunogenicity Assessment (Revision March 2014)
- Quality Issues (Adopted June 2014)
- Nonclinical and Clinical Issues (Adopted December 2014)

Product-Specific Comparability Guidelines[2]

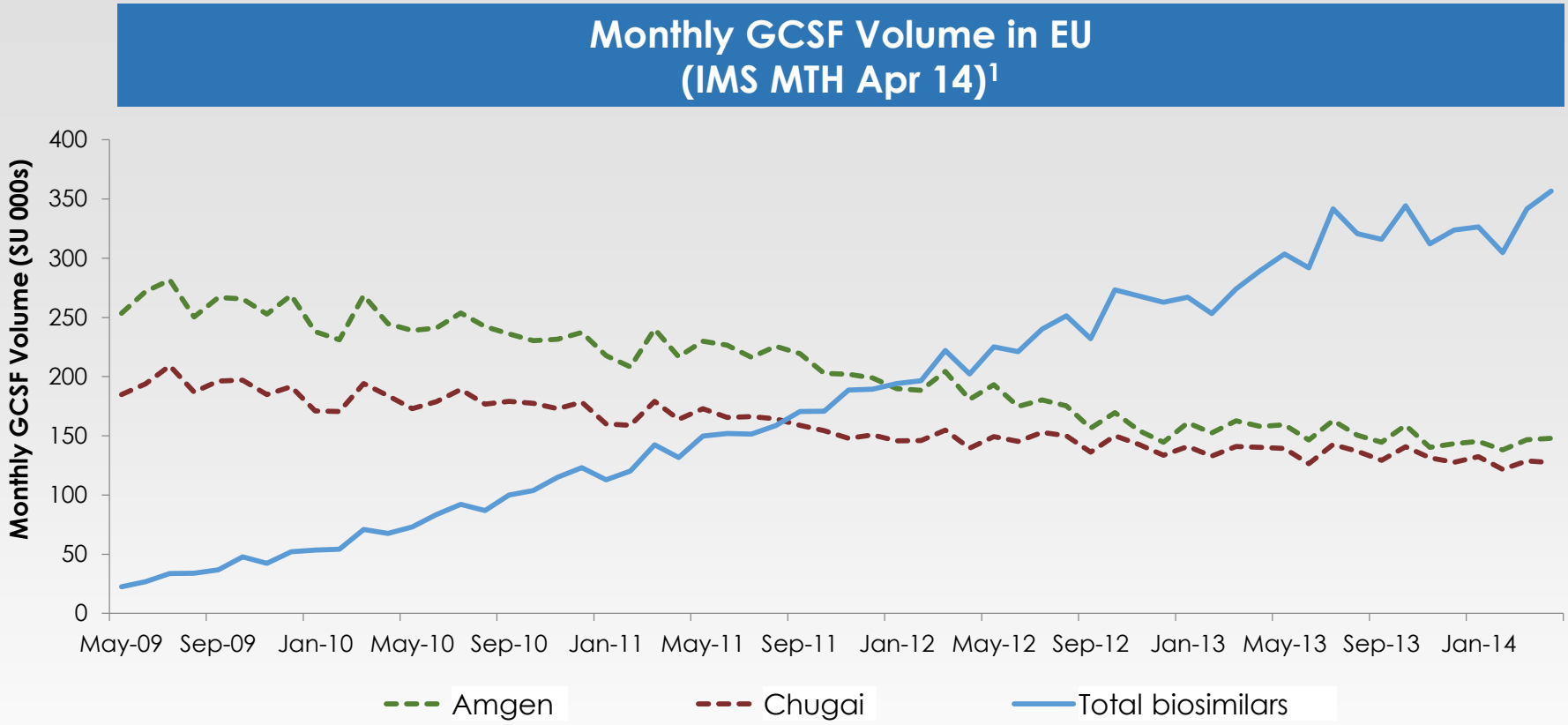
FSH	IFN-β	IFN-a	mAbs	Insulin	EPO	LMWH	GH	GCSF
Non clinical	Non clinical	Non clinical	Non clinical	Non clinical	Non clinical	Non clinical	Non clinical	Non clinical
Clinical	Clinical	Clinical	Clinical	Clinical	Clinical	Clinical	Clinical	Clinical

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.

[a]Original 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.

As Experience Grows in Europe, So Has Uptake of Biosimilar Use[1]



Biosimilars constitute

- 53% of the daily GCSF sales
- 69% of the filgrastim sales

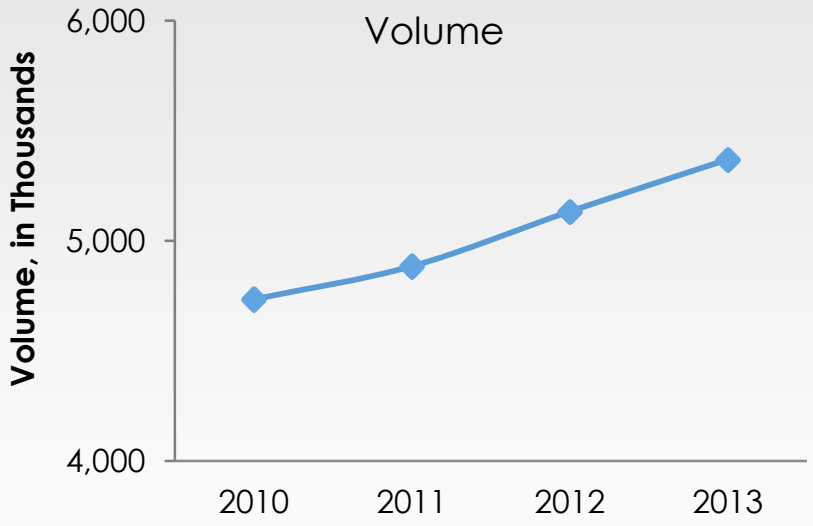
GCSF, granulocyte colony-stimulating factor.

1. IMS MIDAS [database]. Key performance indicators: Monthly GCSF volume in EU. April/May 2014. Data on file. Pfizer Inc, New York, NY.

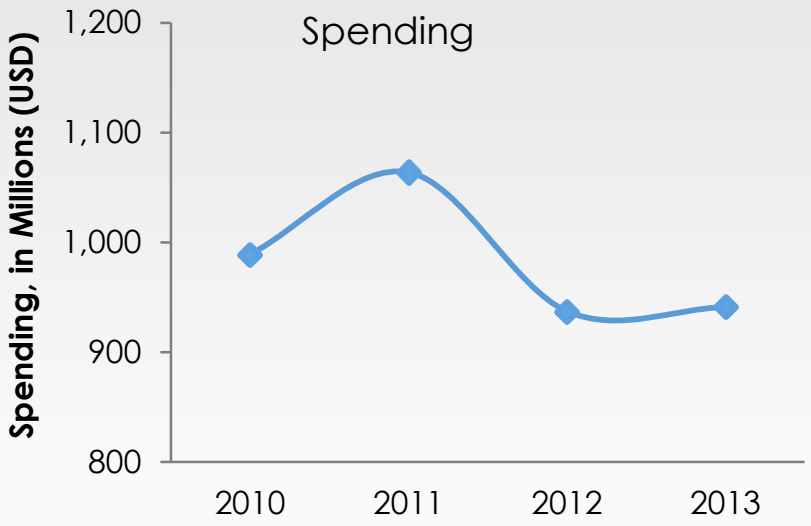
Uptake of Biosimilar GCSFs in Europe Has Coincided With Increased Utilization and Decreased Costs[1]

GCSFs in EU5: Market Volume Versus Spending (2010-2013)

Market volume has increased by 13%…



…at the same time, spending has decreased by 5%



EU5, France, Germany, Italy, Spain, United Kingdom.

1. IMS MIDAS G-CSF Injectable Database. G-CSFs in EU5: Market Volume vs. Spending ('10-'13). December 2013. Data on file. Pfizer Inc, New York, NY.

Cost Savings From Biosimilars to Health Care Systems May Be Significant (Although Estimates Vary)[1-5]

Source	Examples of Estimated Biosimilar Savings
Express Scripts[1]	$250 billion savings during 2014-2024, if 11 likeliest biosimilars enter the market
PCMA[2]	Medicare Part B could save $14 billion over 10 years
EGA[3]	Savings of €1.6 billion assuming a 20% discount for 5 biologic drugs across Europe
IGES[4]	€11.8 billion and €33.4 billion in 8 EU countries from 2007 to 2020
IMS[5]	€50 billion to €100 billion in cumulative savings in the EU5 and United States combined over the next 5 years

EGA, European Generic Medicines Association; IGES, IGES Institut GmbH; IMS, Intercontinental Marketing Services; PCMA, Pharmaceutical Care Management Association.

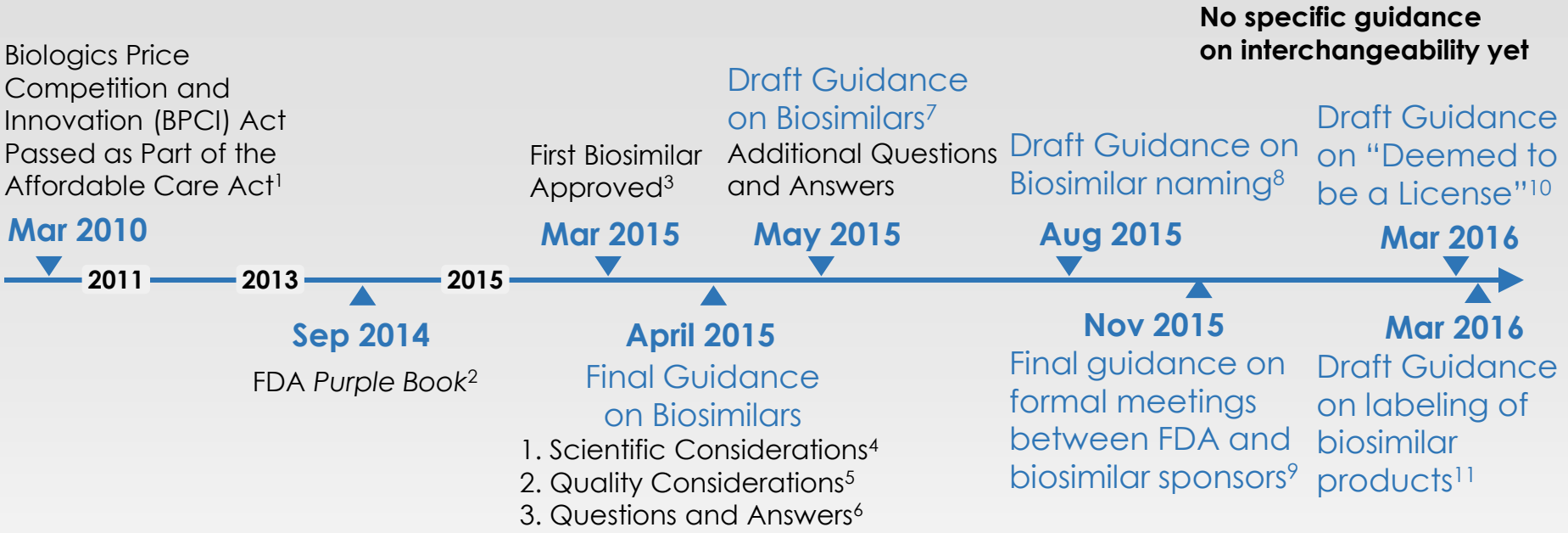
1. Miller S. The $250 billion potential of biosimilars. St. Louis, MO: Express Scripts; April 23, 2013. http://lab.express-scripts.com/insights/industry-updates/the-$250-billion-potential-of-biosimilars. Accessed December 30, 2015. **2.** Engel & Novitt, LLP. *Potential Savings That Might Be Realized by the Medicare Program From Enactment of Legislation Such as* The Access to Life-Saving Medicine Act *(H.R. 6257/S. 4016) That Establishes a New cBLA Pathway for Follow-On Biologics: A Report to Pharmaceutical Care Management Association (PCMA) Based Upon a Preliminary Assessment of Available Data.* Washington, DC: Engel & Novitt, LLP; January 2, 2007. http://c0464402.cdn.cloudfiles.rackspacecloud.com/en_biologics.pdf. Accessed December 30, 2015. **3.** European Generic Medicines Association. *EGA Handbook on Biosimilar Medicines*. Brussels, Belgium: EGMA; 2007. http://www.aff.cz/wp-content/uploads/2011/05/EGA-Handbook-on-Biosimilar-Medicines.pdf. Accessed December 30, 2015. **4.** Haustein R, et al. *GaBI J*. 2012;1(3-4):120-126. **5.** 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
- The uptake of biosimilars in Europe indicates a possible increase in access to medication

Summary of FDA Guidance on Establishing Biosimilarity

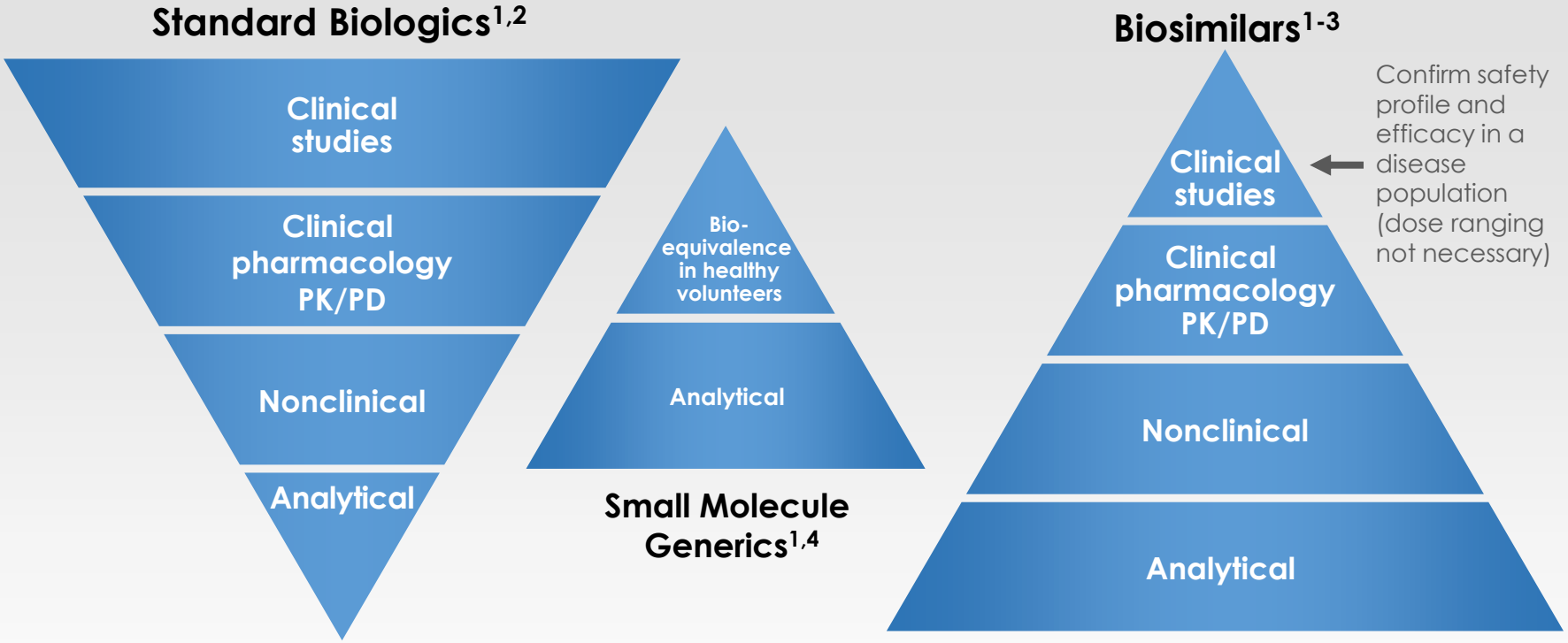
FDA Has Developed Guidance for the Regulatory Approval of Biosimilars[1-9]



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 Benefit[1-4]

Development Pathways



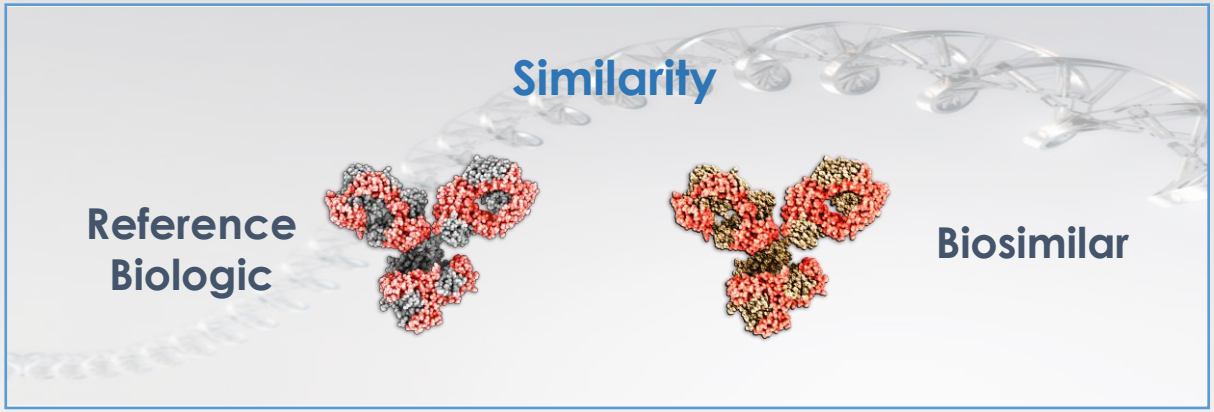
- It is not scientifically beneficial to repeat the entire development program of the reference product[5,6]
- A robust analytical characterization and preclinical foundation reduces the need for extensive animal and clinical testing[7]

PD, pharmacodynamics; PK, pharmacokinetics.

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[1]

- 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

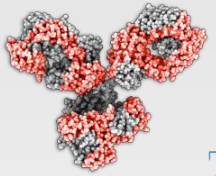
Analytical tests maximize the potential for detecting differences between the proposed biosimilar and the reference product

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.

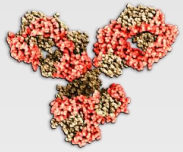
Any Comparative Clinical Evaluation Is Designed on a Case-by-Case Basis[1]

- Comparative safety profile and effectiveness data are necessary if there are residual uncertainties about the biosimilarity of the two products[1]

Reference Biologic



Degree of analytical and functional similarity



Biosimilar

The need for additional studies may be influenced by many factors

- Mechanism of action
- Complexity and heterogeneity
- Structure/ function relationship to clinical outcomes
- Relevance of clinical pharmacology to predicting outcomes
- Clinical experience in therapeutic class

1. US Food and Drug Administration. *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*. Silver Spring, MD: FDA; 2015.

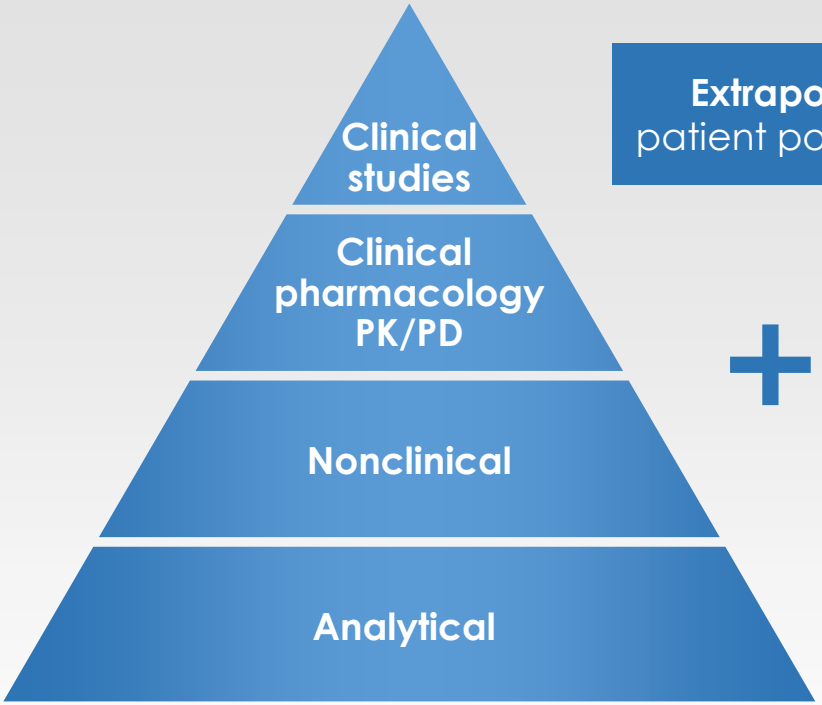
Key Points

- 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 population[1]

\+ Convincing scientific justification to support extrapolation to a reference biologic's approved indications[2]

▶ 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. European Medicines Agency. *Concept Paper on Extrapolation of Efficacy and Safety Profile in Medicine Development* [final]. London, UK: EMA; March 19, 2013. EMA/129698/2012. **2.** Weise M, et al. *Blood*. 2012:120:5111-5117.

Interchangeability of Biosimilars[1]

- 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

1. 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.

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 that bridges all data
  - 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
  - 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[1-3]

According to the Centers for Medicare & Medicaid Services, prescription drug spending growth is projected to average 6.3% annual growth from 2015 through 2024[1]

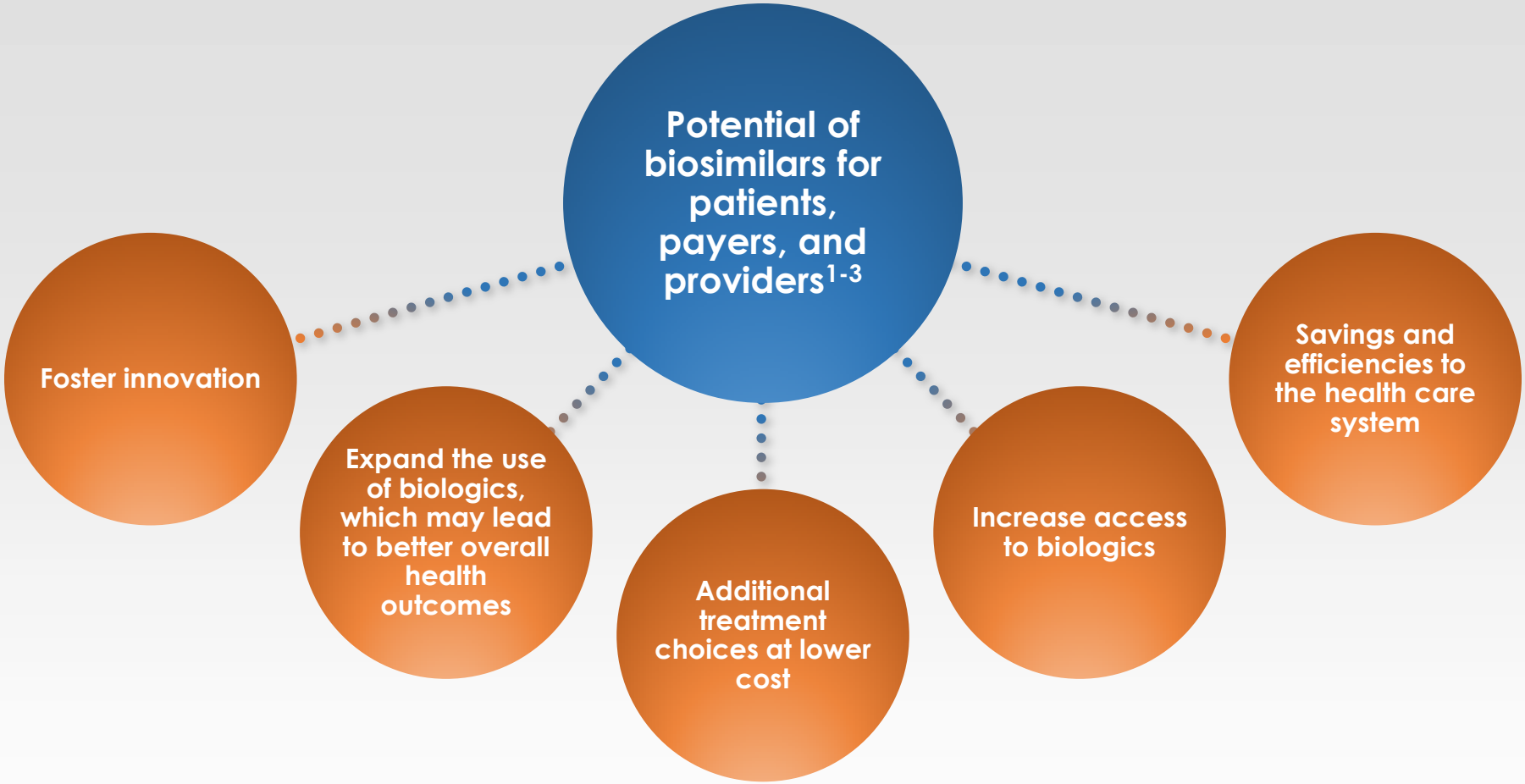
$ 2014-2024 health care spending projected to grow[1] 1.1% faster than the GDP → **5.8% on average**

24% of pharmaceutical products approved in 2015 were biologics[2]

67% 3-year compound increase in US specialty drug spending forecast by the end of 2015[3]

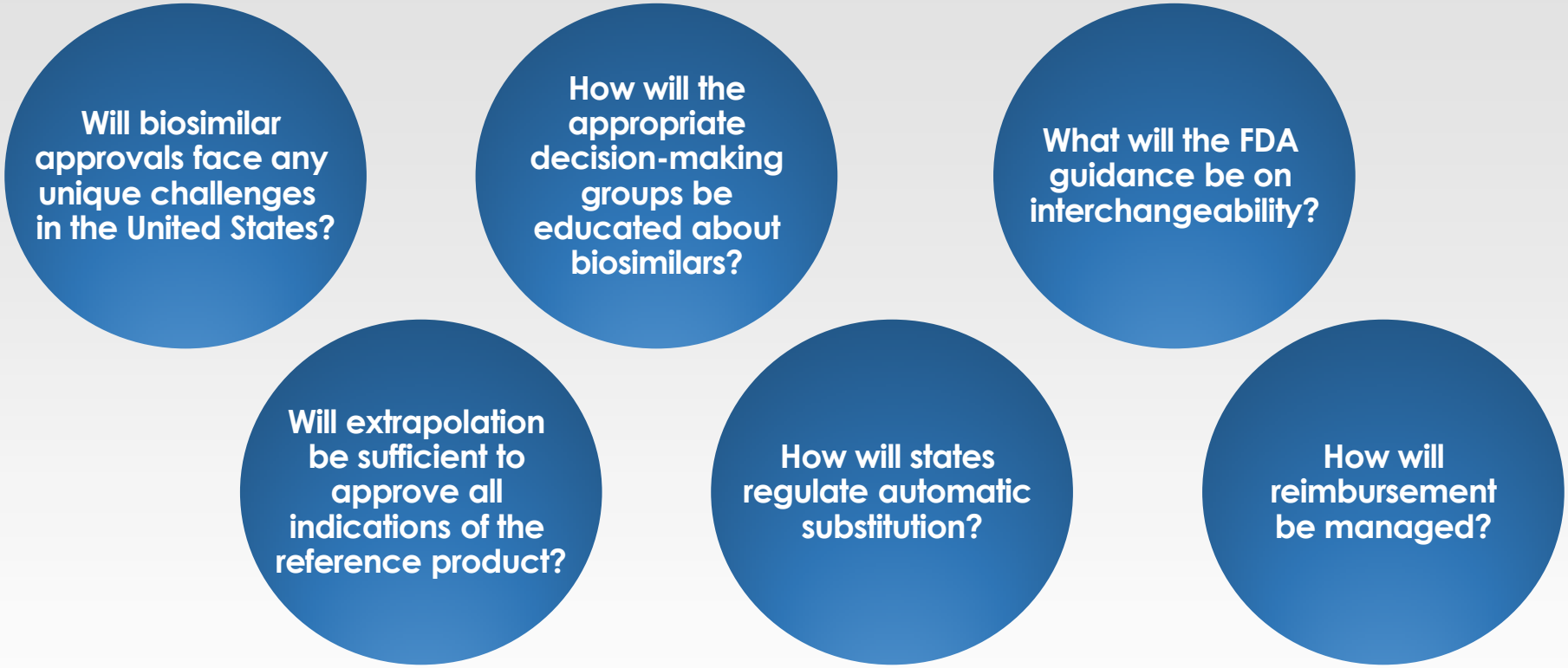
1. Centers for Medicare & Medicaid Services. NHE Projections 2014-2024. https://www.cms.gov/Research-Statistics-Data-and-Systems/ Statistics-Trends-and-Reports/NationalHealthExpendData/NationalHealthAccountsProjected.html. Accessed December 30, 2015. **2.** US Food and Drug Administration. *New Molecular Entity and New Therapeutic Biological Product Approvals for 2015*. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm430302.htm. Accessed December 30, 2015. **3.** Express Scripts. http://lab.express-scripts.com/insights/specialty-medications/specialty-drug-spending-to-jump-67-percent-by-2015. Accessed January 14, 2016.

Biosimilars May Provide Multiple Benefits to the US Health Care System[1-3]



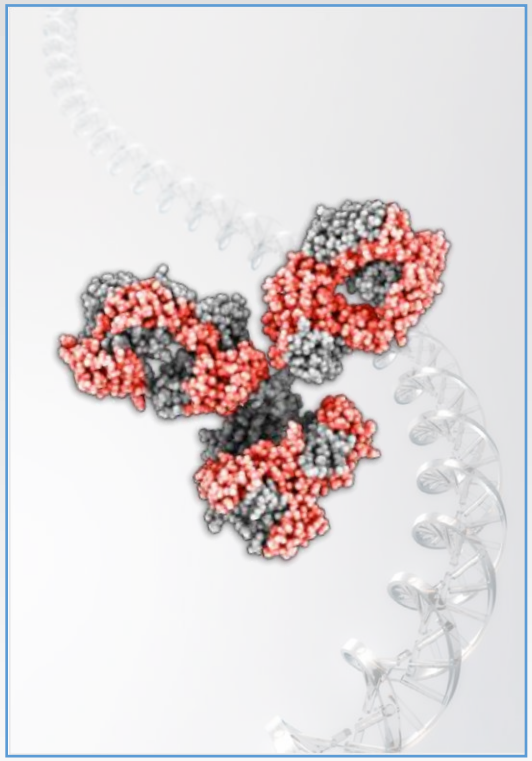
1. Strober BE, et al. *J Am Acad Dermatol*. 2012;66(2):317-322. **2.** Scheinberg MA, Kay J. *Nat Rev Rheumatol*. 2012;8(7):430-436. **3.** Henry D, Taylor C. *Semin Oncol*. 2014;41(suppl 3):S13-S20.

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



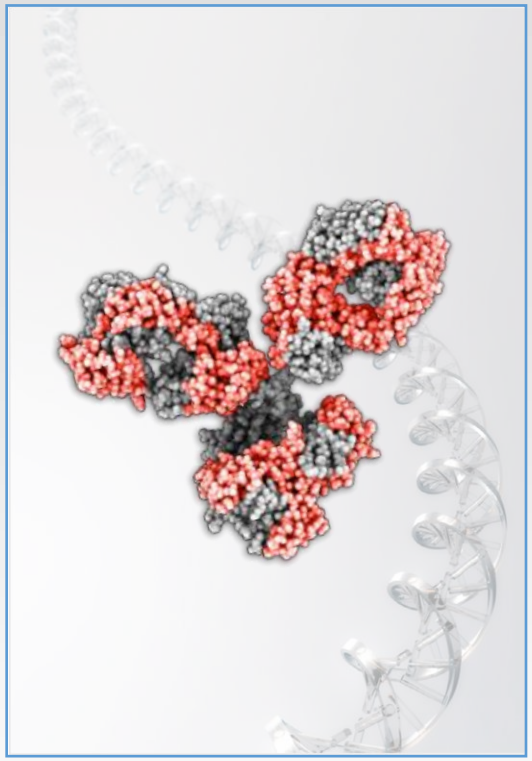
Program Summary

- There is increasing demand for biologics
- The introduction of high-quality, safe, and effective biosimilars may
  - Expand the use of biologics, which may lead to better overall health outcomes
  - Provide savings and efficiencies to health care systems
  - Increase access to biologics
  - Provide additional 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



Thank you!

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