AHR Briefing /
Biosimilars in the U.S. - Current & Emerging Issues /

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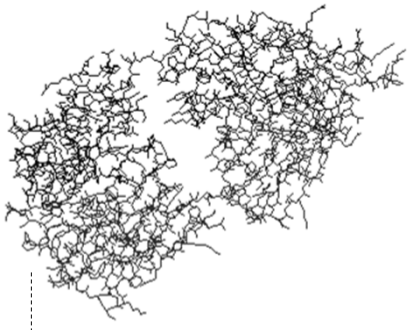
What Is a Biologic Product?

- A biologic is defined in Section 351(i) of the Public Health Service Act (PHSA) as:

> "…a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound…)"



Biologic: medicinal product that is synthesized from a living organism or its products (pictured: therapeutic protein)

Small molecule drug: a drug synthesized via a chemical process (pictured: statin)

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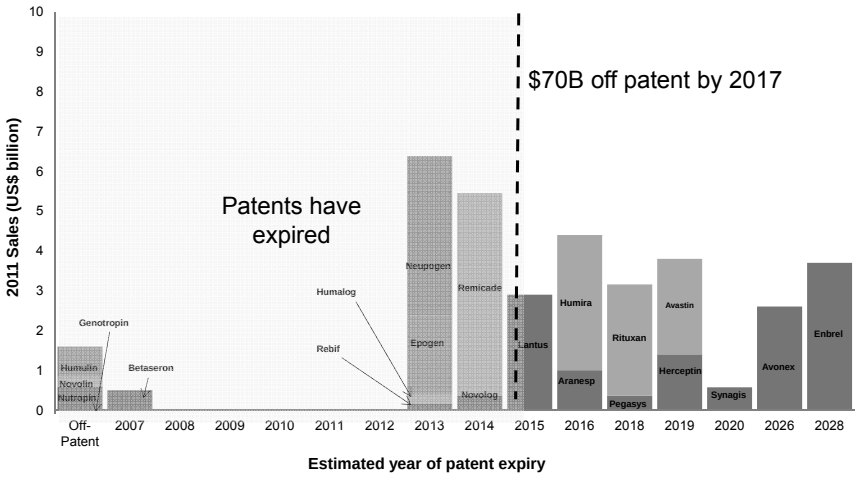
Biologics Facing Patent Expiration and Likely Biosimilar Competition



Adapted from: Lanthier, M., et al. "Economic issues with follow-on protein products." Nature Reviews Drug Discovery 7, (September 2008) 733-737; 2011 sales data sourced from company annual reports

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EU Biosimilars: 13 Development Programs, 20 Products Approved

	Product	Active Ingredient (INN)	Company
2006	Omnitrope®	Somatropin	Sandoz
	Valtropin®	Somatropin	Biopartners
2007	Binocrit®	Epoetin alfa	Sandoz
	Epoetin alfa HEXAL®	Epoetin alfa	Hexal
	Abseamed®	Epoetin alfa	Medice
2008	Silapo®	Epoetin zeta	Stada
	Retacrit®	Epoetin zeta	Hospira
	Biograstim®	Filgrastim	CT Arzneimittel
	Filgrastim Ratiopharm®	Filgrastim	Ratiopharm
	Ratiograstim®	Filgrastim	Ratiopharm
	Tevagrastim®	Filgrastim	Teva
2009	Filgrastim HEXAL®	Filgrastim	Hexal
	Zarzio®	Filgrastim	Sandoz
2010	Nivestim®	Filgrastim	Hospira
2013	Grastofil®	Filgrastim	Apotex
	Remsima®	Infliximab	Celltrion
	Inflectra®	Infliximab	Hospira
	Somatropin Biopartners®	somatropin	Bioton
	Ovaleap®	Follitropin alfa	Teva
2014	Bemfola®	follitropin alfa	Finox Biotech AG
	Abasria® (Positive Opinion)	Insulin glargine	Lilly (BI)

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Affordable Care Act (ACA) Established 351(k), a Regulatory Pathway for Biosimilars in the US

	ACA	Remaining Questions
Terminology	• Biosimilar or interchangeable	• How will FDA determine interchangeability?
Application Process	• FDA has authority to approve a biosimilar, then determine if it is interchangeable	• What will the final FDA process look like?
Clinical Trials	• Clinical studies to establish safety, purity, and potency are required, unless waived by FDA	• Will clinical study requirements vary by molecule?
Coding and Payment	• Coding and payment will be determined by individual payers; Part B biosimilar biologics are paid at their own ASP + 6% of the reference product's ASP	• Do ASP provisions apply in all settings, or physician office/clinic only? • How will codes be assigned to biosimilars? • Will biosimilars deemed interchangeable by the FDA be reimbursed differently by Medicare?
Other	• A non-interchangeable biosimilar is considered to have a new active ingredient • An interchangeable biosimilar is not considered to have a new active ingredient	• What are implications for automatic substitution?
Exclusivity for Innovator	• 12 years initial exclusivity for all reference products; six month extension possible for pediatric studies	
Exclusivity for Biosimilar	• 12 – 42 months for first interchangeable product depending on legal disputes	

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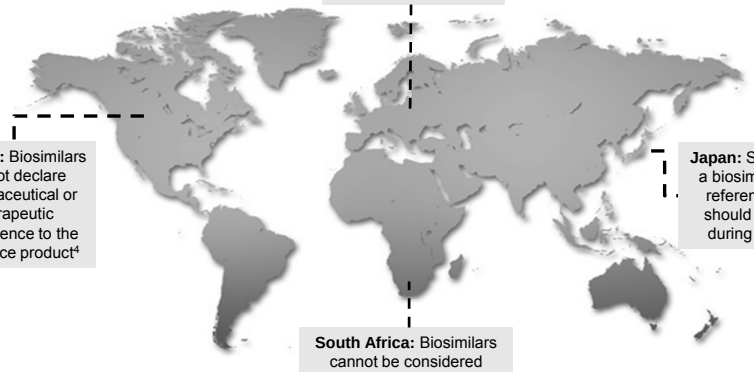
The Patient Protection and Affordable Care Act, Public Law 111-148, 111th Congress, March 23, 2010

"Interchangeability" Is Not a Global Concept

EU: EMA does not have the authority to classify biosimilars as interchangeable[1]



Canada: Biosimilars cannot declare pharmaceutical or therapeutic equivalence to the reference product[4]

Japan: Substitution of a biosimilar with the reference product should be avoided during treatment[2]

South Africa: Biosimilars cannot be considered interchangeable[3]

EU: European Union

Note: Therapeutic equivalence refers to approved drug products that are pharmaceutical equivalents and for which bioequivalence has been demonstrated. Therapeutic equivalents can be expected to have the same clinical effect and safety profile when administered under the conditions specified in the labeling and will receive an "A" equivalence evaluation code in FDA's Orange Book.

1. Committee for Medicinal Products for Human Use (CHMP), CHMP/437/04, Guideline on Similar Biological Medicinal Products (2005) at § 2.1; 2. Guidelines for the Quality, Safety and Efficacy Assurance of Follow-on Biologics (2009); 3. Republic of South Africa, Department of Health, Medicines Control Council, Guidelines for Similar Biological Medicines, at § 5.3 (2010); 4. Health Canada, Guidance for Sponsors: Information on Submission Requirements for Subsequent Entry Biologics (SEBs) (2010).

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Biosimilars Treated Like Single-source or Generic Products Across CMS Programs

When a biosimilar (or follow-on biosimilar[s]) comes to market, relevant determinations will follow conventions similar to…	First Biosimilar			Follow-on Biosimilar(s)		
	Innovator Biologic	Generic Drug	Unique Biosimilar Treatment	Innovator Biologic	Generic Drug	Unique Biosimilar Treatment
Medicare Part D						
Transition Fills	✓			✓		
P&T Committee Formulary Review Timeline	✓			✓		
USP Coverage Requirements		✓			✓	
LIS Cost Sharing	✓			✓		
Coverage Gap Discount Program		✓			✓	
Mid-Year Formulary Changes	✓			✓		
Protected Classes	Unknown			Unknown		
Medicare Part B						
Coverage	✓			✓		
Coding	✓				Unknown	
Payment			✓		Unknown	
Medicaid						
Rebates	✓			✓		

✓ **Known**
✓ **Likely**

Follow-on biosimilar = subsequent biosimilar(s) to a single reference product

Summary of Recent CMS Biosimilars Guidance

Medicare Part D Guidance

- **Summary:**
  - Biosimilars and reference biologics will not be considered different drugs for satisfying the two-drug formulary requirement
  - Midyear addition of a biosimilar and removal of a reference biologic will be considered a non-maintenance change, which requires CMS approval on a case-by-case basis
  - P&T committees must review newly approved biosimilars according to existing formulary management requirements, which include making coverage decisions within 180 days, or 90 days for drugs in the protected classes
  - Part D plan sponsors must treat a biosimilar and its reference biologic as different drugs for the purposes of transition fills
  - Biosimilars do not meet the definition of a multiple-source drug; therefore biosimilars are subject to higher LIS maximum copayments
  - Similar to generic drugs, biosimilars are excluded from the CGDP by the Affordable Care Act (ACA), are therefore considered non-applicable drugs; consequently, non-LIS beneficiaries will not receive the 50-percent discounts from manufacturers in the coverage gap
- **Remaining Questions:**
  - Whether or not plans must cover both a biosimilar and reference product in a protected drug class, or if a plan may substitute the biosimilar for the reference product as is the case with generics

MLN Matters Article (Part B Guidance)

- **Summary:**
  - First biosimilar will receive a HCPCS code separate from reference product
  - First biosimilar paid at its own ASP plus 6% of reference product's ASP
  - Until ASP available, biosimilar paid at 106% of its own WAC
- **Remaining Questions:**
  - Whether all biosimilars to same reference product will share a code
  - Whether payment for all biosimilars to the same reference product will be based on weighted average ASP of all of the biosimilars plus 6% of reference product's ASP

Medicaid Guidance

- **Summary:**
  - Biosimilars are considered brand drugs for purposes of the Medicaid Rebate calculation
  - CMS recommended that states take steps to encourage use of biosimilars (step therapy, prior authorization, use of preferred drug lists)
- **Remaining Questions:**
  - When and if Medicaid agencies will aggressively promote biosimilars

WAC: Wholesale Acquisition Cost; CMS: Centers for Medicare & Medicaid Services; ASP: Average Sales Price; HCPCS: Healthcare Common Procedure Coding System; LIS: Low-Income Subsidy; CGDP: Coverage Gap Discount Program; P&T: Pharmacy and Therapeutics Committee
MLN Matters SE1509: http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/SE1509.pdf; Manufacturer Release # 92 (2015); State Release #169 (2015): http://www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/prescription-drugs/program-releases.html; Health Plan Systems Memo to Part D Plans (March 30, 2015): https://hpms.cms.gov/app/login.aspx?ReturnUrl=%2fapp%2fhome.aspx