Drug Discovery, Development, & Commercialization, 2013

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Overview

- Intellectual Property & Patents
- Biologics Market
- Follow on Biologics & Biosimilars
  - What are they?
  - Are Biosimilars needed?
  - Who are the players?
  - Where are we today?

Intellectual Property & Patents

Provide legal protection for inventors in order to prevent other people from making use of their ideas

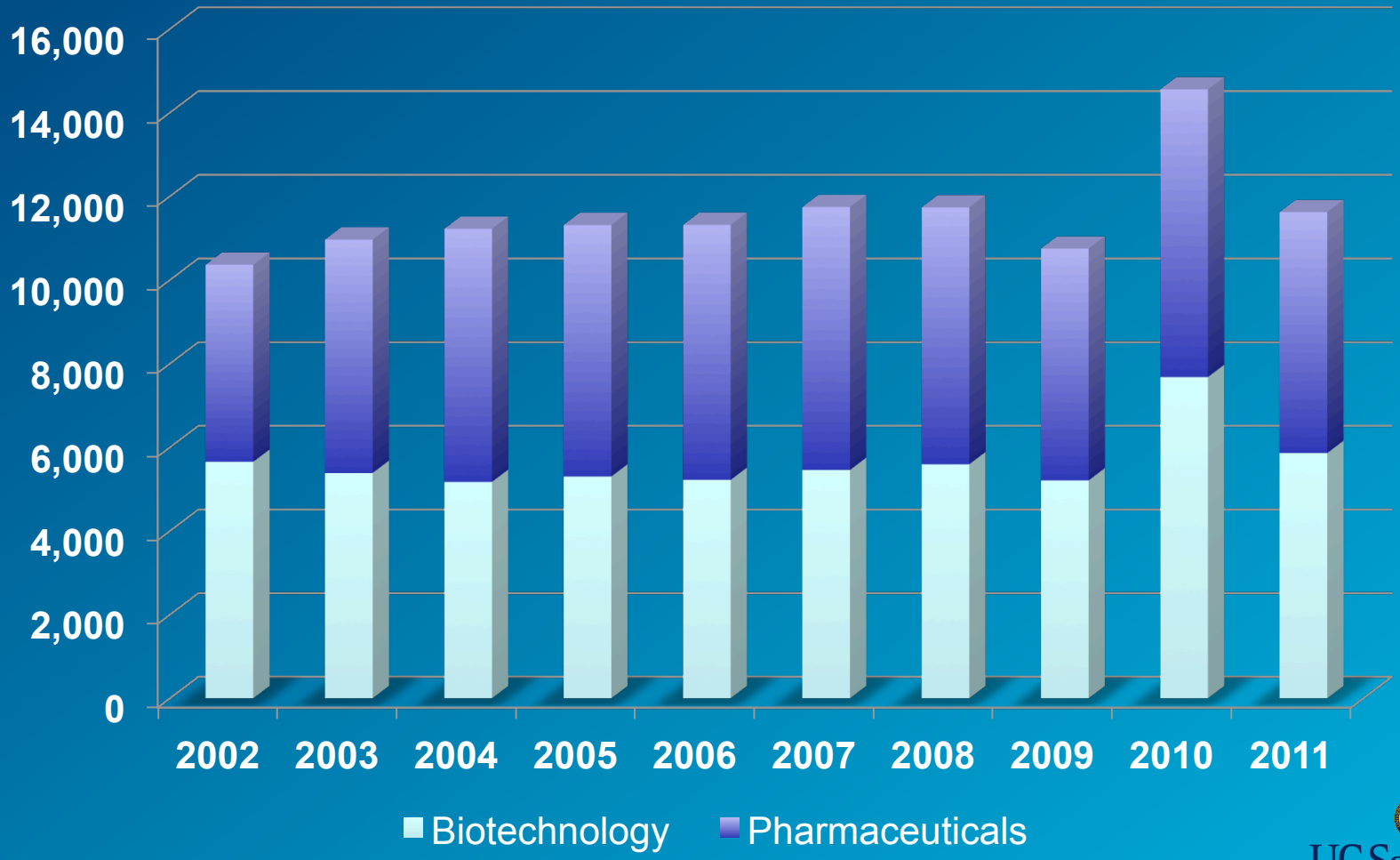
- Exclusive right to a particular invention
- Granted by states or governments to inventor
- Holder has sole rights over invention for a specified period of time
- Invention for patent must be disclosed to the public
- United States Patent & Trading Office (USPTO) *www.uspto.gov*
  - Issue patents & trademark registration
  - To inventors and businesses in order to identify a product or any intellectual property
- European Patent Office www.epo.org

Pharmaceutical Patents

- **Product Patent or Composition of Matter Claim: Novel Drug**
  - Claims active chemical substance, a new chemical entity
  - Either by chemical name, structure, or both
- **Product by Process Patent**
  - Process used to manufacture the drug when the drug is made by the patented process
  - But drug can be made, sold if another company can devise commercially viable process not covered in patent
- **Process patent**
  - Claims chemical or other process used to manufacture the drug
- **Formulation patent**
  - Claims the pharmaceutical dosage form on the drug
- **Method of use**
  - Use of the drug to treat a specific disease

SOURCE: U.S. PTO http://www.uspto.gov/

European Patent Applications 2002-2011



http://www.epo.org/about-us/statistics/patent-applications.html

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America Invents Act (A.I.A.)

President Barack Obama signs America Invents Act on Sept 16, 2011

Sept 2012 US Senate final approval, major reform of the US patent laws

- America Invents Act: **"FIRST TO FILE"**
  - Changes method for determining priority for patent applications to a "first to file" system from "first to invent"

- A.I.A. changes patent system in profound ways
  - Evaluating pre-filing publication of research
  - Adapting to the first-to file law
  - Developing prosecution techniques to ensure timely filings that result in robust patents

SOURCE: U.S. PTO http://www.uspto.gov/aia_implementation/index.jsp

Bayh-Dole Act (U.S. Public Law 96-517)

- University may elect to retain title to inventions developed under federally-funded research programs
- University grants royalty-free, nonexclusive license to government
- Any company holding an exclusive license must substantially manufacture the product in the U.S.
- In marketing of an invention, University must give preference to small business firms (< 500 employees)
- University must share with the inventor(s) a portion of any revenue received from licensing

(Sources: http://www.ucop.edu/ott/faculty/bayh.html

Hatch-Waxman Act

- Legalized generic competition for drugs
- 180-day of exclusivity to first generic drug maker (GDM) to file for approval of generic copy
- GDM can file lawsuit to challenge brand-name drug's patent
- Brand-name drug companies take advantage of that law
  - Originator usually settles patent suit by getting the GDM to agree to stay out of the market for a period of time
  - That first GDM also has exclusivity rights, no other generic companies can enter the market for 180 days

The Hatch-Waxman Act does not apply to biologics

Source: http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf

Pay-for-delay Process

- "Pay-for-delay" process has previously been used to:
  - Maintain market monopoly
  - Maximize possible sales of the brand-name drug
  - Delay generic alternative to enter the market

- Friday, December 7 2012 Supreme Court said it would decide whether a pharmaceutical company should be allowed to pay a competitor millions of dollars to keep a generic copy of a best-selling drug off the market

- Three judges of US Court of Appeals for the Third Circuit ruled that
  - Payments made by pharmaceutical companies to generic competitors to delay bringing their drug to market
  - Considered as evidence of an unreasonable restraint of trade

Source: Fierce Biotech

Case: "Pay-For-Delay"

- In 1995, Upsher-Smith Laboratories and ESI Lederle, generic manufacturers, submitted generic approval applications with FDA claiming that their formulations did not infringe the patent held by Schering-Plough
- Schering sued, alleging that the generic products did in fact infringe
- Before Federal District Court issue an opinion, the parties settled
- **Schering paid Upsher $60 million for various things, including an agreement to drop the suit, and it paid ESI Lederle $15 million**

Source: Fierce Biotech

Biologics Market

Biologics vs. Conventional Drugs

New Molecular Entity Drugs	Biologics
Small Molecules (~500 molecular weight)	Large molecules (>5000 molecular weight)
Chemically synthesized	Biotechnologically produced or isolated from living sources
Simple well-defined structure	Complex structure/mixtures (tertiary structure, glycosylated)
Less target specificity	High target specificity
Oral administration possible (pills)	Generally parenteral administration (intravenous)
Generally not or unpredictably antigenic	Can stimulates the production of an antibody

Top Selling Biologics Peak Years

Generic Name	Brand®	Companies	Primary Indications	Sale $b	Peak Year
Adalimumab	Humira	Abbott	Autoimmune diseases	9.27	2012
Etanercept	Enbrel	Amgen, Pfizer, Takeda	Autoimmune diseases	8.37	2012
Rituximab	Rituxan	Roche	Autoimmune diseases	7.2	2012
Infliximab	Remicade	J&J, Merck, Mitsubishi	Autoimmune diseases	7.67	2011
Bevacizumab	Avastin	Roche	Colon, lung, renal cancer	6.22	2010
Trastuzumab	Herceptin	Roche	HER-2 + breast cancer	5.95	2011
Insulin glargine	Lantus	Sanofi	Diabetes	5.45	2011

Source: Annual reports, Fierce Biotech http://www.fiercepharma.com/special-reports/15-best-selling-drugs-2012

Autoimmune diseases: Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriasis, Psoriatic arthritis, Crohn's Disease; Ulcerative Colitis, Ankylosing Spondylitis, Respiratory syncitial virus
Cancer: Non Hodgkin's Lymphoma, Breast cancer

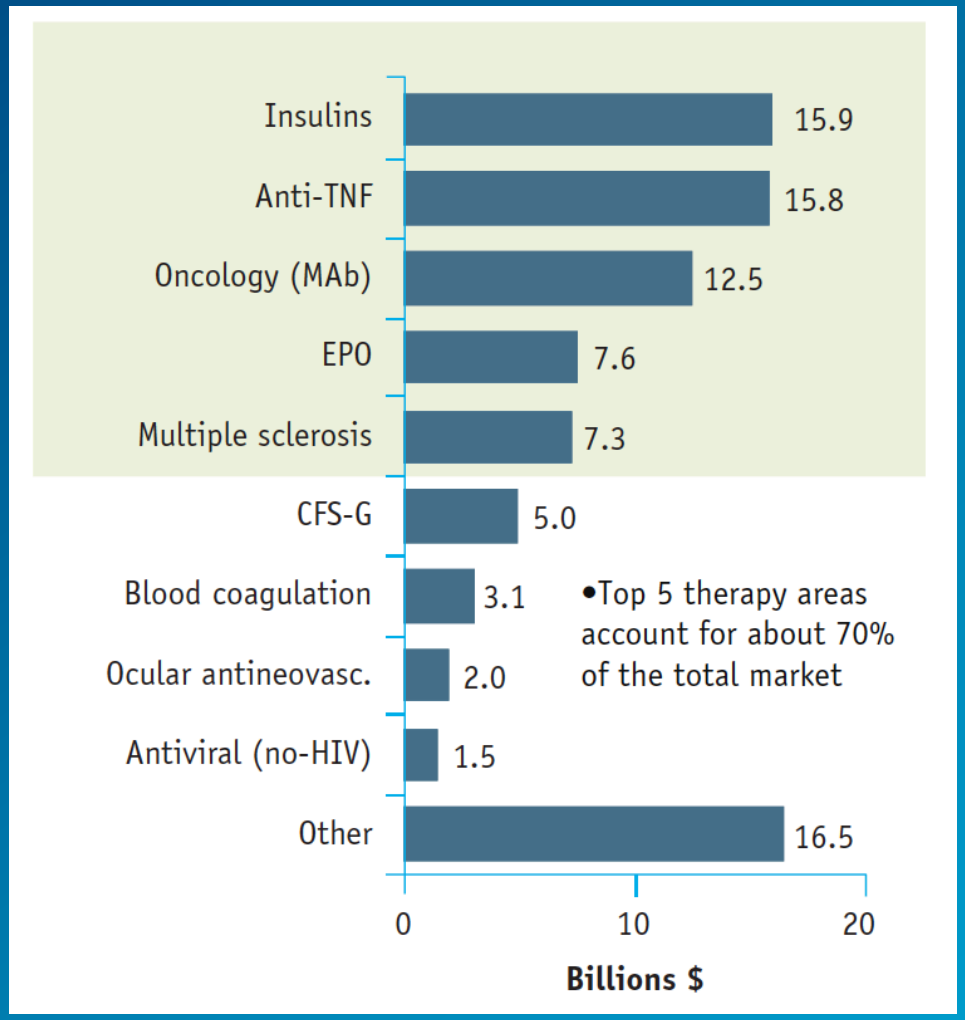
Growing Demand for Biologics

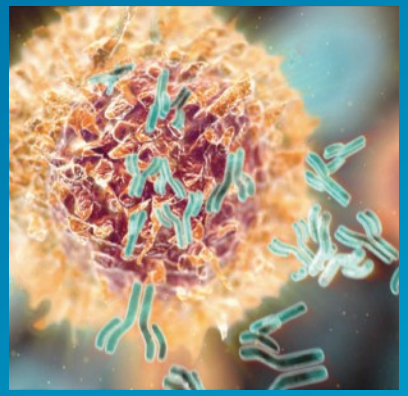
- Find cost-effective alternatives to biologics reflects growing demand
- Since 1980s, biologics prospered into US$138 billion market (2010)
- Fuelled by recombinant insulins, human growth hormone, recombinant tissue plasminogen activators (r-tPAs) alteplase, erythropoietins, granulocyte colony stimulating factors, monoclonal antibodies and others…
- Account for 16% of global pharmaceutical expenditure, significantly outpacing total branded sales
- Patent of expiries driving new potential

SHAPING THE BIOSIMILARS OPPORTUNITY • December 2011, IMS Health

Forefront of New Wave in Cancer, Diabetes, & Rheumatoid Arthritis

Core Therapy Areas for Biologics (MAT 12/2010)





Source: IMS Health

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Biosimilars

- What are they?
- Are Biosimilars needed?
- Who are the players?
- Where are we today?

Definition: Biosimilar in the U.S.

Biologics Price Competition & Innovation Act of 2009

A biosimilar is a biological product that is highly similar to a US-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.

Source: United States Food and Drug Administration
Biologics Price Competition and Innovation Act of 2009:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf

European Medicines Agency Biosimilar Regulatory Basis for Approval

- Focus on demonstration of bio-similarity
- Extensive comparability exercise to ensure similar quality, safety and efficacy
- Intended to be used at same dose & dosing regimen as reference product
- Similar physicochemical characteristics prerequisite for reduction in non-clinical and clinical data requirements

Source: European Medicines Agency: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/12/WC500099907.pdf

Biosimilar in the US

February 10, 2012 FDA announced three draft guidance documents on biosimilar product development to assist industry in developing such products in the US

- Scientific considerations, demonstrating biosimilarity to reference product[1]
- Quality considerations: demonstrating biosimilarity to reference protein product [2]
- Biosimilars: Q&A regarding implementation of the Biologics Price Competition and Innovation Act of 2009[3]

1 www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

2 www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf

3 www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf

Biosimilar User Fee Act (BsUFA)

- The Federal Food, Drug, and Cosmetic Act, as amended by the Biosimilar User Fee Act of 2012
- Authorizes FDA to assess & collect fees for biosimilar biological products from October 2012 through September 2017
- FDA dedicates these fees to
  - Expediting the review process for biosimilar biological products
- Biosimilar biological products represent important public health benefit
- Potential to offer life-saving or life-altering benefits at reduced cost to the patient
- BsUFA facilitates the development of safe and effective biosimilar products for the American public

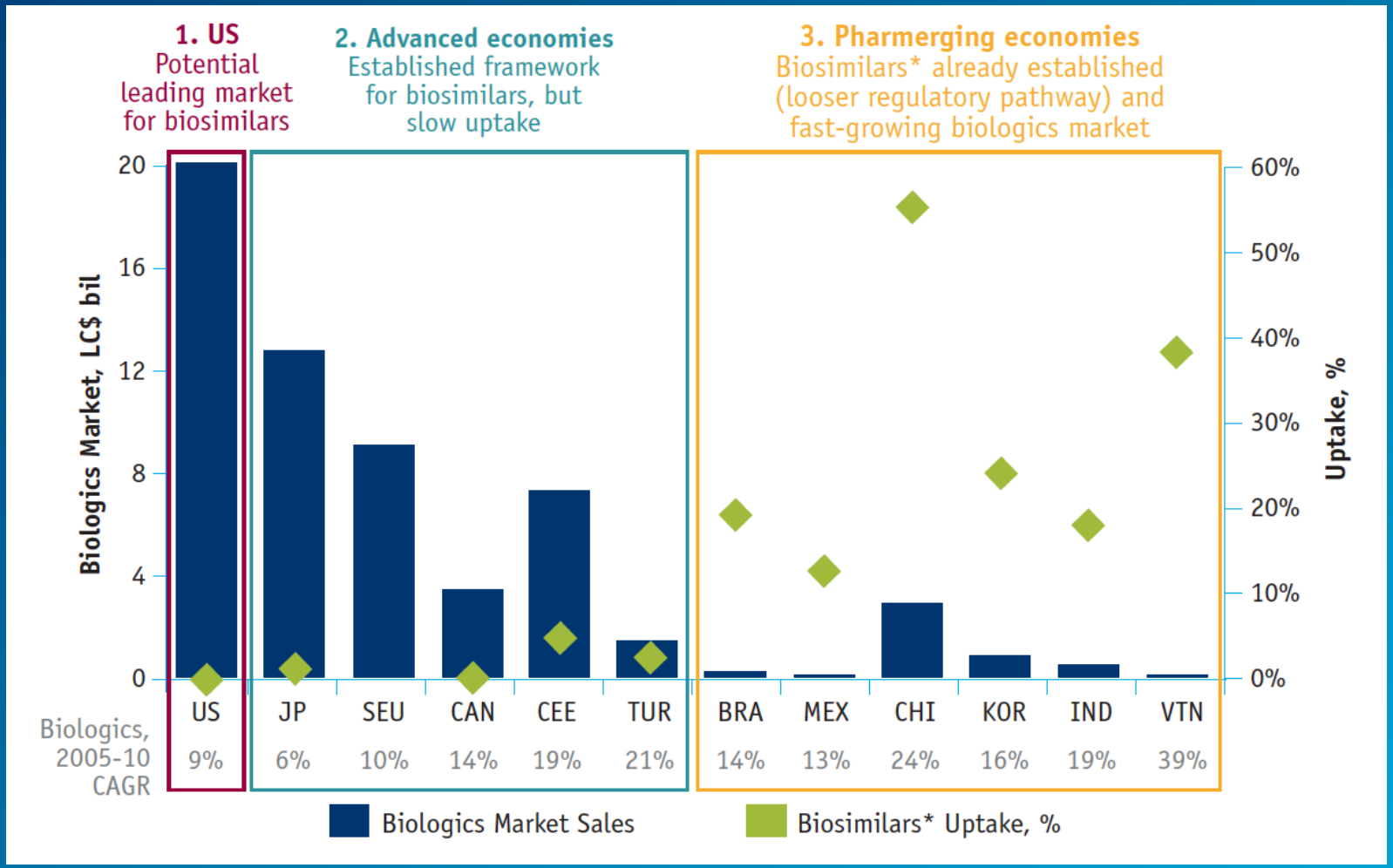
http://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm

Biosimilars Challenges

- Verification of the similarity
- Interchangeability of biosimilars and innovator products
- Possible need for unique naming to differentiate the various biopharmaceutical products
- New regulatory framework
- Commercial opportunities as well as guidelines to assist manufacturers in product development
- Intellectual property rights
- Public safety

Source FDA: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf

Geographical Clusters for Biosimilars



- Biosimilars in Europe and Japan defined by regulatory pathway
- Pharmerging markets approval processes apply for products that resemble biosimilars

Source: IMS Health: http://www.imshealth.com/ims/Global/Content/Home%20Page%20Content/IMS%20News/Biosimilars_Whitepaper.pdf

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Data vs. Market “Exclusivity" in Blockbuster Scrap Over Biosimilars

Divergent positions on the Biosimilar Bill :

- CVS, Aetna, AARP and other payers say that the bill allows for:
  - 4 years of data exclusivity and
  - 12 years of market exclusivity
  - Translate Biosimilar therapy on the market right at the end of the 12-year cap

- Original Biotech developers are saying:
  - 12 years of data exclusivity
  - Prevent biosimilar developers from accessing data for 12 years
  - Significantly delay the entry of competing products, keeping the competition at bay

Governments Use Primarily Pharmacists & Prescribers to Use Generic Drugs

	Policy interventions	UK	GERMANY	SWITZERLAND	SPAIN	FRANCE	CANADA
Physicians	Prescribing controls promote generics	Yes	Yes	Yes	Yes	Yes	Yes
	Prescribing by generic brand	No	No	Yes	No	No	No
	INN prescribing mandatory?	No	No	No	Yes	No	No
	INN prescribing common practice?	Yes	Yes	Yes	Yes	No	No
	Financial reward	Yes	No	No	No	Yes	No
Pharmacists	Substitution allowed	No	Yes	Yes	Yes	Yes	Yes
	Dispensing without prescription	No	No	No	No	No	No
	Financial reward	Yes	Yes	Yes	Yes	Yes	Yes
Low cost generic market (unbranded medicines in volumes out of total generic market)		80%	82%	60%	61%	62%	81%

Impact on generic use

Positive

Negative

Source: IMS Health

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Biosimilars

- What are they?
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Cost Pressures & Patent Expiration

- Financial crisis required healthcare systems to make significant and sustained cost reductions
- Payers in the mature markets
  - Limited economic growth and pressures on healthcare
  - Make the patent cliff a true generic dividend
  - Enable savings to be realized to governments, and patients

In the next five years top-selling biologic brands Herceptin, Enbrel, Humalog, MabThera, Remicade and Aranesp will lose product patent protection

Biologics Prices Into the Stratosphere

- **Soliris, mAb (Alexion) $409,500**
  - Paroxysymal nocturnal hemoglobinuria: Immune system destroys red blood cells at night in 8,000 Americans
- **Elaprase: $375,000 each year**
  - Hunter syndrome, inherited disease caused by a lack of the enzyme iduronate sulfatase
- **Naglazyme, (BioMarin) $365,000**
  - Enzyme replacement therapy for the treatment of muco-polysaccharidosis VI, inherited lysosomal storage disorder
- **Kalydeco, (Vertex) $294,000**
  - First cystic fibrosis drug to address the disease's cause, rather than just its symptoms

Source: http://www.fiercepharma.com/story/how-do-12-priciest-drugs-us-stack/2012-02-07

US National Health Expenditures

- In 2008 NHE $2.3 trillion accounting for 16.2% of national gross domestic product (GDP).
- In 2010 $2.6 Trillion
- In 2019 $4.5 Trillion estimates
- America spends an average of $7,681 per capita annually on healthcare
  - Double that spent by most other industrialized countries

http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf

US: National Census Bureau: National Health Expenditures--Summary, and Projections

BioSimilars Are they Needed?

- By 2015 biologics worth $60 B in annual sales will lose patent protection
- Medicare paid more than $2 B for 3 anti-anemia biologics in 2009
- State pension funds in California and Ohio have called for early access to generic biologics to save money
- New Health-care law doesn't specify "market" or "data" exclusivity

Fierce Biotech, Feb, 2011

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Biosimilars & Follow on Biologics Some of the Players

- Teva in Israel
- Dr. Reddy, Ranbaxy, & BioCon in India
- Sandoz (Novartis), BioPartners in Switzerland
- Merck, Pfizer in the US
- Stada (through Bioceuticals) in Germany

Source: Fierce Biotech

Biosimilars More Players

- Actavis (Watson & Actavis Grp) HQ in Zug, Switzerland
  - Scouring emerging markets for a partner to help it copy complicated biotechnology medicines such as Roche's $7.7B Avastin
  - World's third-largest generic pharmaceutical company
  - Committed to developing & marketing biosimilars products in Women's Health, Oncology and other therapeutic categories

Source: Fierce Biotech
http://www.actavis.com/en/About/Company_Profile.htm

Samsung Group, Quintiles Plan $266 Million Venture to Make Biologic Drugs

- In May, 2011 Samsung set aside $266 for biosimilars
- Samsung Group will also develop biosimilars and begin producing them in 2016 starting with Rituxan
- Rituxan has patent protection in the U.S. until 2018 and in the rest of the world through 2013

Fierce Biotech: http://www.fiercebiotech.com/story/samsung-quintles-team-266m-biosimilars-deal/2011-02-25

Biosimilar Deals: Observations

- Deal making is accelerating in 2011-12, two kinds of deals
- First Kind:
  - **Partner A** = Tier I biopharm with large patent portfolio in large molecules (Amgen, Biogen)
  - **Partner B** = Capital provider with strategic interest (Watson, Samsung)
- Second Kind
  - **Partner A** = Tier 2/3 biopharm with more limited patent portfolio in large molecules (Hanwha, KHK)
  - **Partner B** = Capital provider with strategic interest (Merck, Fuji)

Few Biosimilar Deals 09 - mid 2012

PARTNERS	DATE	VALUE	NOTES
Merck Serono ➔ Dr. Reddy	June 2012	NA	50/50 cost sharing; DRL will manage development through phase II studies Merck Serono will manage development from phase III forward Merck Serono will manufacture from phase III forward
Kyowa Hakko Kirin ➔ FujiFilm	March 2012	ND	Will launch phase I study of Humira adalimumab biosimilar in 1H13 "One new biosimilar to clinic each year" KHK contributes toolbox, IP and manufacturing, Fuji contributes capital
Biogen Idec ➔ Samsung	Dec. 2011	$300 MM	15/85 JV = $45 MM/$255 MM Biogen Idec option to increase ownership up to 49.9% Samsung Biologics responsible for manufacturing Biogen Idec branded Rx NOT included
Amgen ➔ Watson Pharm.	Dec. 2011	$400 MM	Oncology-specific Mabs for WW development & commercialization Amgen responsible for development and manufacturing Watson puts in $400 MM for development Amgen provides its toolbox & IP; NO Amgen branded Rx
Hanwha ➔ Merck	June 2011	$720 MM	Focused on Enbrel etanercept biosimilar in phase III studies (Korea) Merck responsible for worldwide clinical development, manufacturing Hanwha has right to develop/commercialize in Korea and Turkey Merck has worldwide rights to commercialize outside of Korea, Turkey
Biocon ➔ Mylan	June 2009	ND	Biosimilars of Herceptin trastuzumab, Neulasta pegfilgrastim, Avastin bevacizumab, Humira adalimumab, Enbrel etanercept Biocon provides tools and manufacturing. Mylan provides ex-India regulatory and commercial capabilities

*Others include Coherus-Daiichi Sankyo (2012), Momenta-Baxter (2011), and Celltrion-Hospira (2009).

Biosimilars

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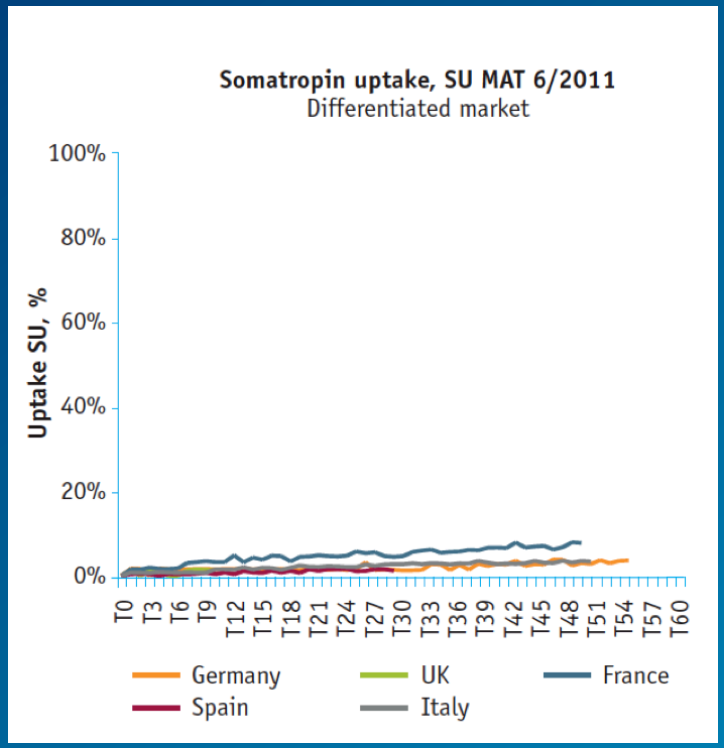
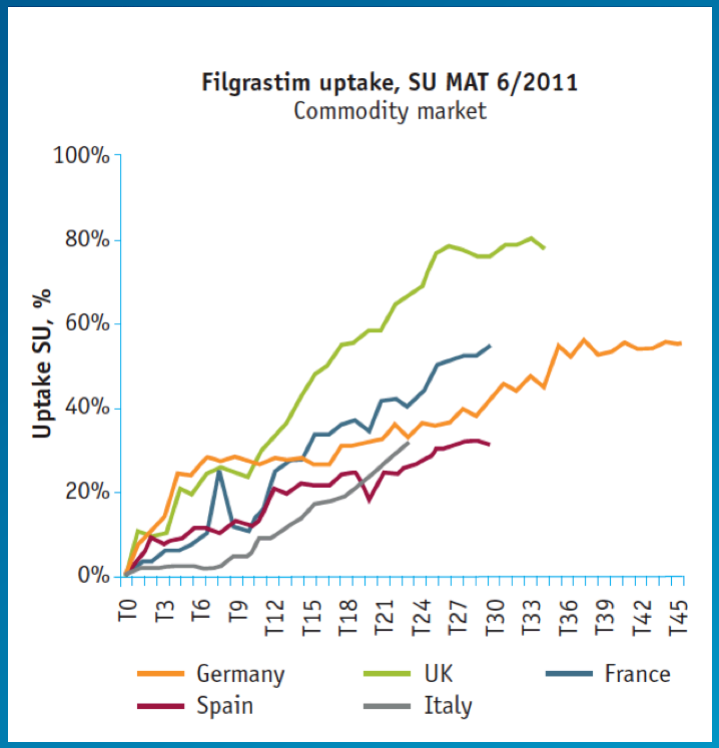
In Europe

Two Uptake Patterns for Biosimilars





Differentiated Market: ex: Somatropin, value proposition is high and market is driven by price

Versus

Commodity Markets: ex: G-CSF; access is mostly controlled by payers and product limited intrinsic value

- Biosimilars have been on the market in Europe since 2006
- First wave of Biosimilars had limited success, compared to uptake of small molecule generics (SMG
- Limited price reductions for Biosimilar :
  average list price cuts ~ 30% vs SMG ~70%-80%

Source: IMS Health; Shaping the Biosimilars Opportunity, Dec 2011
http://www.imshealth.com/ims/Global/Content/Home%20Page%20Content/IMS%20News/Biosimilars_Whitepaper.pdf

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In the United States of America

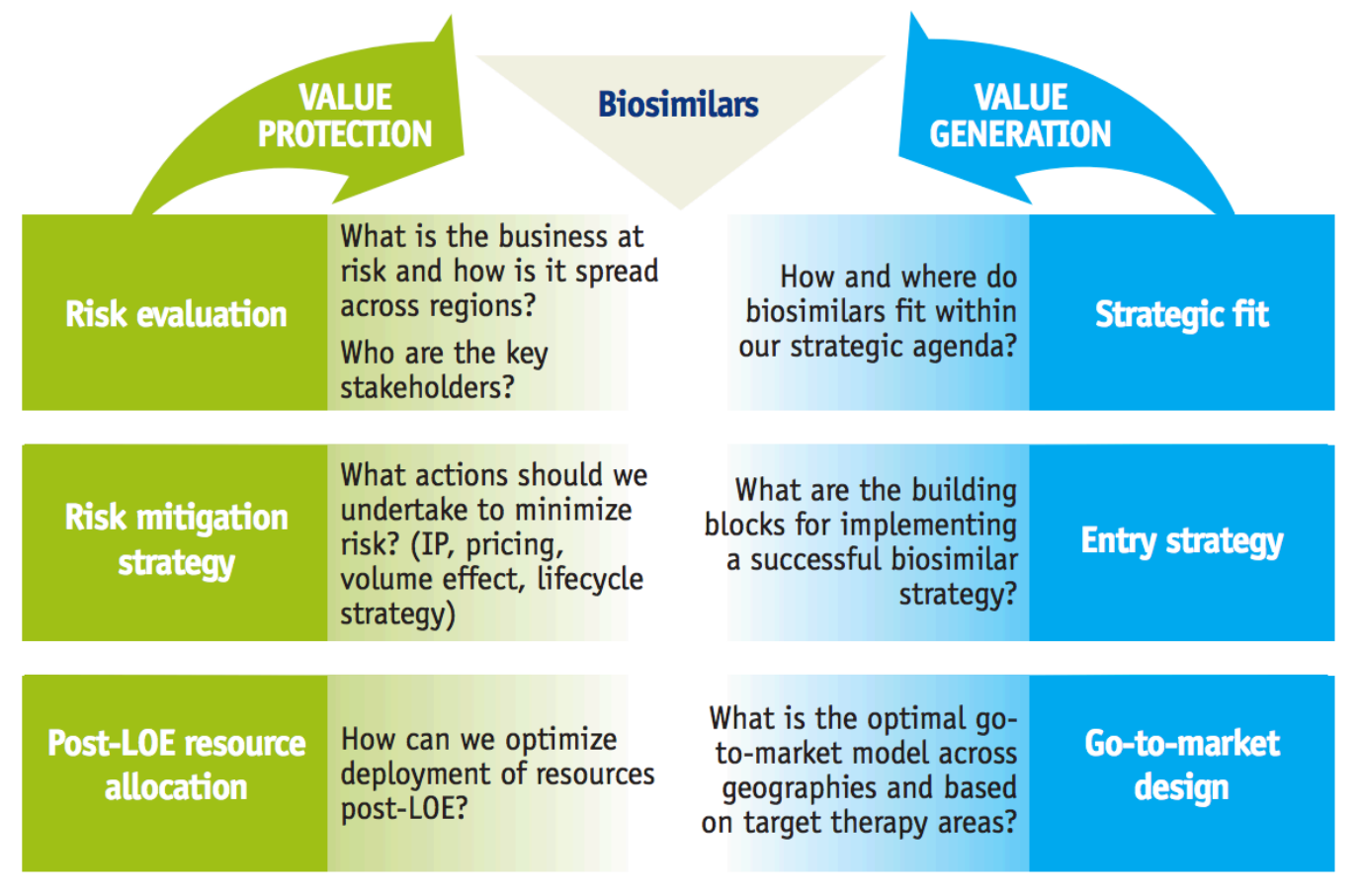
- Companies File Petitions with FDA To Prevent Biosimilars
  - Abbott Laboratories: Filed a citizen's petition with FDA
  - Asks agency not to approve any biosimilar for its Humira treatment for rheumatoid arthritis
  - Argues that, FDA would have to use trade secrets submitted to the agency when approval for Humira was first sought

- Protection Bills:
  - Jan 29, 2013 Amgen, Genentech/Roche push blockbuster protection bills in multiple states
  - Sponsoring legislation in several states to prevent pharmacists from being allowed to swiftly substitute a less expensive biosimilars
  - Winning one vote in the Virginia House of Delegates

March 23, 2010 Biologics Price Competition and Innovation (BPCI) Act was signed into law, giving FDA the authority to approve biosimilars

Source FierceBiotech http://www.fiercebiotech.com/story/amgen-genentech-push-blockbuster-protection-bills-states/2013-01-29#ixzz2JO8cWB1s

Biosimilars Two Different Perspective: Value Protection vs Creation



Source: IMS Health; Shaping the Biosimilars Opportunity, Dec 2011
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To Successfully Exploit Biosimilars Opportunity

FIT WITHIN STRATEGIC AGENDA	NEW GEOGRAPHIC OPPORTUNITIES	NEW THERAPEUTIC OPPORTUNITIES	INVESTMENT AND INFRASTRUCTURE FOR SUCCESS
• How do biosimilars **fit within** a company **strategic agenda**? - Portfolio synergies - Financial suitability - Synergies within the value chain (R&D, manufacturing, sales & marketing) • What are the **financial upsides and risks** of investing in biosimilars? • In **which therapy areas** to pursue this strategy? • How to **develop** a successful biosimilar **entry strategy**?	• The **US** is the biggest biologics market: how to enter it successfully when the biosimilar opportunity opens up? • What **other countries** offer new opportunities for biosimilar markets, and how to enter? • How to maximize uptake in the **EU** landscape? • What are **the likely competitive scenarios** (originators/other biosimilar competitors)? • What are **key drivers and barriers to manage stakeholders** across geographies and how to deal with them (e.g. Branded approach, DTC)?	• **Which biosimilar therapeutic markets** will be the most attractive? • What are the **likely barriers to entry**? - Investment levels (e.g. Marketing capabilities, device)? - Stakeholder management? - Market access approach? (e.g. Pricing, development of the appropriate clinical package) - Launch preparation?	• What is the **optimal go-to -market model** for a successful biosimilars business? - Integration and synergies with existing business - Partnership and strategic alliances • What **skillsets and resource levels** will be needed, internationally and locally, to address new geographic and therapeutic markets? • What **Key Performance Indicators** should be used to manage and measure the business?

Go or no Go **Optimal Approach**

Source: IMS Health; Shaping the Biosimilars Opportunity, Dec 2011
http://www.imshealth.com/ims/Global/Content/Home%20Page%20Content/IMS%20News/Biosimilars_Whitepaper.pdf

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