ECRON ACUNOVA

OMICS Group

Accelerating Pharma time-to-market, cost effectively



Asia



Europe



Americas

POTENTIAL VALUE OF BIOSIMILARS

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3rd INTERNATIONAL CONFERENCE AND EXHIBITION ON BIOWAIVERS, BIOLOGICS AND BIOSIMILARS

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Biosimilars…

The World Health Organization describes biosimilars (which they refer to as Similar Biotherapeutic Products (SBPs) as

“a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product”



What's in the Name?

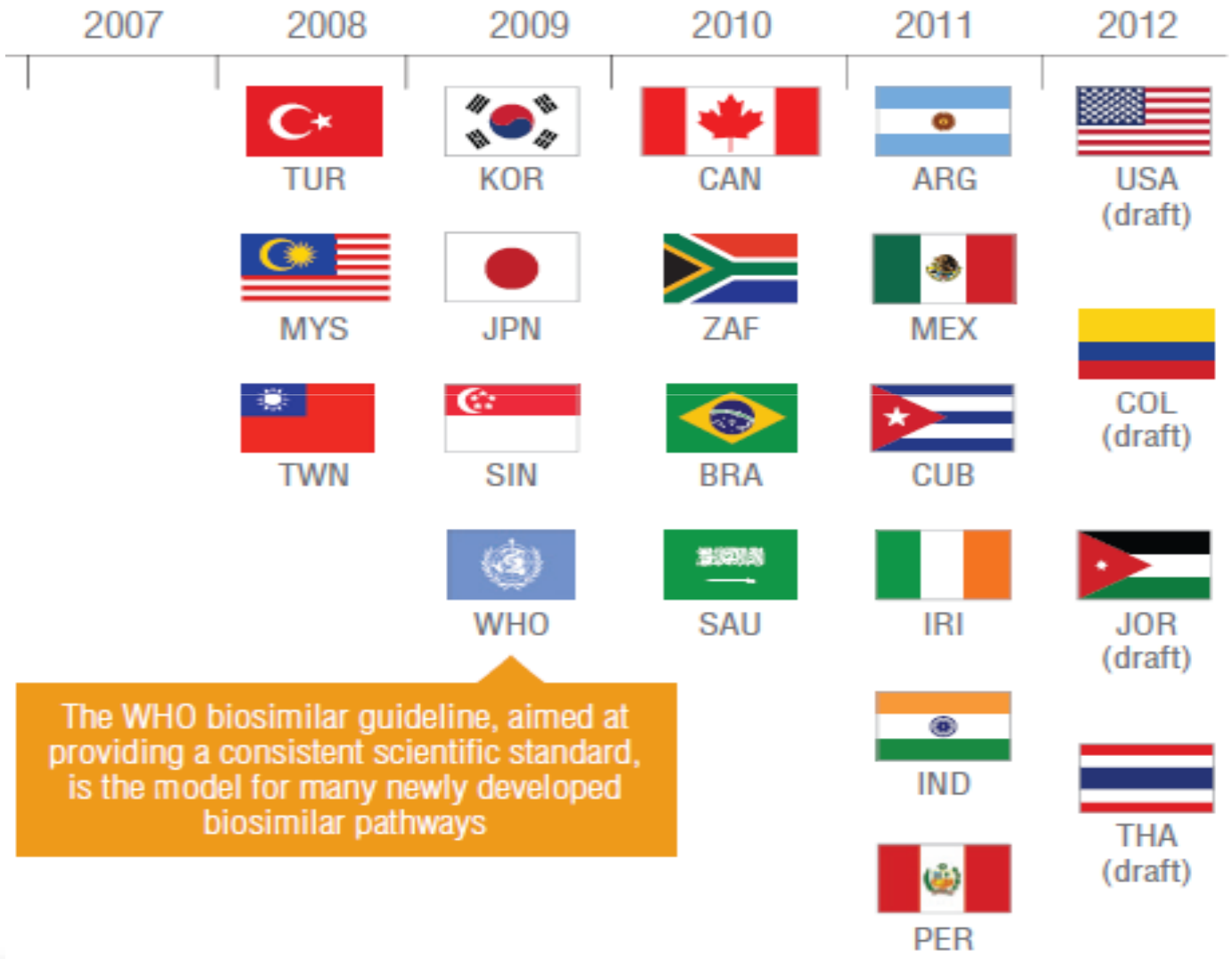
- ~~Biogeneric~~
- ~~Generic biologic~~
- ~~Multisource product~~ / Me-too

Biosimilar …. Europe, Australia, Malaysia, Singapore, etc.
Subsequent entry biologic (SEB) …. Canada
Similar biotherapeutic products (SBPs) …. WHO
Known biological product (KBP) …. Cuba
Follow-on biologic (FOB) ….. Japan *(*label Omnitrope BS)*, USA
Biological products …… Brazil

Key points

- A biosimilar is a copy of a biopharmaceutical for which patent protection no longer applies
- A biosimilar is comparable with the selected reference product in terms of quality, safety and efficacy
- A biosimilar is **not a generic** biopharmaceutical
- Biosimilar is also a regulatory pathway

Biosimilar Regulations/ Guidelines Development



Regulatory Framework – A Comparison

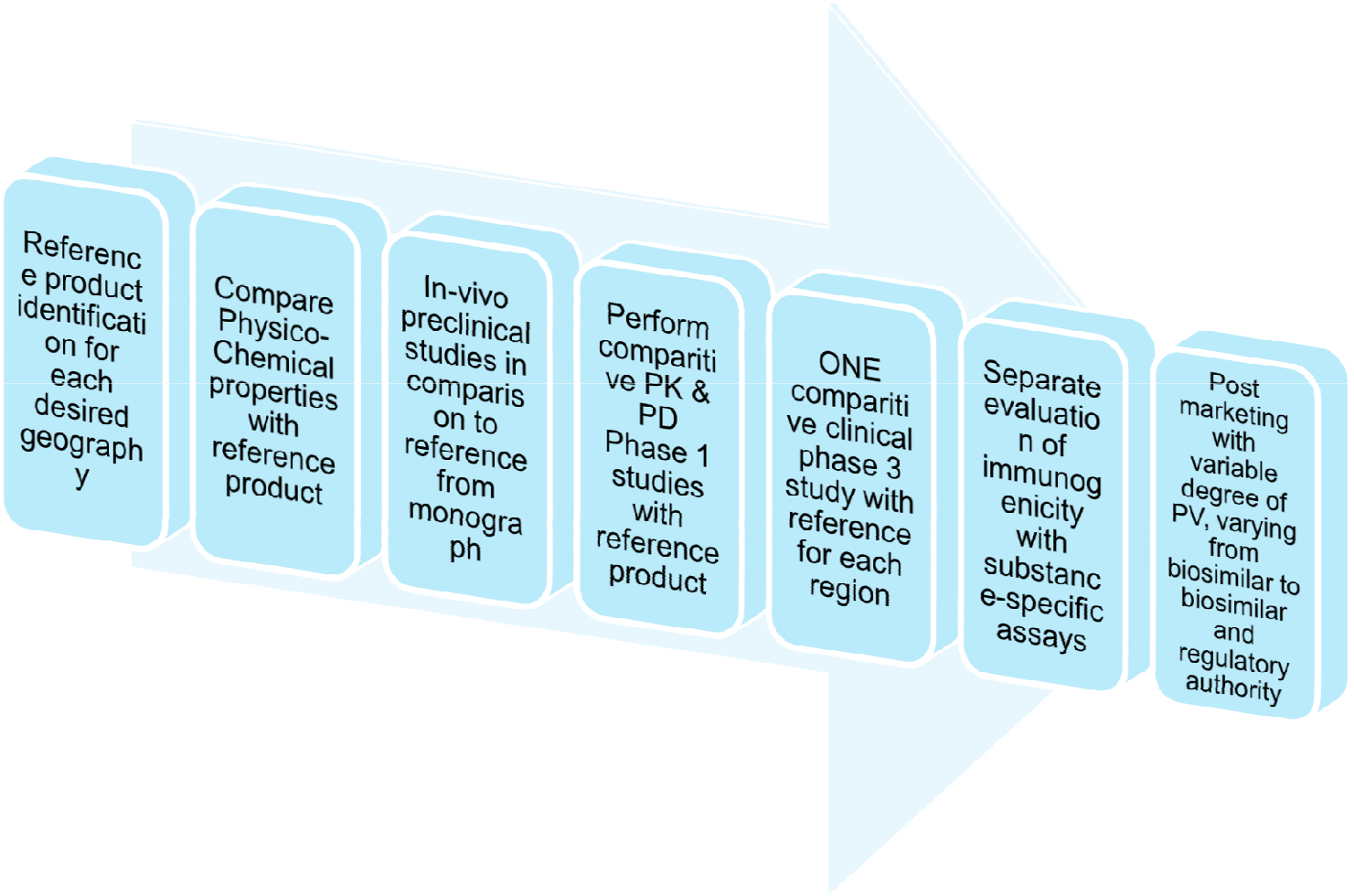
	Similarity concept	Interchangeability & Substitution	Extrapolation across indications	Immuno-genicity	Unique INN; pharmaco-vigilance required
EUROPEAN MEDICINES AGENCY	Concept created by EU	Decided at member state level in EU	Ok if justified both in the EU and in the WHO guidance	Needs to be studied in human pre and post approval in EU and according to WHO guideline	INN is independent from the regulatory pathway used for approval PV is needed for all products in EU and according to WHO guideline
World Health Organization	Experience of EU considered by WHO No product specific (non-clinical or clinical) guidelines	Not addressed in WHO guidance			

WHO specific | EMA specific | Guidance common to both agencies

Key Insight

Countries adopting EMA and/or WHO guidance will have a robust biosimilar approval pathway

Stages of Biosimilar Registration



US FDA Pathway for Biosimilars (Follow-on Biologics)

- Largest potential market
- Biosimilars managed by FDA section dealing with innovator biologics
- Abridged routes planned in principle under Sec 505(b)(2)
- Obama administration prioritized to improve access at economical cost
- In March 2010, Health Canada released Govt. guidelines on Biosimilars - US FDA pathway for Biosimilars (follow-on biologics)
- US lacks clear regulatory pathway for Biosimilars
- Wise to design CDP to comply with draft FDA guidelines

Biosimilars - Food and Drug Administration
www.fda.gov/.../therapeuticbiologicapplications/biosimilars/default.htm

EMA's Pathway for Biosimilars

- Guidelines provide clear pathway. Guidelines by protein class issued
- Clear comparability of quality, safety & efficacy to reference product
- Minor structural differences in active substance is acceptable
- Step wise demonstration of similarity
- Study conduct with an optimal mix of western and eastern European countries reduces time to market at optimal cost
- Long term follow up of study participants is required
- Substitution by prescribing physician and not Pharmacist
- Provides market access to 27 EU and Japan. Data is also helpful to enter Swiss and Turkish markets (34 nations)
- Clear guidelines & attractive market –Companies choose Europe EMA's pathway for Biosimilars

A Few Guidelines on..

- Recombinant follicle-stimulating hormone
- Interferon beta
- Monoclonal antibodies
- Recombinant erythropoietins
- Low-molecular-weight heparins
- Recombinant interferon alpha
- Recombinant granulocyte-colony stimulating factor
- Somatropin
- Recombinant human insulin and insulin analogues

Multidisciplinary: **Biosimilar - European Medicines Agency**
www.ema.europa.eu Scientific guidelines Multidisciplinary

WHO (Geneva CH) Guidelines for Biosimilars

- Globally harmonized framework for licensing in multiple countries
- Global standard against which experimental values can be compared
- Stepwise comparability exercise: 1.Quality 2.Non-clinical 3.Clinical data
- Differences in quality attributes known to have potential impact on clinical activity is not acceptable e.g. glycosylation patterns
- Immunogenicity-should always be investigated in humans
- Extrapolation of efficacy and safety data to other indications is possible
- WHO approval provides a low cost access to markets: No profit sharing with local partners due to WHO tendering process
- Access to Korea, Malaysia which have harmonized with WHO
- Malaysian approval provides access to middle east & gulf countries
- India, S Africa etc using abbreviated guidelines likely to adopt WHO

WHO | **Biosimilars**
www.who.int/medicines/services/inn/inn_bio/en/

WHO - Expert Committee on Biological standardization (ECBS)

- The proceedings of the meetings of the ECBS are published in the WHO Technical Report Series (TRS)
- They provide the information on the establishment, discontinuation and replacement of the WHO Biological Reference Materials as well as on the adoption of Guidelines and Recommendations
- The TRS are available electronically as well as publications, and relevant topics can be searched either by the TRS number or by topic, using the navigation bar on the left-hand side of the web page

ECBS – A Few Guidelines..

WHO/BS/2012.2190: Report of a Collaborative Study to assess the suitability of a candidate replacement International Standard for antibody to pandemic H1N1 influenza virus

WHO/BS/2012.2191: Collaborative Study to Evaluate the Proposed 1st WHO International Standard for Antibodies to Human Papillomavirus Type 18

WHO/BS/2012.2192: Collaborative Study for the calibration and commutability assessment of the proposed 1st International Standard for Diphtheria Antitoxin Human

WHO/BS/2012.2194: Report on a Collaborative Study for proposed 2nd International Standard for Interleukin -2 (IL-2)

WHO/BS/2012.2195: WHO International Collaborative Study of the proposed 3rd International Standard for Erythropoietin, recombinant, for bioassay

WHO/BS/2012.2196: WHO International Collaborative Study of the proposed 5th International Standard for human, urinary Follicle-Stimulating Hormones and Human, urinary Luteinizing Hormone, for bioassay

WHO/BS/2012.2207: Collaborative Study for Value Assignment of 3rd IS for Low Molecular Weight Heparin

WHO/BS/2012.2208: Value Assignment to the WHO 2nd IS for Fibrinogen Concentrate (09/242)

WHO/BS/2012.2209: Report on an International Collaborative Study to establish the 2nd WHO International Subtype Ref. panel for HIV-1 NAT Assays

WHO/BS/2012.2210: Collaborative Study for Value Assignment of 4th IS for Factor II and X, Concentrate

Clinical Development Challenges

- Convince regulators to abridge toxicology and pre clinical studies.
- Biosimilars are injectables. Emergency response time available in an AE is much less. Study design/ site selection to anticipate and mitigate risk.
- Biologics elicit immune response-sometimes life-threatening. Immune response can also manifest as reduced efficacy.
- If subjects become immune, can they switch to reference product ?
- Safety issues call for luminary tertiary care sites. Luminaries prefer to work on innovator drugs, than on Biosimilars.
- Long term follow up of trial subjects is a requirement for Biosimilars.
- Merck - Parexel & Samsung -Quintiles tie-up indicate need for a long term association of CRO with Biosimilars company.

Way Forward

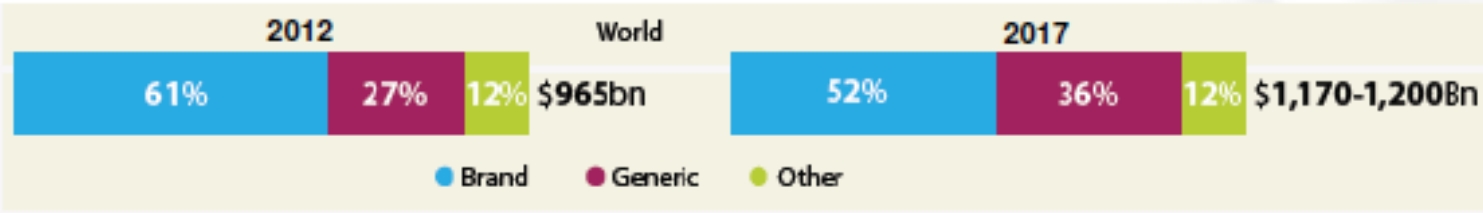
- One comprehensive comparability package against a reference product authorized in a highly regulated market for all regions developing an international mutual recognition.
- Will the impact of ethnicity and differences be acceptable.
- Adopting WHO SBPs, chapters on pharmacovigilance, interchangeability and substitution, labelling and prescribing information.
- Global reference information.
- Global monograph for finished product with elaborate information – cell banks, characterizations, impurities, post – translational modification.
- Establishing regional or national network for information sharing, learning experience among NRAs, in this regulatory area.

Future Evolution: 2020 Outlook

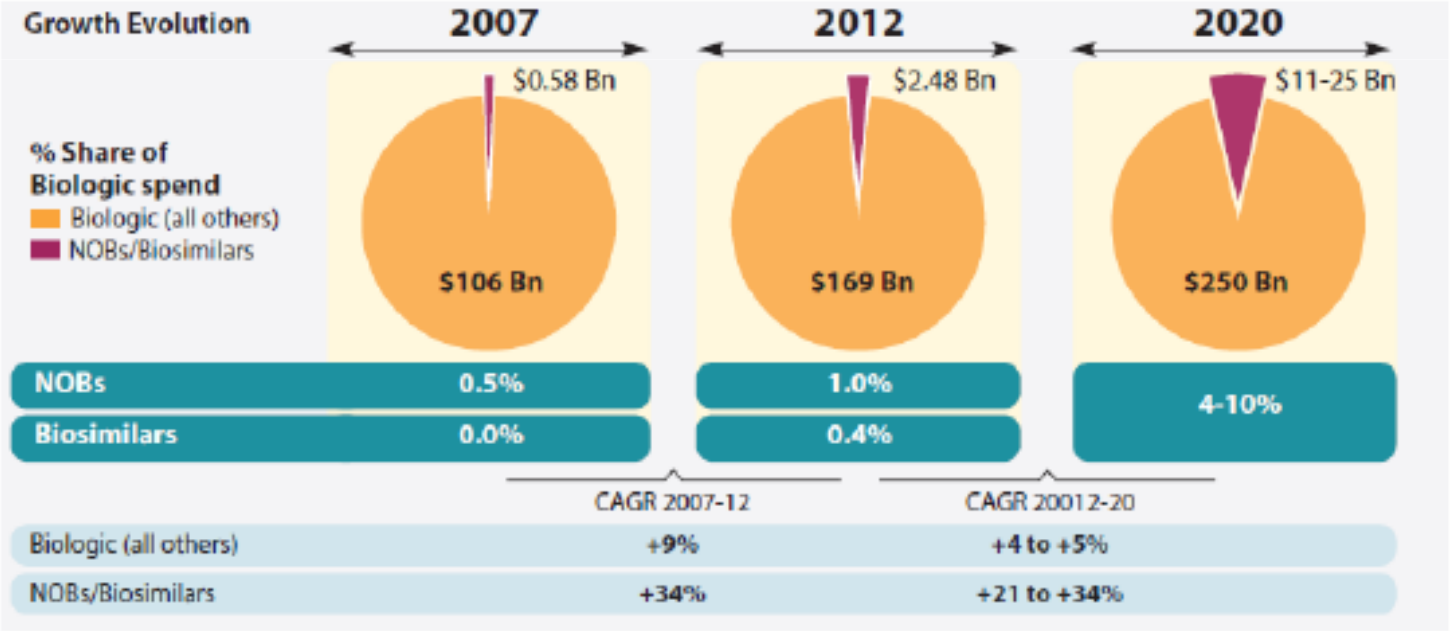
- By 2015, sales of biosimilars are expected to reach between US$1.9-2.6 billion, up from US$378 million for the year to the first half of 2011.
- Biologics – among the most expensive pharmacotherapies available - potentially represent the most lucrative source of savings on drug expenditure for Western nations after 2015.
- Biosimilars also bring clear potential for payers in the emerging pharmaceutical or “pharmerging” markets, such as Brazil, India and China.
- Biologics will continue to out-perform the global market as more innovative products deliver new treatment options for a growing range of indications.
- A number of top-selling biologic brands, including Herceptin, Enbrel, Humalog, MabThera, Remicade and Aranesp, are due to lose product patent protection over the next five years, opening up a wealth of new possibilities for biosimilars players.
- Key therapy areas such as cancer, diabetes and rheumatoid arthritis (RA) will spearhead this new wave of biosimilars, with attention focused on the real prizes of anti-TNFMAbs, MAbs for oncology, and insulins.

Market Scenario

Global Spending, 2012 and 2017 – Sales of Generics



The Biologics Market



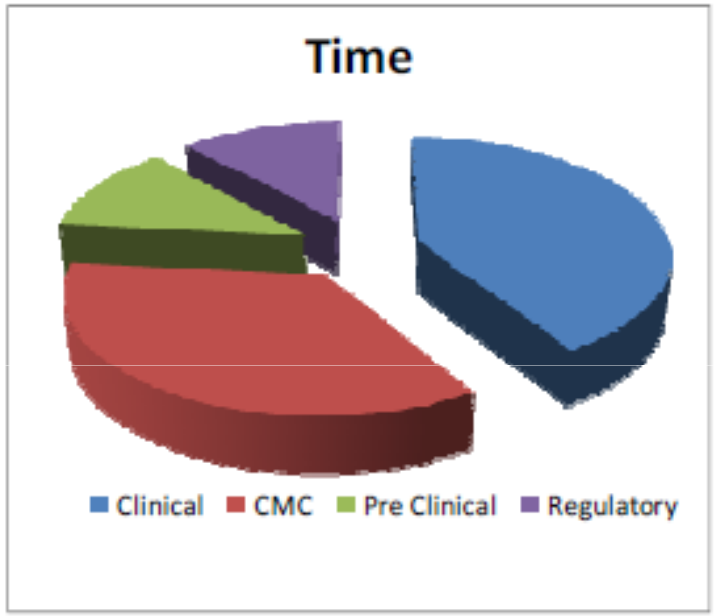
1. IMS Health Thought Leadership, September 2013
2. Searching for Terra Firma in the Biosimilars and Non-Original Biologics Market: Insights for the Coming Decade of Change, IMS Health, 2013

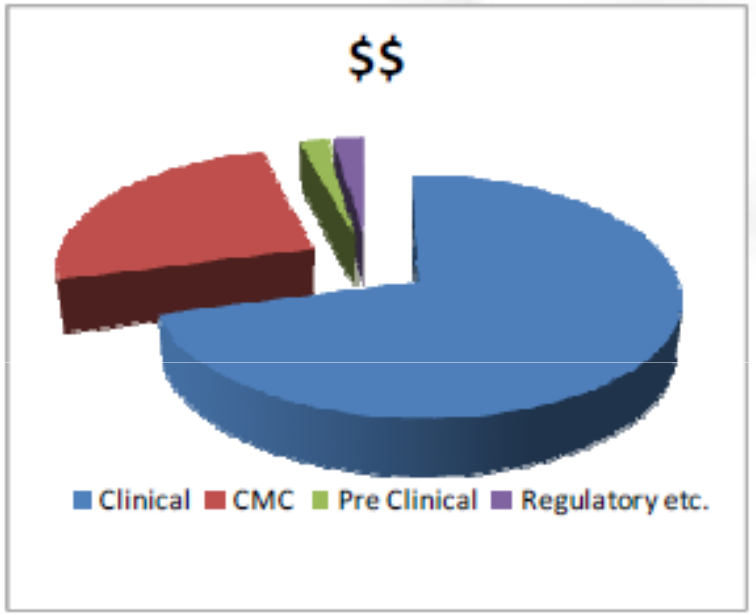
Market Scenario – Cont.

Brand Name	Global Sales (USD)	Company	Patent Expiry (EU/ US)
Humira	10.7	Abbott/ EISAI	Apr 18/ Dec 16
Remicade	8.9	Merck/ Mitsubishi	Aug 14/ Sep 18
Rituxan	8.6	Roche/ Biogen	Nov 13/ Dec 18
Enbrel	8.3	Amgen/ Pfizer/ Takeda	Feb 15/ Nov 28
Lantus	7.8	Sanofi	2014
Avastin	7.0	Roche	Jan 22/ Jul 19
Herceptin	6.8	Roche	Jul 14/ Jun 19
Neulasta	4.4	Amgen	Aug 17/ Oct 15

- Seven of the top eight best-selling drugs for 2013 were Biologicals
- The patents on almost all of these biological blockbusters will be expiring by 2020
- Just these eight Biologicals, will open up a market of around USD 63 billion for Biosimilars

Slow & Costly

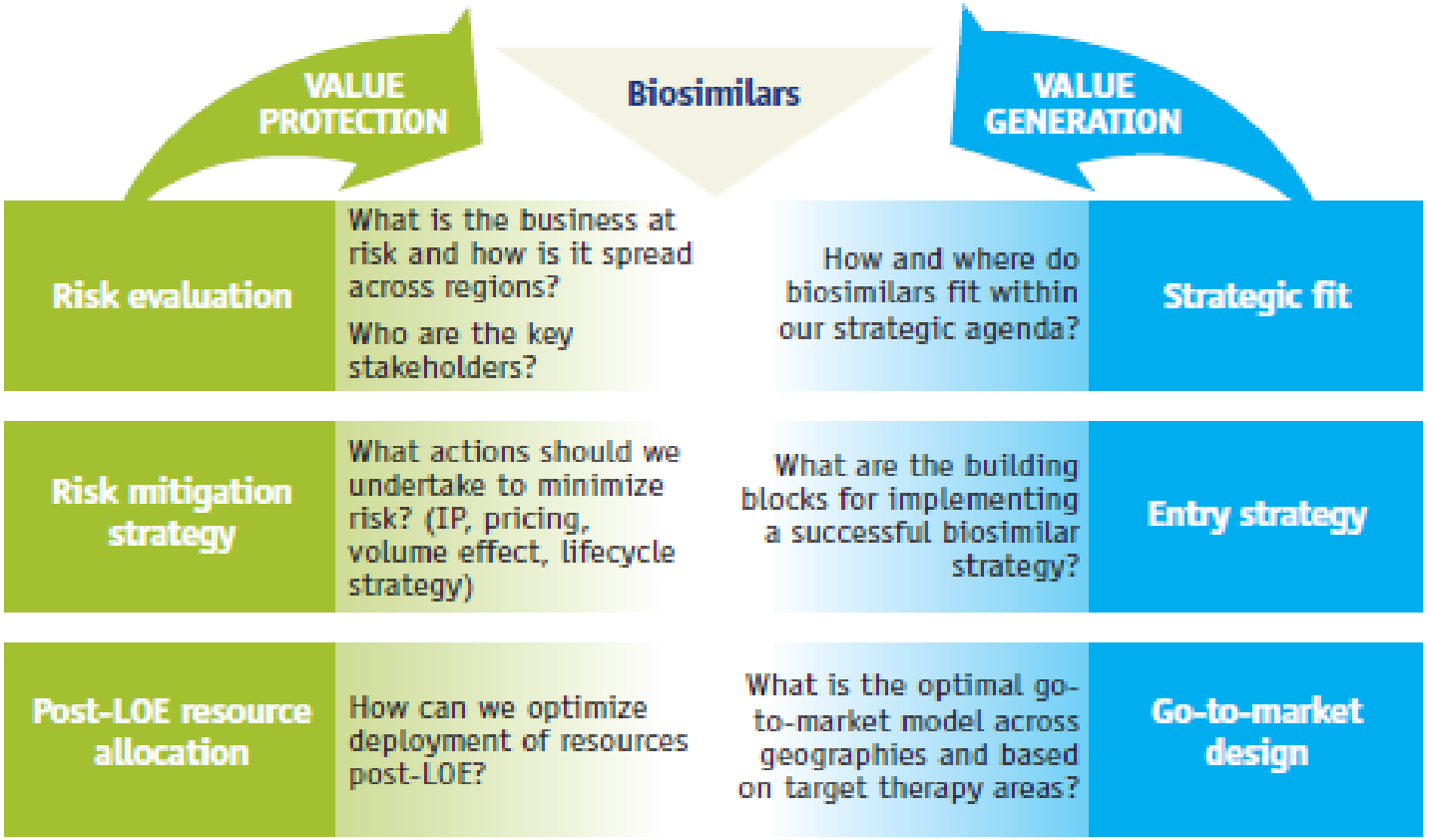




Average development cost estimates:

- Biosimilars: USD 20 to 100 million
- Small molecule generics: USD 1 to 5 million

View From Two Different Angles



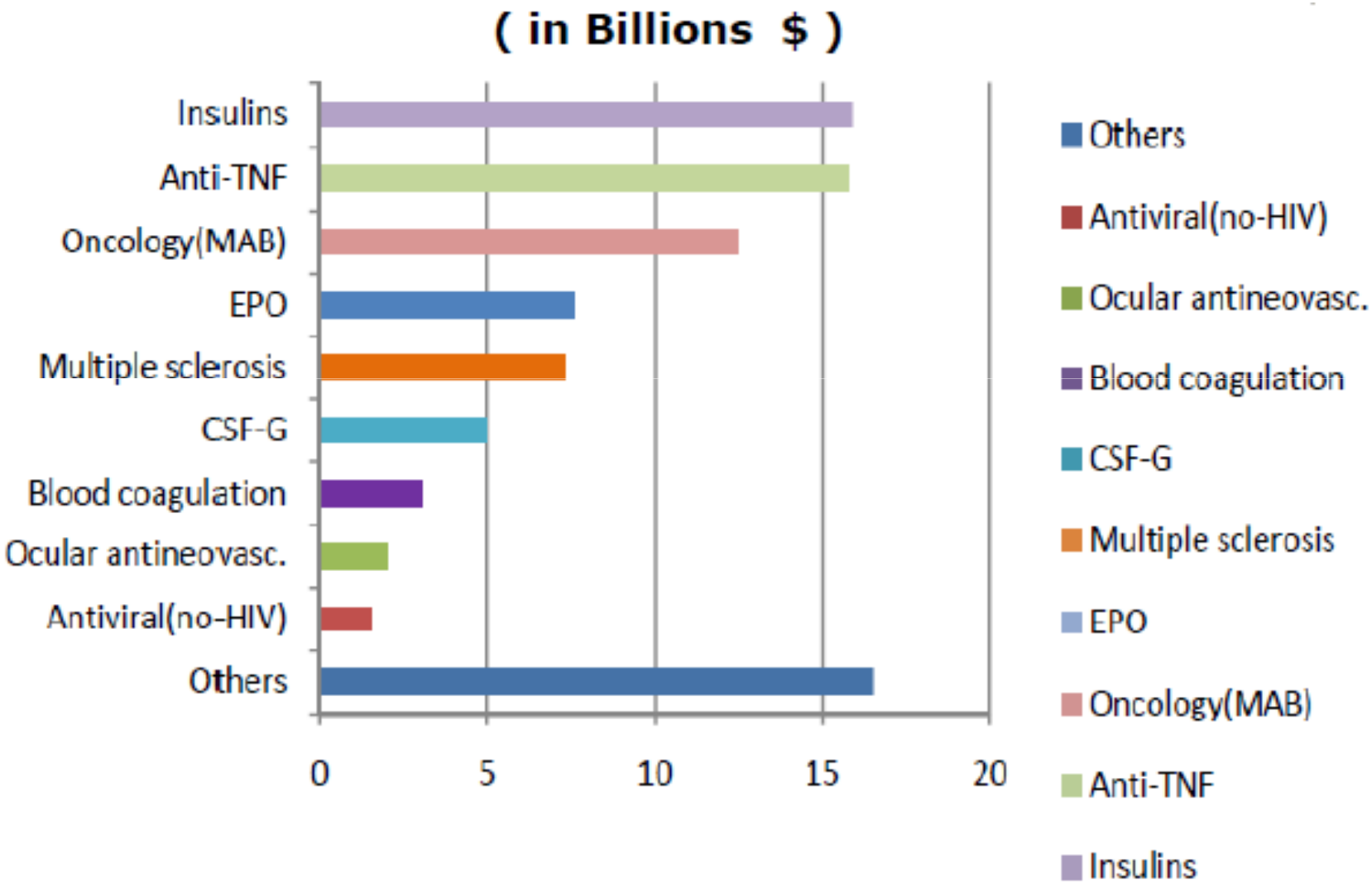
Source: IMS Health

Market Attractiveness & Solutions

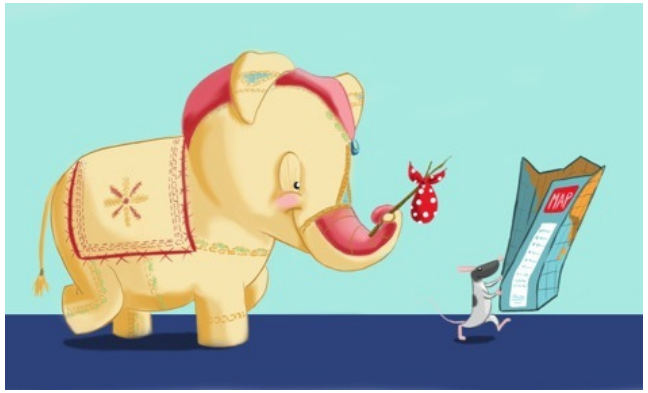
Parameters	R	SR	UR	Market Solution
Cost of R & D/ Production	U	F	F	Shift R & D/ Production to SR markets
Mfg & Clinical Trial Capabilities	F	N	U	MNCs to partner with low-cost area firms and easy access
Govt. support of industry	N	F	N	Upcoming biosimilar firms in India, etc
Regulatory rigidity	U	N	F	Pharm giants and small firms navigation
Attractiveness of Biosimilars to Physicians & Consumers	F	N	U	High-product adoption and aggressive marketing

U – Unfavorable; F – Favorable; N – Neutral
R – Regulated; SR – SemiRegulated; UR - UnRegulated

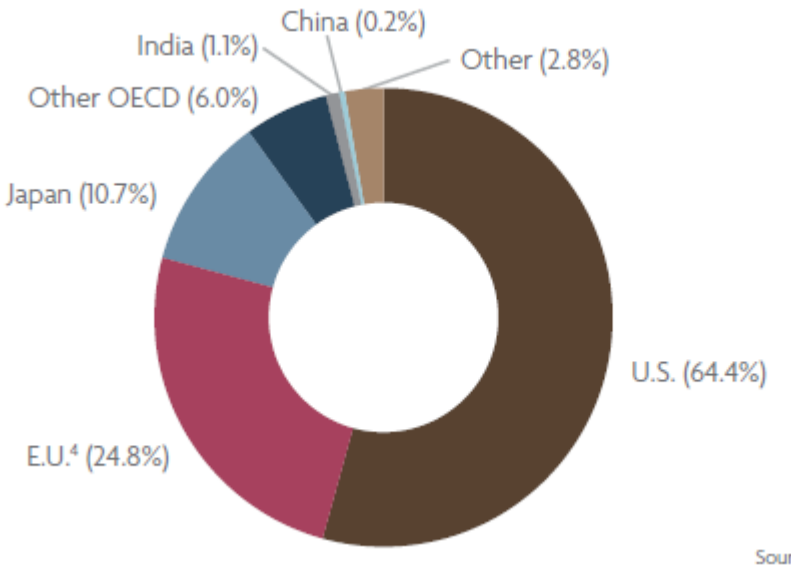
Costs on Core Therapeutic Areas



U.S. Leads in Biopharmaceutical Intellectual Property



U.S. Biopharmaceutical Patents 1990–2002, by Location of Inventors



Source: J.T. Macher and D.C. Mowrey[3]

The Ripple Effect of High-Value Biopharmaceutical Jobs



Biopharma Jobs

Total Jobs Supported

Potential Value

- The price difference between innovator biologic drugs and biosimilar drugs - far narrower than the price between brand-name chemical drugs and their generic counterparts.
- In Europe, the market cost of a biosimilar drug is roughly 20% to 30% of the innovator price.
- As a biosimilar is likely to be less expensive than the reference biopharmaceutical, the assessment of the cost-effectiveness of a biosimilar depends on the relative effectiveness.
- Appropriately designed clinical studies and cost-minimisation analysis demonstrate equivalent effectiveness between a biosimilar and the comparator
- By 2020 the savings through biosimilars would be more than 8 billion EUR.

In a Nutshell..

- The global landscape is evolving - calls for a consistent and efficient approach to their regulation.
- The regulatory standards and approval pathways will have to go beyond cost-effectiveness to protect public health.
- Continuing demand for WHO assistance, leadership, guidance, support and collaboration.
- Global consistency and harmonization – match guidelines to the genuine risks and benefits associated with biosimilars.
- Biosimilar medicines can be expected to be offered at a price lesser than that of the reference product, as a result of production process efficiencies, reduced costs of a streamlined development program and as a result of competition.
- This price differential should lead to a significant release of healthcare funds.

Key factors for a CRO Selection

- CRO who understands Biosimilars industry dynamics
- Conversant with regulatory pathways including WHO
- Who can recruit from western and eastern Europe, Korea, Malaysia, South Africa and India.
- Relationship with tertiary care luminary sites interested in conducting Biosimilar studies.
- Can select sites with emergency response.
- Has a competent PV service

Ecron Acunova CRO meets above criteria

Ecron Acunova Biosimilars Experience

Indication	Product
Immunology	Vaccines
GVHD	Stemcell
Cardiovascular	Stemcell
Solid Tumors	Monoclonal AB
Breast Cancer	Bispecific AB
Rheumatoid Arthritis	MAB
Soft Tissue contour deficiency	Collagen based Biomatrices
Respiratory	Immuno-modulator
Cardiology	Monoclonal antibody
Alcohol Addiction	Amino Acid
Multiple Sclerosis	Recombinant Humanized MAB
Diabetes	Botanical Bioactive

Architecture-similars..!!



Sagrada Familia - Barcelona



Charminar



Dubai Towers

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Thank You