Manufacturer's Perspective

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February 10, 2014

Agenda

Emerging Biosimilar Market
Defining "Biosimilars"
Path to Regulatory Approval
Experience in Europe
Emerging Market Dynamics in the US
Conclusions

Biosimilar by the numbers

Blockbuster biologics expected to go lose exclusivity in the next 5 years → Avonex, Remicade, Lantus, Humira, and Avastin.

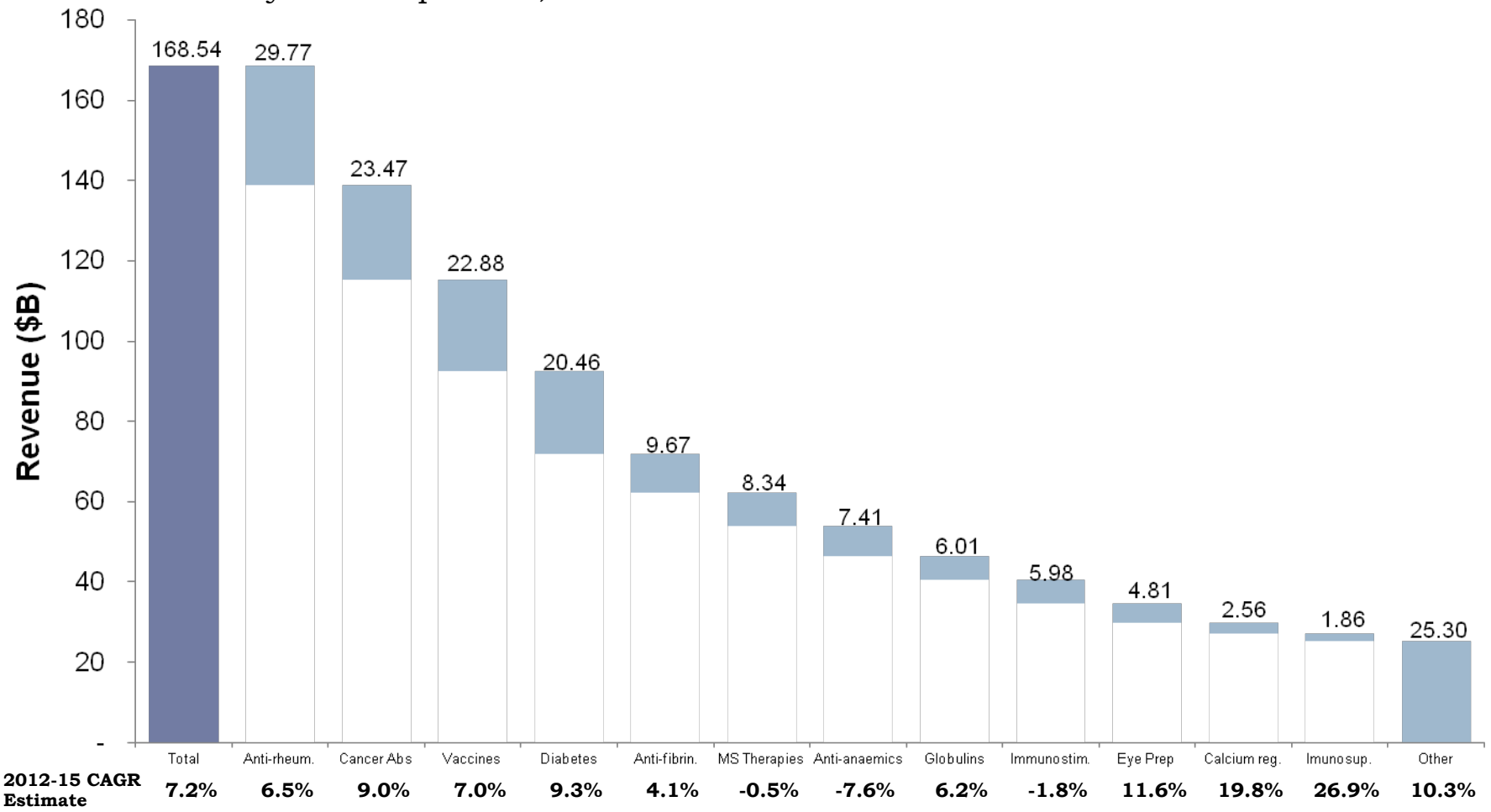
Expected biosimilar market size by 2020 → US, Japan, China, South Korea, and EU as the key source of business.

Manufacturers investing in biosimilar development, manufacturing and commercializing capabilities → Key players in US, Japan, China, South Korea, Germany and India.

Source: Campbell Alliance Analysis of Evaluate Pharma and Citeline, 2013

Biosimilars represent a sizeable and growing opportunity

Breakdown of Branded Biologic Industry Revenues
By class of product, 2012



Source: Campbell Alliance Analysis, 2013, EvaluatePharma.

The definition of biosimilar varies

World Health Organization

A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product[1]

A biological medicine that is developed to be similar to an existing biological medicine (the 'reference medicine'). When approved, a Biosimilar's variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness[2]

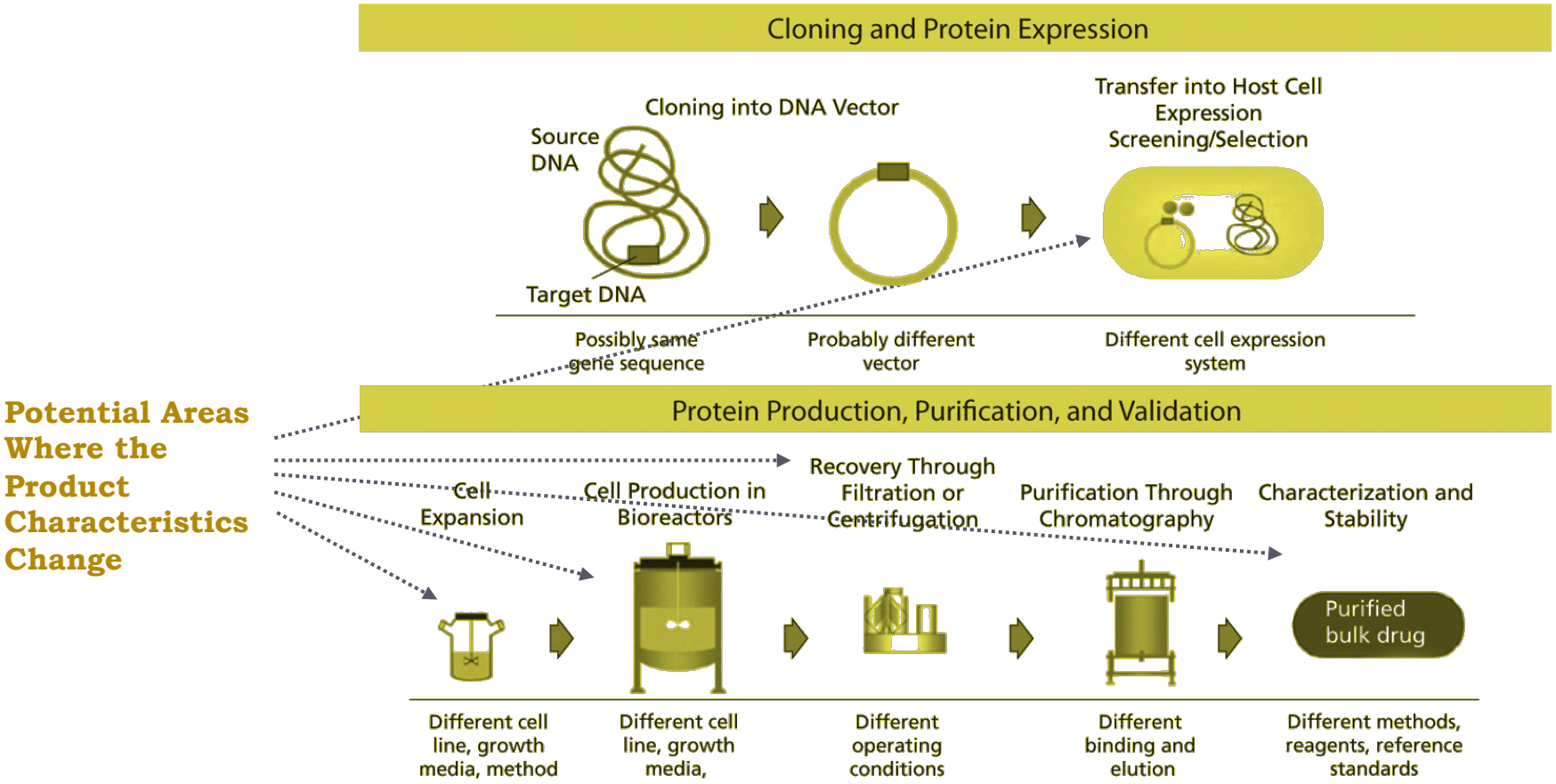
Biological product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product[3]

1. World Health Organization. Expert Committee on Biological Standardization. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). World Health Organization. [Online] October 23, 2009. [Cited: March 23, 2012.] http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf.
2. European Medicines Agency. Questions and Answers on biosimilar medicines (similar medicinal products). European Medicines Agency. [Online] September 27, 2012. [Cited: October 1, 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf. . EMA/837805/2011.
3. U.S. Food and Drug Administration. Guidance for Industry: Quality considerations in demonstration biosimilarity to a reference protein product. Washington DC: U.S. Food and Drug Administration, 2012

Biosimilars are not the same as generics

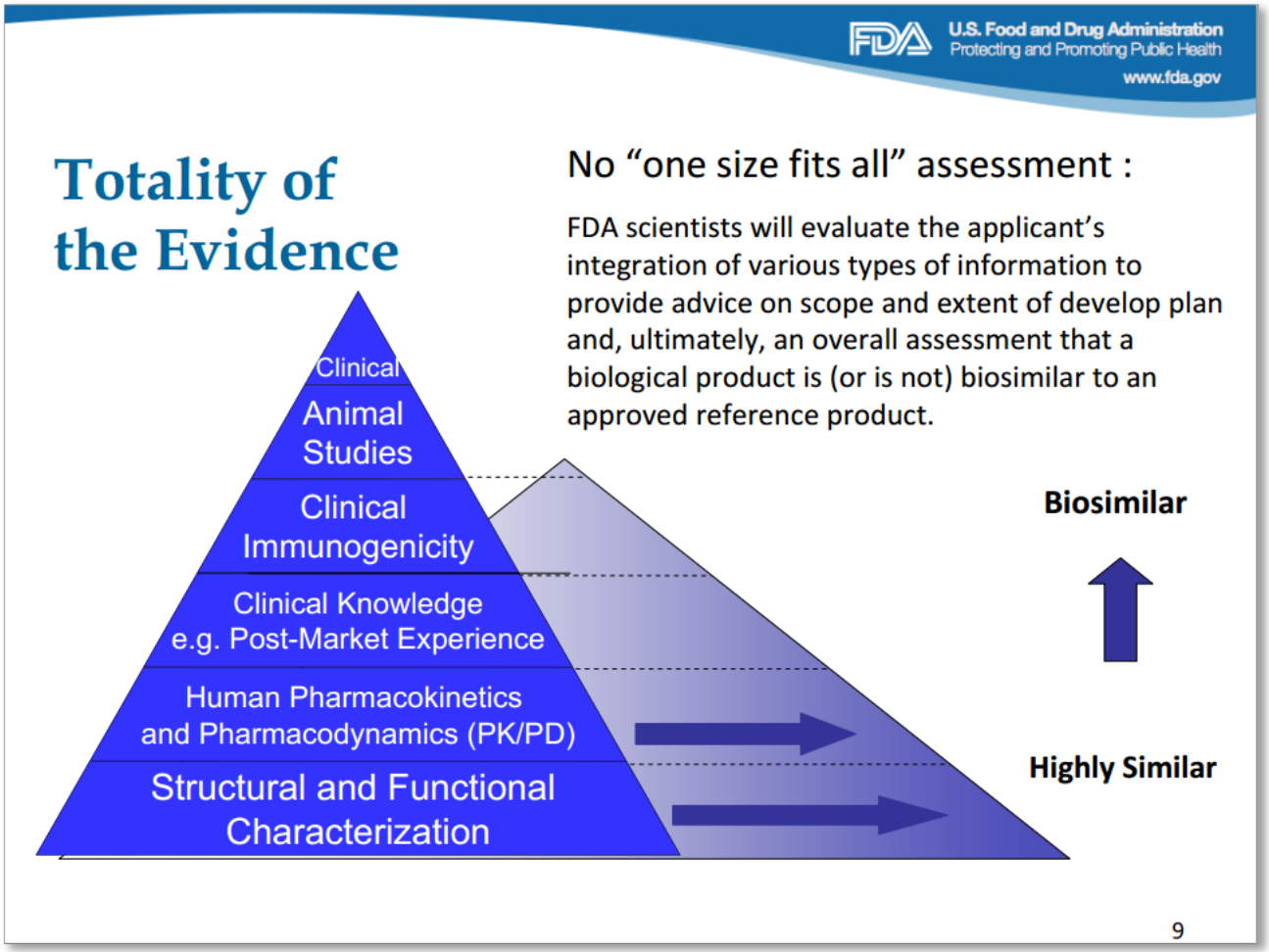
Biosimilars	Generics
Similar, not the same as reference product	Bioequivalent to branded product
Biologics Price Competition and Innovation Act	Hatch-Waxman Act
Approval will be through preclinical and clinical trials	Approval with ANDA demonstration of bioequivalence
Anticipated cost differential 20-30%	Cost differential can be as high as 90%
Considerable manufacturing expertise required (development cost of $30 to $100M)	Manufacturing expertise not as complex (development cost of $3M to $5M)
May have unique non-proprietary name	Generics from various manufacturers all have single generic name
Trade secrets, IP, cell lines, and manufacturing/purification/packaging information about reference product is not readily available	Easy to duplicate chemical formula of branded product; usually simple packaging
Biosimilar designation ≠ interchangeable (TBD)	Generic = interchangeable

Even if biosimilar uses the same human gene as the originator, *different process = different product*



Source: Biologics manufacturing process. From Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. Ann Oncol 2008;19:412–419; by permission of Oxford University Press.

In the US, extensive non-clinical and clinical evidence will likely be required for the relevant TA



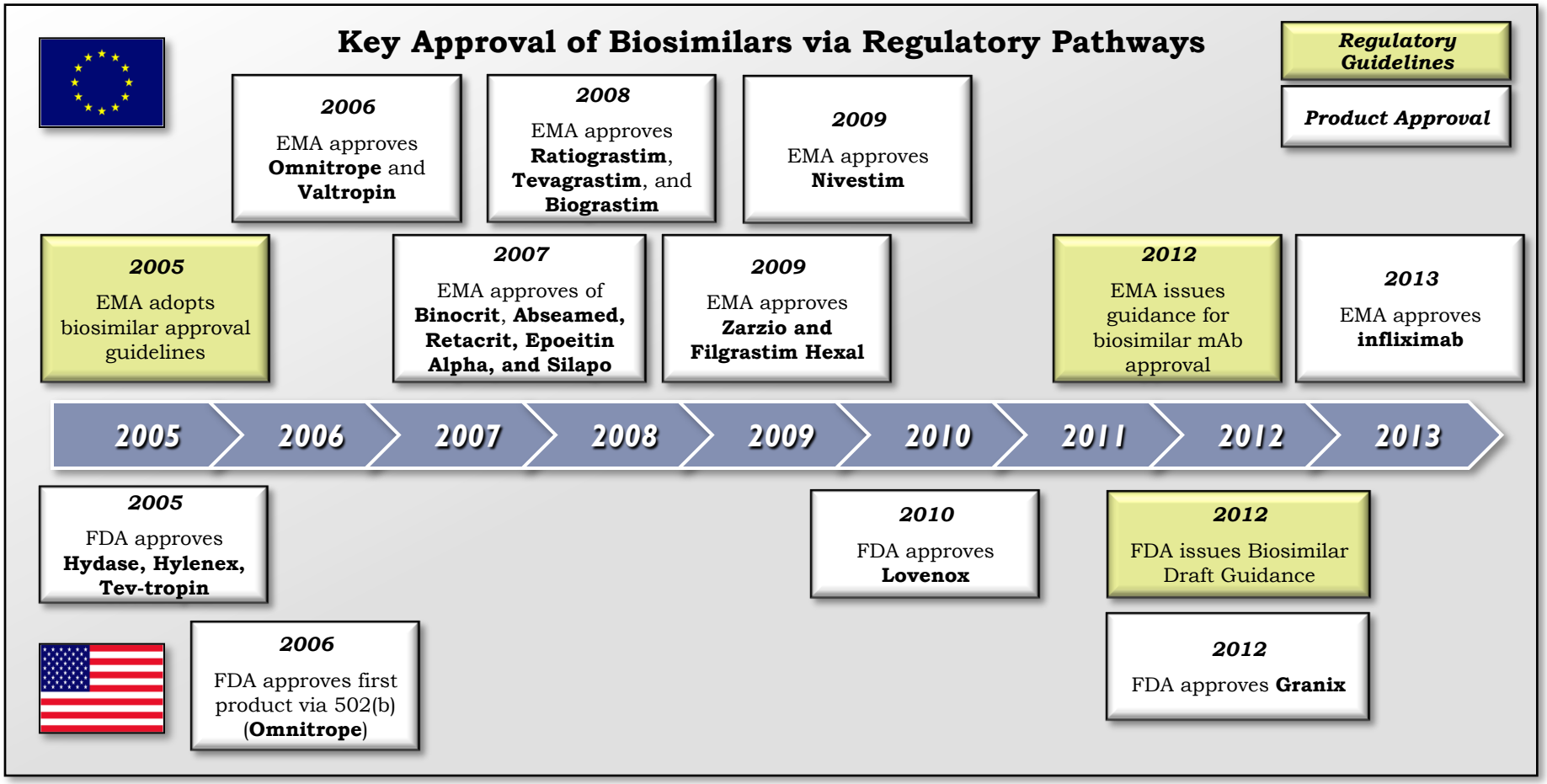
Technical Evidence

- Cell Line Quality
  - ✓ Host cell line
  - ✓ Transfection/amplification pool
  - ✓ Genetic set up of clone
- Manufacturing Process
  - ✓ Growth medium composition
  - ✓ USP type & regime
  - ✓ Culture history
  - ✓ Hold times
  - ✓ Storage
- Structure/Functional Characterization
  - ✓ Structure (e.g., peptide mapping)
  - ✓ Impurities (e.g., oxidation)
  - ✓ Biological Activity (e.g., binding)
  - ✓ Higher Order Structure
  - ✓ Post Translation Medication

Clinical Evidence

- Tailored toxicology, efficacy & safety in relevant species models
- PK/PD equivalence
- Biosimilarity, but not safety and efficacy de novo
- Post-Approval

The EU market for biosimilars is significantly less restricted than the US market

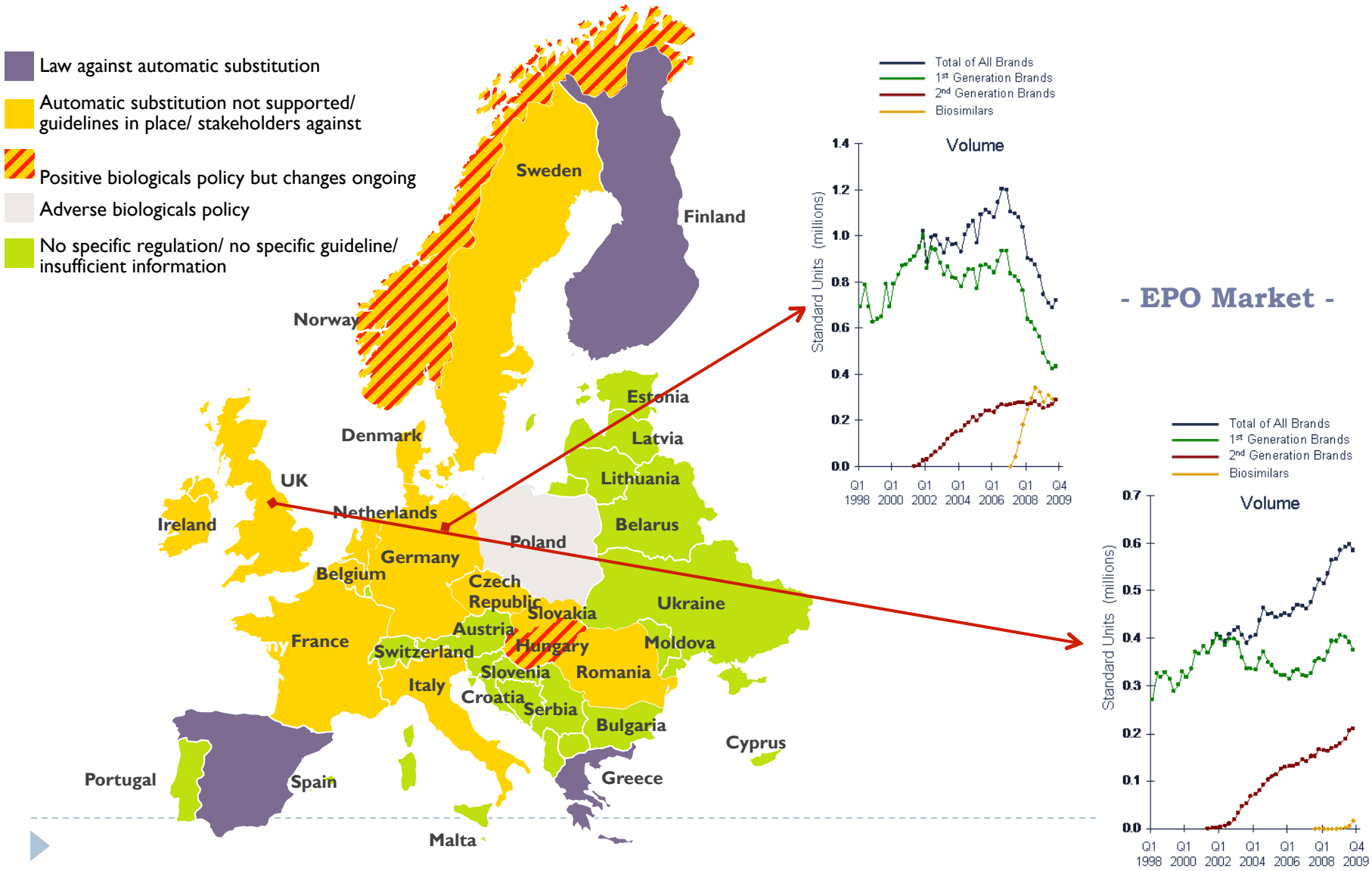


Source: GBI Research Market Research Report. July 2012. EMA. www.ema.europa.eu/. Fiercebiotech. www.fiercebiotech.com/. Manufacturer Press Releases. Accessed October 2012.

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**	Dissolved partnership with Lonza (Rituximab)
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 (current status unknown)								
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/ COHERUS AND							X (Coherus)		Three biosimilars in development with Momenta

Country-specific healthcare policies have had an impact on biosimilar adoption in the EU



Perceptions of biosimilars vary between US and EU physicians. Payers in both regions view biosimilars as a cost containment necessity

Physician Insights

- Physicians believe that **concerns about efficacy and safety** will be major factors in constraining the use of biosimilars but most expect to prescribe them within one year of launch.
- The majority of physicians agree that regulatory agencies should require manufacturers to **establish REMS programs** for both branded biologics and biosimilars.
- US physicians would be **most likely to prescribe "biobetter" drugs** that demonstrate improvements in efficacy, safety, or dosing.
- More **European physicians** than US physicians **believe that biosimilars and branded biologics are very similar** and have non-clinically significant differences.

Payer Insights

- **Payers view biosimilars as necessary to contain costs** and expect significant price discounts to incentivize uptake. EU payers anticipate branded price cuts to follow.
- Payers will likely **require more clinical information than what might be accepted by the FDA** for approval when evaluating biosimilar therapies due to concerns about efficacy and safety.
- Payers **perceive large biotechnology** companies as the **most trustworthy when developing a biosimilar** therapy.
- US payers expect **pharmacy-level substitution to be applied** to biosimilars within five years.

Source: Decision Resources Market Research; Campbell Alliance Insights 2012

The "simple" biosimilars will focus on creating a commodity market

Likely Biosimilar Go-To-Market Approach	"Simple" Biosimilar *(e.g., somatropin, filgrastim, epoetin alfa)*
Market Segmentation / Customer Analysis	➢ Focus on highly cost-sensitive markets, such as the hospital segments
Positioning & Messaging	➢ Develop corporate level confidence in safety, efficacy, and supply with all customers ➢ Message on simplicity of biologic structure and history of use in EU
Pricing & Contracting	➢ Discount up to 20% with contracting for key segments
Field Force	➢ Provide traditional sales and account management teams
Customer Support Services	➢ Develop baseline level of customer support services
Lifecycle Management	➢ --

In this market, the originators will maintain their pricing strategy and compete with contracting and value-added support services

Likely Brand Competitive Response	"Simple" Biologic *(e.g., somatropin, filgrastim, epoetin alfa)*
Market Segmentation / Customer Analysis	➢ ***Pre-launch:*** Focus on cost-sensitive markets with contracting ➢ ***Post-launch:*** Focus on clinically focused/evidence based markets
Positioning & Messaging	➢ ***Pre-launch:*** Focus on safety and confidence of overall brand performance ➢ ***Post-launch:*** Focus on history and safety of brand
Pricing & Contracting	➢ ***Pre-launch:*** Contract with cost-sensitive market ➢ ***Post-launch:*** Maintain pricing strategy and contract for continued access
Field Force	➢ ***Pre-launch:*** Target account management activities ➢ ***Post-launch:*** Continue field support
Customer Support Services	➢ ***Post-launch:*** Provide exceptional value added services and support
Lifecycle Management	➢ Pursue lifecycle management opportunities in advance of LOE

The "complex" biosimilars will focus on creating trust and seek payer / regulatory support

Likely Biosimilar Go-To-Market Approach	"Complex" Biosimilar *(e.g., monoclonal antibodies, botulinumtoxin, etc.)*
Market Segmentation / Customer Analysis	➢ Focus on highly controlled payer segments to direct use and physician segments focused on "cost recovery" model through buy and bill
Positioning & Messaging	➢ Develop corporate level confidence in safety, efficacy, and supply with all customers ➢ Target "interchangeability" and "extrapolation" of indications at approval
Pricing & Contracting	➢ Discount less than 20% with contracting for key segments
Field Force	➢ Provide traditional sales and account management teams with focus on field reimbursement specialists
Customer Support Services	➢ Develop significant level of customer support services
Lifecycle Management	➢ Investigate opportunities for development of "bio-betters"

In this market, the originators will focus heavily on safety messages lack of interchangeability

***Likely* Brand Competitive Response**	**"Complex" Biologic** *(e.g., monoclonal antibodies, botulinumtoxin, etc.)*
Market Segmentation / Customer Analysis	➢ ***Pre-launch:*** Message all customers on safety ➢ ***Post-launch:*** Focus on clinically focused/evidence based markets
Positioning & Messaging	➢ ***Pre-launch:*** Focus on "non-interchangeability" and ➢ extrapolation of indications ➢ ***Post-launch:*** Focus on history and safety of brand
Pricing & Contracting	➢ ***Pre-launch:*** Contract with cost-sensitive payers ➢ ***Post-launch:*** Maintain pricing strategy and contract for continued access and volume discounts
Field Force	➢ ***Pre-launch:*** Target physician customers with messaging strategy ➢ ***Post-launch:*** Continue field support with focus on complexity of biologics
Customer Support Services	➢ ***Post-launch:*** Provide exceptional value added services and support
Lifecycle Management	➢ Pursue lifecycle management opportunities in advance of LOE ➢ Focus on new administration devices and extended release formulations (in chronic therapeutic areas)

Conclusions

US Regulatory Approval	• Success or failure of biosimilars will be heavily dependent on FDA determination of interchangeability designation, as well as on the extrapolation of indications at approval
Commercialization	• Biosimilars should be considered similar to branded biologics in that traditional commercialization strategies and tactics will be required for success
Pricing & Contracting	• Unlike in the EU market, biosimilars are not expected to enter the market at significant pricing discounts to originators given the marketing spends that will be required for success
Uptake	• Overall biosimilar use will likely be slow and require significant time in the market to develop the confidence needed to drive utilizaiton