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Biosimilars Update

Conflict of Interest Disclosure

- *We have no actual or potential conflict of interest in relation to this program and presentation.*
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  - Patrick Leary
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A conflict of interest exists when an individual is in a position to profit directly or indirectly through application of authority, influence, or knowledge in relation to the affairs of PENS. A conflict of interest also exists if a relative benefits or when the organization is adversely affected in any way.

The Biosimilar Roadmap
"From concept to delivery"

** Describing the difference between biologics and biosimilar medicine*
** The emerging role of biosimilars and the cost involved*
** Identify the benefits of biosimilars*

Before we get started…key definitions

Biologics

- Pharmaceuticals produced from living organisms
- Offer real hope for many unmet needs, particularly complex diseases
- Bind to specific targets within the body – simply not possible with other medicines
- Contribute significantly to improved survival rates, enhanced longevity, and better quality of life

Biosimilars

- Biologics approved via a recognized approval pathway ("biosimilar" is a regulatory term)
- Successor of a biopharmaceutical for which patent protection no longer applies
- Comparable with the selected reference product in terms of quality, safety, and efficacy

A biosimilar is NOT a generic biopharmaceutical due to complexity: size, structure, and manufacturing

What Are Biosimilars?

US BPCIA Definition*

- The biological product is *highly similar* to the reference product notwithstanding minor differences in clinically inactive components

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

Biological medicines and Biosimilars

- During the past 15 years, biological medicines have had a profound impact on healthcare
  - > primarily in the areas of rheumatology and oncology
  - > as well as endocrinology, cardiology, dermatology, gastroenterology, and neurology
- Many of the world's top-selling medicines are now biological medicines
- However, biological medicines are expensive (sometimes by several orders of magnitude more than small-molecule chemical drugs), limiting patient access
- As many biological medicines come off patent globally, there is great interest in the development of biosimilars, which are likely to be more affordable
- It has been estimated that 31 different companies were developing biosimilar monoclonal antibodies (as of March 2012), compared with 18 companies as of Sept 2011 – an increase of 67% in a 6-month period.[1]

Biological medicines due to come off patent

2010–2015	2016–2020	Post–2020
Patent expiries expected: 99	Patent expiries expected: **91**	Patent expiries expected: **46**

Biologics are more complex than small molecules…

Aspirin®

small chemical molecule

Molecular weight
= 180 Daltons
0 amino acids

Calcitonin

simple biologic

Molecular weight
= 3,455 Daltons
~ 32 amino acids

- w/o host cell modifications
- produced in yeast, bacteria

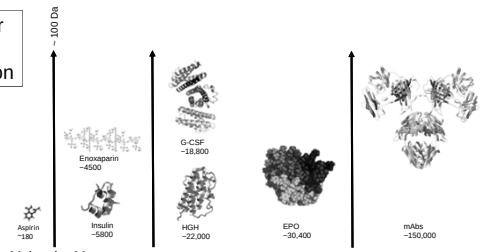
Monoclonal Antibody (IgG)

complex biologic

Molecular weight
= 150,000 Daltons
~ 1300 amino acids

- w/host cell modifications (glycosolations, etc)
- produced in mammalian cells

Molecular Mass Comparison



Generic	Biosimilars 1.0	Biosimilars 2.0
Same Structure = Same Function	Similarity in Structure	

Biosimilars development requires substantive investment and time – "closer to originators than generics"

	Generics*	Biosimilars*	Originators*
Development investment	USD 2 – 3m	USD 75 - 250m	USD 800m
Time to market	2 – 3 yrs	7 – 8 yrs	8 – 10 yrs
# of patients for approval[1]	20 – 50 pts	~ 500 pts	800 – 1000 pts

By 2016, 7 of the top 10 pharmaceuticals worldwide will be biologics[1]

Product	Type	2016 Rev. (USD bn)	2010 Rev. (USD bn)
1: Humira	Biologic	10.0	6.7
2: Avastin	Biologic	7.7	6.2
3: Rituxan	Biologic	7.6	6.1
4. Enbrel	Biologic	7.1	7.3
5: Crestor	Small molecule	7.5	6.0
6: Seretide / Advair	Respiratory / device	6.7	7.9
7. Remicade	Biologic	6.2	6.5
8: Herceptin	Biologic	6.3	5.2
9. Revlimid	Small molecule	6.1	2.5
10: Lantus	Biologic	5.3	4.7

Differences in 351(a) Pathway vs 351(k)

351(a)	351(k)
"Traditional" process for biologic approval	**Stepwise** approval process
Compares biological drug with placebo or active comparator	Compares biosimilar with reference product
Clinical trials required (Phases 1-3)	"Data derived from analytical studies, animal studies, and a clinical study or studies are required to demonstrate biosimilarity unless FDA determines an element unnecessary."
Indications based on clinical trials	Allows for extrapolation, if justified, up to **all indications** of innovator (including pediatrics)
No substitution	**Potential for substitution**
One Approval	**Two Levels of Approval**
New Biologic Drug	**Biosimilar Drug OR Interchangeable Biosimilar Drug**

FDA Levels of Similarity

Not Similar
- Further development through 351(k) not recommended

Need to pursue changes in manufacturing process

Similar
- Additional analytical data or other studies needed to determine if product is highly similar to reference

Highly Similar
- High confidence in similarity
- Targeted and selective clinical studies recommended **to resolve residual uncertainty**

Highly Similar With Fingerprint-Like Similarity
- Very high confidence in similarity
- More targeted and selective clinical studies recommended **if residual uncertainty remains**

High **Residual Uncertainty** **Low**

Interchangeable Biosimilar Has Additional Requirements Beyond a Biosimilar

Biosimilarity

Highly similar and an absence of clinically meaningful differences

Interchangeability

1) Biosimilar

2) Expectation of same clinical result in any given patient

3) No additional risk to safety or efficacy as a result of switching

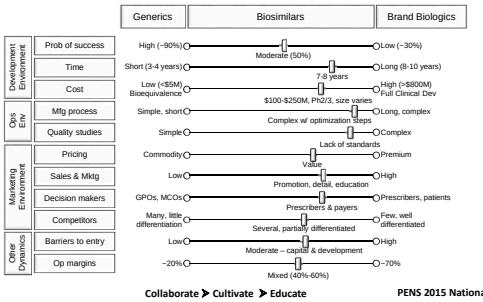
- US is only jurisdiction with specific definition for an interchangeable biologic
- FDA still to determine requirements for satisfying the definition

The "Unknowns" of Biosimilars Will Become More Clear Over Time

The Promise of Savings…
Increased competition in specialty care should drive greater cost savings

The Mix of Unknowns…
- Extrapolation
- Interchangeability
- Nomenclature
- Acute vs Chronic
- Naïve vs Stable patient mix (payer mandate)
- Physician attitudes
- Patient preferences
- Pharmacovigilance
- Pricing/rebates
- Manufacturing expertise
- Coverage and reimbursement

Biosimilars Will Likely Fall Between Generics and Branded Biologics in a Number of Areas



Biosimilar Market Opportunity

18 Blockbuster biologics expected to go off-patent in the next five years, including Avonex, Remicade, Lantus, Humira, and Avastin.

$30B Expected market size by 2024 (US as the key source of business).

>150 Manufacturers investing in biosimilar development, manufacturing, and commercializing capabilities (key players in US, Japan, China, South Korea, Germany, and India).

Biosimilar Applications Pending at FDA

Biosimilar Applications Pending at FDA

Sponsor and Product	Reference	Date of Filing	Estimated User Fee Date	Advisory Committee
Sandoz, filgrastim	Amgen's *Neupogen*	May 2014	March 2015	Voted unanimously Jan. 7, 2015 to recommend approval ("Sandoz Biosimilar Filgrastim Sails Through FDA Panel"— *"The Pink Sheet" DAILY*, Jan. 7, 2015)
Celltrion, infliximab	Johnson & Johnson's *Remicade*	August 2014	June 2015	Scheduled for March 17 ("Remicade Biosimilar Review Where 351(k) Pathway Bumps Into Orphan Drug Rules"— *"The Pink Sheet" DAILY*, Feb. 9, 2015)
Apotex, pegfilgrastim	Amgen's *Neulasta*	October or November 2014	August or September 2015	no announcement yet
Hospira, epoeitin alfa	Amgen's *Epogen* and Janssen's *Procrit*	Dec. 16, 2014	October 2015	no announcement yet
Apotex, filgrastim	Amgen's *Neupogen*	December 2014	October 2015	no announcement yet

Source: Company announcements and other information

Biosimilars Challenges / Risks

Originator Tactics	• Entrenched competitors aggressively defending their market • IP and lifecycle defense strategies • Contracting strategies to match value proposition of biosimilars • Seeding doubts about safety and efficacy of biosimilars
Biosimilars Competition	• Maintaining price in the face of increased number of competitors • Competitive tactics from a mix of high and low quality competitors • Certain countries favor local players or accept lower quality standards
Execution Risk	• Rapid program development has inherent risks that need to be mitigated • Nimble decision-making required to address issues and maintain timelines • Adequately prioritized resources for development and commercialization • Deprioritizing oncology programs would risk harming Actavis partnership
Regulatory / Legal / Policy	• Lack of regulatory clarity and experience with biosimilar pathways • Scientifically complex and difficult to design and manufacture • Key policy issues (i.e. substitution) may impact attractiveness of business • Stakeholder uncertainty regarding biosimilars

Critical to Resource Business for Success

The Landscape Is Competitive

Multi-National BioPharmas	Multi-National Generic Companies	Primarily Local Players (List Not Exhaustive)
• Amgen	• Celltrion	• Apotex
• Boehringer Ingelheim	• Sandoz/Novartis	• Biocon
• Samsung – Merck & Biogen	• Mylan (Biocon)	• Cipla
• Pfizer / Hospira	• Momenta	• CP Guojian
• Serono		• Dong-A
• Eli Lilly		• Hanwha
		• Gedeon Richter
		• KHK/Fujifilm
		• Ranbaxy
		• Wockhardt

Managing and Setting Expectations

ESI Projects $250 Billion Potential of Biosimilars

Express Scripts® projects the US would save $250 billion between 2014 and 2024 if just the 11 likeliest biosimilars would enter the market[1]

?

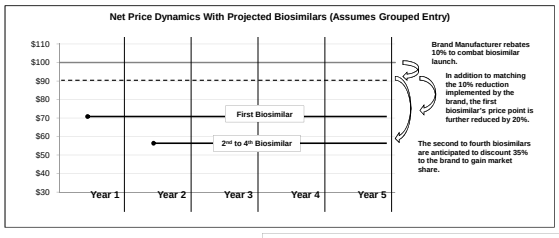
CBO Projects $25 Billion in Savings[2]

Congressional Budget Office expects $25 billion reduced total expenditures on biologics over the 2009-2018 period[2]

Over that 10-year period, such savings would equal roughly 0.5 percent[2]

EXPRESS SCRIPTS®

The cornerstone of a biosimilar's value proposition is 20% to 30% discounted pricing



The price levels of a biosimilar depends on the pricing and reimbursement environment, the competitiveness, and the desire to encourage future development of new products in each market.

The competitor-set is rapidly growing

	Oncology Biosimilars				Inflammation Biosimilars			Other Biosimilars	Additional Information
	Herceptin	Avastin	Rituxan	Erbitux	Humira	Remicade	Enbrel		
Amgen	x	x	x	x	x	x			
Sandoz/ Novartis			x				x	• Epoetin • Filgrastim • Omnitrope • Pegfilgrastim	Up to 7 biosimilars may be in development
Pfizer	x		x			x			Two additional biosimilars in development (not yet named)
Teva			x					• Epoetin • Filgrastim • Pegfilgrastim • Follitropin alfa	
Hospira/ Celltrion	x		x			x		• Epoetin • Filgrastim • Pegfilgrastim	Up to 11biosimilars may be in development
Boehringer-Ingelheim		x	x		x				
Merck & Co/ Samsung Bioepis	February 2013: reported they had entered into an agreement to develop a multiple of pre-specified but undisclosed biosimilar candidates								
Merck Serono/ Dr Reddy's	June 2012: announced a partnership to co-develop a portfolio of biosimilar components in oncology, primarily focused on monoclonal antibodies								
Baxter/Partnerships with Coherus and Momenta							x (with Coherus)		Three biosimilars (inflammation/oncology in development with Momenta)

US Payers express a high degree of anticipation and uncertainty on Biosimilars.

""Much like we saw with small molecules when generics entered, the price point should drop for this drug class."
-PHARMACY DIRECTOR (22M lives)

"Unsuccessful initial launch may place a 'black cloud' over the biosimilar experience , delaying the opportunity for savings"
-MEDICAL DIRECTOR (10M lives)

"For us to switch patients to biosimilars, we would expect discounts in the 40% range"
-PHARMACY DIRECTOR (15M lives)

"Clinically, if there's no issue … at the end of the day it will come down to pricing ."
- PHARMACY DIRECTOR (3M lives)

"Monoclonals are killing us in terms of pricing. I hope biosimilars are competitively priced. We'll have to see how far they drop in price"
-ONCOLOGIST, ACAD. CTR. (2M lives)

5 Key Commercial Considerations

Country
- Different levels of IP protection, regulatory pathways and policies on interchangeability/ automatic substitution
- Geographic scope and **go-to-market strategy/sequence** is a critical strategic consideration

Category
- Relatively new and evolving category with several moving parts: regulatory pathways, substitution policies
- Opportunity to weave a **cohesive communication story to raise awareness** on Biosimilars and **set expectations on the value** of the category to patients and the healthcare system

Company
- Establish **confidence with stakeholders** on organization commitment, level of investments, development & manufacturing processes, patient services, and asset similarity
- Develop **corporate identify** in Biosimilars

Competition
- Significant number of competitors interested in capitalizing on the opportunity
- Separation exists between niche players and larger big pharma
- Map & address **originator messaging and policy initiatives**

Customer
- **Complex mosaic** involving physicians, payers, regulators & advocacy groups
- Mixed reviews on Biosimilars in general
- **Oncology and rheumatology distinct differences**, with structural hurdles – may limit oncologist from capitalizing on the opportunity of Biosimilars

Reference/Resources

- Biologics Price Competition and Innovation Act, 42 USC 262(i)(2)
- US Food and Drug Administration. www.fda.gov/downloads/Drugs/Guidances
- US Food and Drug Administration. Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product.
- Express Scripts. http://lab.express-scripts.com/insights/industry
- Congressional Budget Office
- Campbell Alliance Insights
- inVentiv Health Biosimilar Stakeholder Interviews conducted by Campbell Alliance