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THE FUTURE OF CLINICAL DEVELOPMENT



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Biosimilars in emerging markets- regulatory and Commercial considerations

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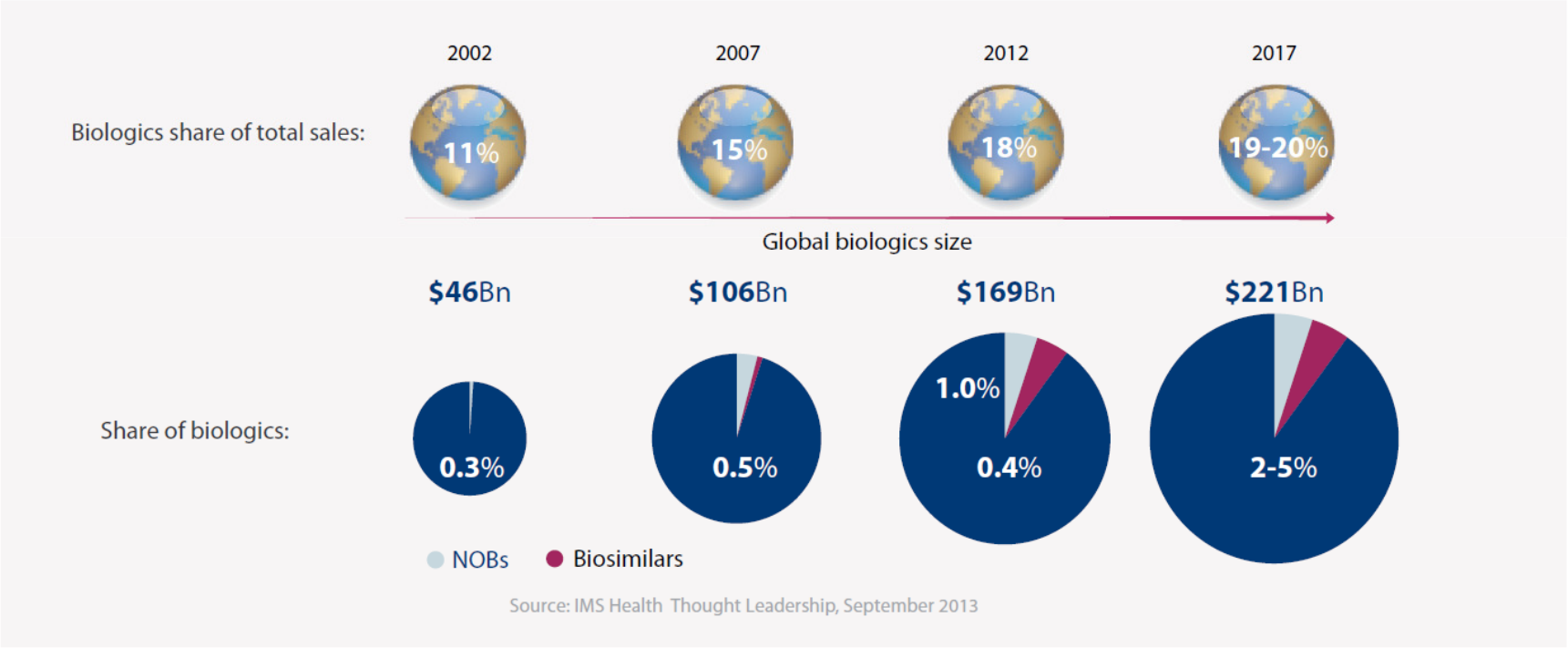
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Biologic Molecules

- Biologic molecules are complex macromolecules with some form of polymer structure. They can be purified from naturally derived substances, produced by recombinant DNA technology or chemically synthesized.
- Biosimilars are defined as non-original biologic copies of innovative brands that have been approved by a dedicated regulatory pathway
- Non-original biologics (NOBs) are copies that have not been approved through such a dedicated pathway and generally did not undertake stringent comparability and bioequivalence studies.

Biologic market

The biologics market



Source: IMS Health Thought Leadership, September 2013

Biologic Growth

- Biologics growth is driven by Monoclonal Antibodies (MABs) and human insulin, with four out of the top five biologics in 2012 being MABs
- In many countries with less rigorous IP protection laws we have seen a recent surge of NOBs.
- In pharmerging markets, both governments and patients struggle to pay for biologics and hence NOBs, encouraged by market demand and government policy, have grown very quickly.

Biosimilar Guidelines and Regulations are being Developed all over the World



Emerging markets

Biosimilars will follow a SPECIFIC BIOSIMILAR approval pathway in:

- Malaysia
- Taiwan
- Singapore
- South Korea
- Japan

Biosimilars will follow a SIMPLIFIED NEW PRODUCT approval pathway in:

- China
- Indonesia
- Thailand

Biosimilars will follow a GENERIC DRUG approval pathway in:

- Philippines
- India
- Vietnam

INDIA

- Department of Biotechnology (DBT) and Central Drugs Standard Control (CDSCO)
- Guideline June 2012
- Stepwise approach
- Similar to EU &US

INDIA

- Extensive Quality Characterization
- RP licensed in India and if not at least 4 years use in highly regulated market
- Detailed requirement for animal
- Potential reduced clinical
- Can waiver Safety/Efficacy dependent on PD markers

“Similar Biologics” approved in India

Product Name	Active Substance	Therapeutic Area	Company
Alzumab	Itolizumab	Psoriasis	Biocon
Basalog	Insulin glargine	Diabetes	Bicon
BioMab EGFR	Nimotuzumab	Head and Neck Cancer	Biocon
CanMab	Trastuzumab	Breast Cancer	Biocon
Grafeel	Filgrastim	Neutropenia, hematopietic stem cell transplantation, cancer	Dr. Reddy’s
Insugen	Human Insulin	Diabetes	Biocon
MabTas	Rituximab	Lymphoma, Non-Hodgkin’s Lymphoma	Intas Biopharmaceuticals
Nufil	Filgrastim	Cancer, neutropenia	Biocon
Filgrastim	Filgrastim	Neutropenia	Lupin
Peg-filgrastim	Pegfilgrastim	Cancer, neutropenia	Lupin
Peg-grafeel	Pegfilgrastim	Cancer, neutopenia	Dr. Reddy’s
Reditux	Rituximab	Leukemia, Lymphoma, Rheumatoid Arthritis	Dr. Reddy’s
Relibeta	Interferon beta-1a	Multiple Sclerosis	Reliance Life Sciences
Religrast	Filgrastim	Neutropenia	Reliance Life Sciences
Rituximab	Rituximab	Non-Hodgkin’s lymphoma	Zenotech Laboratories

NOB or Biosimilars?

- Majority approved prior to the “biosimilar guideline”
- Are these then true “biosimilars”?
- More recent approvals:
  - Human growth Hormone-LG Life Science Dec 2013
  - Infliximab- Epirus September 2014

Data submitted

- Difficult to find
- Lack of transparency
- No publically available source e.g. EU EPARs and FDA SBAs
- Clinicaltrial.gov India
- Information only available when companies announce publically
- Clinical data not specified in the label

INDIA- Summary

- Semi-regulated
- In-house development- substantial cost advantage
- Less stringent regulatory framework
- Low clinical development cost
- Unhindered product launches –different patent landscape
- Cheap workforce
- Interchangeability immediate
- Therapy primarily chosen by physician

CHINA

- Growing number of middle-class consumers with increasing purchasing power
- Increasing incidence of chronic diseases
- No abbreviated pathway available
- Any biopharmaceutical drug (biologic or biosimilars) must be filed as new drug application

Approval Path

- New biologics with clinical trials requirements
- Does not require “non-innovative” biologics to prove equivalence in efficacy, quality, and safety through systematic comparison with the originator
- SFDA admits unavailability of technical requirements and quality control rules written specifically for biosimilars

Regulatory

- No statuary definition or regulatory pathway for biosimilars in China.
- Most biological products in China are “generics” but not like US/EU defined biosimilars.
- Biosimilars can be registered as a new drug or a generic drug in China depending on whether its product standards are in the Chinese Pharmacopeia
- CFDA is in the process of developing technical guidelines for biosimilars
- Indication expansion is highly unlikely
- PD/PK consistency to be established by comparing the biosimilar to the originator drug in a Phase I study
- Combined Phase II/III study is possible but does not require any reference drug

Data Requirements

Clinical trial requirements for therapeutic biologics: CFDA Drug Registration Rules (2007)

- Phase I: >=20 subjects
- Phase II: >=100 subjects
- Phase III: >=300 subjects
- Phase IV (post marketing trial): >=2000 subjects

Biosimilar Guideline

China prepares new biosimilar guidelines

10 September 2014

- The China Food and Drug Administration has worked up draft biosimilar guidelines that it plans to post for comment by Chinese New Year in 2015, according to Joe Zhang, executive deputy head of the Center of Medical and Translational Sciences at Shanghai CP Guojian Pharmaceutical Co.
- The guidelines will be quite similar to existing biosimilar guidelines from the European Medicines Agency and World Health Organization

Expectations?

“Unlikely that China will follow Malaysia which has adopted EMA biosimilar guidelines”

"China would want its own trials and data for biosimilar approval”

"How far it would go in accepting other data is probably limited, though the language of the regulations could be very similar to EMA and others."

Approved “Biosimilars”

- Interferon- several approved
- Insulin- several approved
- Erythropoietin- several approved
- Interleukin- several approved
- G-CSF- several approved
- Etarnacept (8 applications at least 3 local)
- Infliximab (2 applications pending)
- Adalimumab (nine applications with one approved)
- Bevacizumab- 6 applications 2 approved
- Tratsuzumab- seven applications one approved
- Rituximab- 8 pending applications
- Cetuximab- 3 pending applications
- Nimotuzumab one pending

Development considerations

- Lack of transparency
- Data not available in the public
- Lack of experience in developing biosimilars
- Lack of experience in the SFDA in assessing applications
- Require local trials
- Five to 10 years and cost from 1 to 10 million US $
- Domestic manufacturing or up to 2 years for GMP certification

Russia

- No accelerated marketing approval procedure currently exists in the Russian Federation for biosimilars
- A full clinical development program must be completed
- The submission of documents and timelines for biosimilars is the same as for the registration of a biological product (which is considered to be a “pharmaceutical product”.

Clinical Studies

The scope of the clinical studies depends upon:

(a) Pharmaceutical product type, form and route of administration (original or generic)

(b) Pharmacotherapeutic group and indications for use;

(c) Scope of clinical trials conducted abroad- Clinical studies conducted abroad do not have to be repeated; nonetheless, a manufacturer is not exempt from conducting at least one clinical study in Russia. However, the clinical studies conducted abroad influence the scope (number of patients, indications) to be conducted in Russia

(d) Whether an international, multi-center study was conducted and whether part of the study was conducted in Russia (If Russia was included then additional studies probably will not be needed).

Approved biosimilars- Russia

- Epoetin Beta
- Interferon beta-1b
- Filgrastim
- Rituximab

"True biosimilar"?

Brazil

2010: ANVISA issued new set of regulations: a public Consultations 49/2010 (CP 49/10); End 2010 New regulation RDC 55/2010 published

Two regulatory pathways

- *Individual Development Route*
- *Comparative pathway*
- *Approval time for both route the same*

Individual Development Route

An applicant submitting a new biological product or biological product registration application under this route must submit sufficient information and data (through nonclinical and clinical studies) to demonstrate the quality, safety and efficacy of the new biological product or biological product:

- A reduced dossier can be presented; phase I, II and III studies are required with phase III studies being absolutely mandatory
- Clinical studies may be conducted in or outside Brazil
- Complete quality data package- does not have to be comparative
- Non-clinical and clinical studies can be reduced depending on the knowledge of the pharmacological properties, safety and efficacy
- At least one comparative study phase III with originator-mandatory
- Extrapolation of indications not accepted

Comparative Pathway

- Similar to EU and WHO guidelines
- Reference previously authorized in Brazil
- All stages comparative: Quality, Safety and Efficacy
- The pharmacodynamic and pharmacokinetic clinical studies can be Combined provided that the pharmacokinetic/pharmacodynamic relationship is characterized.
- Any comparative clinical studies must demonstrate the comparability in terms of the safety and efficacy profiles between the biological product and the comparer biological product.
- The design and comparability margins of any safety and efficacy studies must be statistically and clinically supported. Finally, data from a phase IV study must also be submitted if available
- The analytical procedures used are sufficient to point out any relevant differences that could impact the safety and efficacy of the biological product and/or the relationship between specific quality attributes, safety and efficacy have been established.
- Extrapolation is accepted

Approved Biosimilars- Brazil

- Somatropin (a growth hormone) which is marketed by Sandoz Do Brasil Indústria Farmacêutica LTDA, Merck S/A, Laboratorios Pfizer LTDA, Laboratório Químico Farmacêutico Bergamo LTDA Bergamo LTDA, Biosintética Farmacêutica LTDA, Novo Nordisk Farmacêutica Do Brasil LTDA and Aspen Pharma Indústria Farmacêutica LTDA;
- Filgrastim (a granulocyte colony-stimulatory factor) which is marketed by Produtos Roche Químicos e Farmacêuticos S.A, Laboratório Químico Farmacêutico Bergamo LTDA, Blausiegel Indústria e Comércio LTDA, Dr. Reddys Farmacêutica Do Brasil LTDA, Teva Farmacêutica LTDA, and Biosintética Farmacêutica LTDA;
- Enoxaprin (a low molecular weight heparin) which is marketed by EUROFARMA Laboratórios S/A, Instituto Biochimico Indústrua Farmacêutica LTDA, Cristália Produtos Químicos Farmacêuticos LTDA, Sanofi-Aventis Farmacêutica LTDA, Blausiegel Indústria e Comércio LTDA and Aspen Pharma Indústria Farmacêutica LTDA;
- Etanercept (a fusion protein) which is marketed by Wyeth Indústria Farmacêutica LTDA; and
- Recombinant erythropoietin (a hormone) which is marketed by Biosintética Farmacêutica LTDA and Chron Epigen Indústria e Comércio LTDA.
- Several biosimilars for the treatment of RA are under development by Productive Development Partnerships (PDPs): strategic partnerships comprising government-funded laboratories, local manufacturers, and multinational corporations.
- Several biosimilars are expected to launch in the next three years: biosimilars of Amgen/Pfizer's Enbrel [etanercept], Janssen/Merck's Remicade [infliximab], Roche's MabThera [rituximab], AbbVie's Humira [adalimumab], and UCB/Astella's Cimzia [certolizumab pegol].

Development Consideration BRIC

- Large population with unmet medical needs
- Benefit vs. risk
- Head to head- timely, costly and delays to market
- High cost of biologics limiting access

Hence

- Abbreviated clinical packages
- Need stringent post marketing safety follow up to identify any safety signals

Harmonization

In principle YES

- Step wise approach
- Quality aspects key
- Non-clinical and clinical
- Bioanalytical methodology key
- Totality of the evidence
- Post marketing safety

Divergence

- The regulation frameworks are inconsistent with global norms and can expose patients to unknown risk.
- Adapting generic-like pathways to approve biosimilars- “looser approach”
- Lack of Robust Pharmacovigilance systems hinders signal detection

But

Does the benefit outweigh the risk?

Clinical study designs- divergence

- Statistical considerations
  - Effect size and equivalence margins
- Sample size
- Use of comparator head to head
- Waiver phase I or phase III
- Unblinded open label

Biosimilars in development- sample size

Rituximab

- Sandoz n=915
- Biocad n=442
- Pfizer n=551
- Dr Reddy n= 67 (open no-comparative)

Infliximab

- Celltrion n=856
- Epirus n= 273

Sustainability of Biosimilars

- Biosimilars offer the chance to get treatment otherwise prohibited by cost of originators
- Do we need extensive clinical comparability studies which are costly and timely?
- Can we do less clinical and more quality?
- Case by case?
- Safety should not be compromised
- One serious safety case due to “substandard quality” can risk the sustainability of biosimilars!
- Prescribers and users must have confidence in the products!



Thank You

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