Market Opportunity Analysis for Biosimilars from perspective of regulatory environment offered in EU5, U.S., Japan and Pharmerging Markets

Internship Training
at
ZS Associates India Private Limited
(February–April 2014)

By
Ankuri Setia

Under the guidance of
Dr. Anoop Khanna

Post Graduate Diploma in Hospital & Health Management
2012–14

IIHMR UNIVERSITY
Institute of Health Management Research
Jaipur
2014

INSTITUTE OF HEALTH MANAGEMENT RESEARCH
1, Prabhu Dayal Marg
Sanganer Airport, JAIPUR - 302 011, INDIA
Tel. : 3924700, 2791431-32
Fax : 91-141-3924738
E-mail : iihmr@iihmr.org
URL : http://www.iihmr.org
Gram : HEALTHINST

TO WHOMSOEVER MAY CONCERN

This is to certify that student of Post Graduate Diploma in Hospital and Health Management (PGDHM) from Institute of Health Management Research, Jaipur has undergone internship training at ZS Associates India Private Limited from 3 February, 2014 to 8 May, 2014

The Candidate has successfully carried out the study designated to her during internship training and her approach to the study has been sincere, scientific and analytical. The Internship is in fulfillment of the course requirements.
I wish her all success in all her future endeavors.

Dean, Academics and Student Affairs
IIHMR, Jaipur

Professor
IIHMR, Jaipur

May 12, 2014

EXPERIENCE CERTIFICATE

This is to certify that Miss Ankuri Setia (8432) has served in our organization from February 3, 2014 to May 8, 2014. At the time of leaving she was working in the capacity of Knowledge Management Associate - Intern and based at New Delhi office. .

This is to confirm that all information\Projects shared\worked in your Internship period is confidential and are not liable to be shared with anyone outside ZS network.

At last, wish you all success in future endeavors

For ZS Associates India Pvt Ltd

Stephen Redden
Office Managing Principal

ZS Associates India Private Limited
Gurgaon
HR

INSTITUTE OF HEALTH MANAGEMENT RESEARCH
1, Prabhu Dayal Marg
Sanganer Airport, JAIPUR - 302 011, INDIA
Tel. : 3924700, 2791431-32
Fax : 91-141-3924738
E-mail : iihmr@iihmr.org
URL : http://www.iihmr.org
Gram : HEALTHINST

INSTITUTE OF HEALTH MANAGEMENT RESEARCH, JAIPUR

CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled "Market Opportunity Analysis for Biosimilars from perspective of regulatory environment offered in EU5, U.S., Japan and Pharmerging Markets" and submitted by Dr. Ankuri Setia Enrollment No 1294 under the supervision of Prof. Anoop Khanna for award of Postgraduate Diploma in Hospital and Health Management of the Institute carried out during the period from 3 February, 2014 to 8 May, 2014 embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other Institute or other similar institution of higher learning.

Ankuri Setia
Signature

Executive Summary

The pharmaceutical industry is experiencing change in ways it hasn't ever before. On the demand side, we are seeing an aging population, increased prevalence of "Western" diseases, and a dramatic growth in global access to pharmaceuticals. On the supply side, we are seeing increased competition from emerging market players, and a shift in the way drugs are being developed, manufactured, and delivered. Meanwhile, policy makers are struggling with an inherent conflict between desire to provide improved access to better medicines and the need to curb the growth of healthcare expenditures.

One topic at the centre of all of these changes is the Biosimilars market. Biosimilar products will offer competition to some of the most expensive drugs on the market, but also require high investment.

The promise of biosimilars is to provide cost savings, increase patient access, and promote innovation[1]

Regulatory environment plays a very big role in determining the market for biosimilars in all geographies across the globe. Regulations have been set in place in order to prevent the launch of such inappropriate biosimilars in market and thereby prevent associated adverse events (due to their complex molecular structure and consequent difference in immunological reaction offered by the body on their intake). So they need to undergo stringent regulatory approval process before they can be brought into the market for selling. This offers entry barrier for new players willing to enter this market space and also even the established pharmaceutical manufacturers first need to know the suitable markets in terms of market demand for biosimilars based on need analysis and also regulatory setting that exists there so that they can check the feasibility for

themselves before investing in to biosimilars market which requires a huge lot of investment right from manufacturing till their approval for getting launched in the market. So the manufacturers would definitely wish to know by researching that which geographies or markets across the globe will offer maximum opportunity for biosimilars approval and consequently their sales that help them earn revenue in return of huge investment.

In response to this requirement and need raised by pharma clients, the study involves carrying out of investigation of the regulatory environment in specific geographies that constitutes seven Major Markets (EU5, U.S., Japan) and two Pharmerging markets (China and Russia) taking specific regulatory parameter into consideration.

This study helps finding out the most opportunistic markets from around the globe depending upon available forecasted secondary data. Opportunity assessment will help pharma MNC's to decide upon which geographies they should go to for investment into biosimilars depending upon favourability of market from regulatory perspective this is because biosimilars involve huge investment.

Research Questions were developed like

a) What are the common regulatory perspectives being considered across the target geographies in relation to the biosimilar regulatory approval process ?
b) Which geography/geographies offer the most opportunistic market from a regulatory perspective to the players interested in entering the biosimilar landscape?

Accordingly, Research Objectives were formulated such as

a) To study the overall regulatory environment for biosimilars in the 7 major markets (EU5, U.S., and Japan) and two Pharmerging markets (China and Russia).
b) To determine and pick up those biosimilar regulatory parameters that has greatest influence in determining the regulatory scenario in these geographies.
c) To determine compliance of geographies under consideration to the decided parameters and allotting the ranks accordingly.
d) To determine the most opportunistic geography/geographies as a biosimilar market from regulatory environment perspective based on rankings

The Methodology was followed to fulfil and achieve all objectives that involved deciding upon study geographies followed by literature review of regulatory setting that exists in these geographies for biosimilars, followed by deciding upon the parameters that need to be assessed. The following parameters have been taken into consideration: Existence of legislation for regulatory approval pathway for biosimilar, Reference Product Approval required in the Domestic Country, Status of Indication Extrapolation of Biosimilars, Support by the government policies to Local /MNCs biosimilar manufacturer, Status of Biosimilar Interchangeability, Status of Biosimilar Substitutability, Domestic trial requirements.

As per the various variations of the definition of the parameters that came into knowledge on studying these parameters in the geographies under study and accordingly, **Likert's scale** was used as a tool to rank the regulatory scenario with respect to above seven parameters on a scale of 1 to 5 where 1 means least opportunistic

(most restrictive market) and 5 being most opportunistic (least restrictive market) This way a spectrum of opportunity was seen to get developed in relation to study geographies. Later weights have been allocated to study parameters taking allotted weights into consideration relative ranking was calculated for study geographies and lastly, overall relative ranking is carried out which is a cumulative score for the study geography based on the ranking achieved by it with respect to all seven study parameters. The highest rank achieved thus, helps us in determining the most opportunistic or least restrictive markets from regulatory perspective for biosimilars.

Finally findings were obtained where United States achieved the highest overall relative rank thereby suggesting that it offers least restrictive market for biosimilar regulatory approval followed by its launch in the market , the next best market is offered by Germany and Italy among all other EU5 countries.

Conclusion

Based upon the study results the United States came out to be most opportunistic or in other way least restrictive market for biosimilar manufacturers because of certain parameters that are less restrictive in U.S. market such as the U.S. government in order to go global and establish themselves as a big biosimilar market has allowed use of reference product from other countries as it is provided their standards are almost same as FDA e.g. International Conference on Harmonization (ICH Countries) unlike Europe where only approved drugs in the country can be just outsourced in batches from other countries.

Other reasons for being at an upper edge to Europe is their regulation that formally announces and accepts “Interchangeability”(this term has been introduced by United

States) and Substitution unlike in Europe where interchangeability is not accepted in real terms but as a consequence of physician prescription only then substitution can been carried out by pharmacist.

However, United States need to look up to Europe for creating more positive regulatory environment for biosimilars in terms of allowing for indication extrapolation as in U.S. extrapolation is permitted, provided there is scientific evidence irrespective of number of indications for which extrapolation is being done unlike Europe where extrapolation is permissible based on overall evidence of comparability, with adequate justification. One set of studies may be required, whereas for two very different indications, more than one set of studies will be required

Also, Europe's whose biosimilar legislation which is well established and accepted as a gold standard across the globe by all geographies entering in to biosimilar market space and even United States itself.

On comparing United States to other study geographies it has definitely got an upper edge over them in terms of regulatory scenario being offered by it such as government support being offered by it except for China where too government is highly supportive, also it is more flexible for allowing interchangeability and substitution however, interchangeability will be allowed in Russia as well once biosimilars are launched in their market. Lastly, in terms of existence of legislation which is better defined in U.S. than all other geographies and also reference product approval for which Japan is not at all flexible and for other two geographies data is not available.

Acknowledgement

I would like to express the deepest appreciation to my Project Lead Dr. Mohit Saxena (Consultant ZS Associates, Knowledge Management) for the vision and foresight which inspired me to conceive this project.

I am particularly indebted to my Project Manager Karishma Trikha who has shown the attitude and the substance of a genius: she continually and persuasively conveyed a spirit of adventure in regard to research and scholarship, and an excitement in regard to teaching. Without her supervision and constant help this dissertation would not have been possible.

I would like to thank my Team members for being of constant source of motivation in difficult times.

My heartfelt thank you to Professor Anoop Khanna, who had a been a constant support and provided me guidance to steer my research and come out with conclusions, without your guidance Sir things would have not got directions and dissertation had not been successfully completed.

I want to pay my gratitude towards the IHMR, Jaipur for providing me with the opportunity to work with such good organization.

To my mother for the unwavering love, faith and continued support and reassurance over the years.

By extension I'd like to offer my thanks to all the staff of the ZS Associates for their kind and polite behaviour that made work more fun and comfortable to cope up with.

With warm regards,

Dr. Ankuri Setia

Table of Contents:

Contents

List of Tables

List of Figures

1. Introduction

I started my internship on February 3rd, 2014 at ZS Associates India Private Limited in Knowledge Management Practice Area that lies under Business Consulting Track of ZS Associates in Gurgaon (Global Head quarters) , Haryana.

On my first day I was issued the ZS ID card and I carried out all the HR formalities.

The next day I had my meeting with my Project Lead, Project manager and other team members. We discussed the dissertation topic for a while and then made a draft of target research heads and timeline of completion of research on the respective research heads.

There were already a part time team working on Emerging Trends in the KM Team and Biosimilars was one of the study subjects for them but my role was to carry out Full time dedicated research on the Biosimilars and Impact they have brought on global pharmaceutical market space.

During the first week of my Internship I was told to read about the Organization and in particularly about the Basic definitions and terms associated with biosimilars. I found it very interesting.

Later from the second week onwards I started working on my specific Research heads which required literature review on

Biosimilar approval pathways in detail in geographies like Europe where they first came

in to existence followed by study of United States regulatory Environment where biosimilar are soon to get launched and compare both the markets and bring out the differences between the two.

This was followed by study carried out in Japan and later in pharmerging markets like China and Russia

This led to the clarity in the topic under discussion and further led to formulation of a research question after observing the regulatory settings trends which guided the study further.

I started searching internal data sources* which were leveraged by the team for their research as well along with them publically available secondary data sources like Google and online available articles and pharma industry specific literature grey literature simultaneously stored the references

Note*

(Names of data sources are confidential and cannot be shared as per the company policy)

2. A Brief Overview of ZS Associates:

A Foundation of Innovation and Academic Rigor

ZS Associates is rooted in an academic partnership that began in the early 1970s. In **1973**, Andy Zoltners completed a PhD in integer programming algorithms at Carnegie Mellon University, devoting a chapter in his dissertation to sales territory alignment problems. Andy subsequently accepted a teaching position at the University of Massachusetts (UMass).

The following year, Andy crossed paths with PhD student Prabha Sinha, who was exploring the use of higher math in meal planning for the military. The two collaborated on the Multiple Choice Knapsack problem and co-wrote a paper on the topic. Eventually they realized that this line of thinking was highly applicable to the problems of sales force sizing and resource allocation.

Over the next several years, the pair worked with a number of companies, gaining practical experience applying modelling techniques to sales force problems.

In **1982**, Andy presented his and Prabha's mathematical models for sales force sizing and territory alignment to the Pharmaceutical Management Science Association (PMSA), using an early Apple computer to display sales territories on-site. Executives from many of the attending companies were stunned by the model's ability to quickly solve sales force sizing, sales resource allocation, and territory alignment issues and see solutions visually in real time, with one exclaiming, "I've been waiting my whole life for this!"

By **1983**, both Andy and Prabha were teaching at Northwestern's Kellogg School of Management. They lectured by day, and by night they worked on the many client projects that came their way. Already having consulted to eight companies, the two professors concluded that there was an opportunity to help many clients address critical sales force effectiveness issues, and so they incorporated ZS Associates, Inc.

2.1 About the work at ZS Associates

ZS Associates is one of the world's largest business services firms specializing in transforming sales and marketing from an art to a science. They help clients gain market share at lower cost by creating data-driven strategies that they can implement rapidly. They also take on complex sales and marketing operations to make their clients more competitive.

ZS focuses exclusively on the two areas that create customer demand: sales and marketing. As a result, their expertise in this domain is both broad and deep. They provide a vast range of marketing- and sales-related services in the industry, from customer insight, product development, and sales and marketing strategies, to sales compensation planning and even plan administration, to name just a few. Their consultants leverage the firm's deep knowledge of the range of sales and marketing activities and how they interact in order to anticipate the upstream and downstream effects of virtually any decision. Thus, they offer clients the unique advantage of understanding what will work best for their company as a whole.

Since 1983, ZS has been working shoulder to shoulder with leaders at hundreds of the world's top corporations. Their clients typically are large and mid-sized companies whose success depends on the effectiveness of their sales and marketing. They help them gather and analyze data to create the best strategies; orchestrate sales and marketing activities to increase demand efficiently; and change quickly to become more competitive. Their clients work with them year after year because we are responsive, collaborative and flexible – and, not least of all, because they are passionate about what

they do.

Today more than ever, executives must drive their sales and marketing strategies and operations with data – and the expertise to interpret it. That's where ZS comes in. We're in the business of turning the art of demand generation into a science.

2.2 ZS Associates Global Offices

ZS Associates is one firm with multiple offices positioned to provide the highest quality and most attentive service to our clients. Each office can effectively serve local or regional clients while also contributing to project teams working around the world, assembling the optimal mix of capabilities, experience, geography, language and culture.

Americas	**Europe**	**Asia**
Boston	Barcelona	New Delhi
Chicago	Frankfurt	Pune
Evanston	London	Shanghai
Los Angeles	Milan	Tokyo
New York	Paris	
Philadelphia	Zurich	
Princeton		
San Diego		
San Francisco		
São Paulo		
Toronto		

2.3 ZS Offerings to clients

2.3.1 Services

- Sales
- Marketing

2.3.2 Expertise

- Consulting
- Outsourcing
- Technology
- Software

3. Background for business question

Question is about finding out the most opportunistic /least restrictive market for biosimilars from perspective of biosimilar specific regulatory environment that exists in these geographies

The pharmaceutical industry is experiencing change in ways it hasn't ever before. On the demand side, we are seeing an aging population, increased prevalence of "Western" diseases, and a dramatic growth in global access to pharmaceuticals. On the supply side, we are seeing increased competition from emerging market players, and a shift in the way drugs are being developed, manufactured, and delivered. Meanwhile, policy makers are struggling with an inherent conflict between desire to provide improved access to better medicines and the need to curb the growth of healthcare expenditures.

One topic at the centre of all of these changes is the Biosimilars market. Biosimilar products will offer competition to some of the most expensive drugs on the market, but also require high investment.

The promise of biosimilars is to provide cost savings, increase patient access, and promote innovation[1]

"Biosimilar drugs" are less expensive alternatives to biologic drugs (most expensive pharmacotherapies available) represent one of the upcoming segments of the pharmaceutical industry. Rationalizing use of "Biologics" has been an ongoing challenge for payers so introduction of biosimilars is likely to be accepted by physicians, payers and patients consequent to patent expiration of biologic drugs in pharmaceutical major markets like Europe and U.S thereby, help in containing ever-increasing pressure on healthcare budgets, broaden healthcare coverage to large populations which must be balanced against limited budgets and growing demand for innovative drugs.

Regulatory environment plays a very big role in determining the market for biosimilars in all geographies across the globe. Regulations have been set in place in order to prevent the launch of such inappropriate biosimilars in market and thereby prevent associated adverse events (due to their complex molecular structure and consequent difference in immunological reaction offered by the body on their intake). So they need to undergo stringent regulatory approval process before they can be brought into the market for selling. This offers entry barrier for new players willing to enter this market space and also even the established pharmaceutical manufacturers first need to know the suitable markets in terms of market demand for biosimilars based on need analysis and also regulatory setting that exists there so that they can check the feasibility for themselves before investing in to biosimilars market which requires a huge lot of investment right from manufacturing till their approval for getting launched in the market. So the manufacturers would definitely wish to know by researching that which geographies or markets across the globe will offer maximum opportunity for biosimilars approval and consequently their sales that help them earn revenue in return of huge investment.

4. Rationale of study:

In response to this requirement and need raised by pharma clients, the study involves carrying out of investigation of the regulatory environment in specific geographies that constitutes seven Major Markets (EU5, U.S., Japan) and two Pharmerging markets (China and Russia) taking specific regulatory parameter into consideration. Thereafter, respective ranking of geographies on the likert's scale based on regulatory parameters scenario being offered in study geographies thus at last creating a spectrum of opportunity from most restrictive market to least restrictive market.

This study helps finding out the most opportunistic markets from around the globe depending upon available forecasted secondary data. Opportunity assessment will help pharma MNC'S to decide upon which geographies they should go to for investment into biosimilars depending upon favourability of market from regulatory perspective this is because biosimilars involve huge investment.

5. Research Questions:

a) What are the common regulatory perspectives being considered across the target geographies in relation to the biosimilar regulatory approval process?

b) Which geography/geographies offer the most opportunistic market from a regulatory perspective to the players interested in entering the biosimilar landscape?

6. **Aim:** To determine and analyze Market Opportunity for biosimilars by means of secondary/desk research carried out on the regulatory environment that exists and also that is predicted in the geographies under study.

7. Objectives:

a) To study the overall regulatory environment for biosimilars in the 7 major markets (EU5, U.S., and Japan) and two Pharmerging markets (China and Russia).

b) To determine and pick up those biosimilar regulatory parameters that has greatest influence in determining the regulatory scenario in these geographies.

c) To determine compliance of geographies under consideration to the decided parameters and allotting the ranks accordingly.

d) To determine the most opportunistic geography/geographies as a biosimilar market from regulatory environment perspective based on rankings

8. Study design and methods:

a) Type of study: Exploratory Secondary/Desk Research

b) Geographies under study:- EU5 (United Kingdom, France, Germany, Spain, and Italy)

United States of America

Japan

Pharmerging markets (China, Russia)

c) Study subjects: Biosimilar molecules and their respective manufacturers in the geographies under study.

d) Data (information) to be collected: Recording of regulatory scenario in study geographies with respect to regulatory parameters under consideration.

e) Data collection tools: ZS Specific data sources and publically available secondary research data sources will be deployed to derive data.

9. Methodology:

9.1 Deciding study geographies: First of all study geographies were decided based upon the requirement of the organization i.e. geographies of interest to them were shortlisted out of all the geographies where biosimilars are in existence based on:

i) Discussions based on the market trends seen for biosimilars uptake

ii) The projected potential markets based on forecasted sales in the geographies

iii) Taking into consideration the regulatory setting and environment existing for biosimilars already launched in the market in the geographies.

Thus, out of all geographies shortlisted ones are:

- 7 major markets (7 MM) comprising of
  - EU5: Germany, Spain, Italy, France, United Kingdom
  - United States of America
  - Japan
- Pharmerging markets:
  - China

9.2 Literature Review:

- ZS specific Data sources*are search for English language reviews and reports on biosimilars regulatory pathways
- Popular websites specific to Europe (European Medicines Agency), United States (Food and Drug Administration), and Japan (Ministry of Health, Labour and Welfare) were visited and studied thoroughly. The links for them are: http://www.ema.europa.eu/ema/ , http://www.fda.gov/ , http://www.mhlw.go.jp/english/
- Apart from these websites next moist visited website was http://www.gabionline.net/ this is a dedicated source of information on biosimilars.
- Grey literature was referred to e.g. various articles found on Google search using various strings and keywords related to biosimilars.

Note* (names of data sources are confidential and cannot be revealed here)

9.3 Deciding upon the parameters: out of all the regulatory parameters at each step of

Quality studies

Non-clinical studies

Clinical studies

Those parameters that were most discussed in all the secondary research articles and were mentioned in a way such that they were found to be most influential in determining the launch of biosimilars in the respective geographical market were taken into consideration

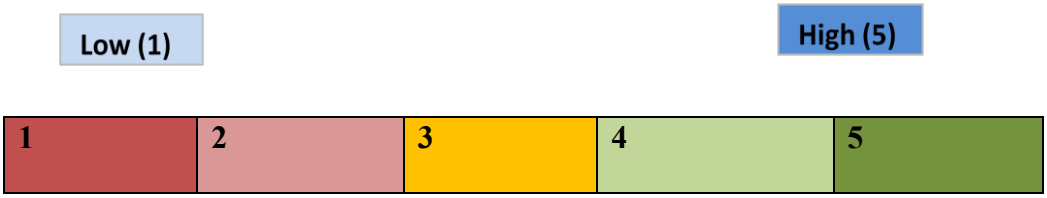
The following parameters have been taken into consideration:

1. Existence of legislation for regulatory approval pathway for biosimilars
2. Reference Product Approval required in the Domestic Country
3. Status of Indication Extrapolation of Biosimilars
4. Support by the government(Local Vs MNCs)
5. Status of Biosimilar Interchangeability
6. Status of Biosimilar Substitutability
7. Domestic trial requirements

10. As per the regulatory scenario as was encountered and observed in the secondary literature review the definition for each of the seven regulatory parameters was developed.
11. As per the various variations of the definition of the parameters that came into knowledge on studying these parameters in the geographies under study and accordingly, **Likert's scale** was used as a tool to rank the regulatory scenario with respect to above seven parameters

12. Definitions for each parameter along with the definition of liker scale ranking (1 to 5) of respective parameter was identified and discussed with the consultants and later finalised.
13. While reviewing the literature about the regulatory setting in respect to biosimilars of each of the parameters simultaneously the respective Likert's scale ranking was allotted on the scale of 1 to 5
14. Where 1 means least opportunistic (most restrictive market) and 5 being most opportunistic (least restrictive market) this way a spectrum of opportunity has been tried to be built upon.

Relative Level of attractiveness (Spectrum of opportunity offered)



9.4 Allocation of weights to regulatory parameters

Regulatory parameters	Allocated weights
Status of Indication Extrapolation of Biosimilars	25%
Existence of legislation for regulatory approval pathway for biosimilars	15%
Support by the government(Local Vs MNCs)	15%
Status of Biosimilar Interchangeability	15%
Status of Biosimilar Substitutability	15%
Reference Product Approval required in the Domestic Country	10%
Domestic trial requirements	5%

These weights have been allocated based upon the secondary research data where in articles have determined the extent to which these parameters have determined the regulatory approval process and consequently the launch and performance of the biosimilars launched in the respective markets.

9.5 Calculation of relative ranking:

After allocation of ranks to each of the seven regulatory parameters in each of the study geographies on the likert's scale next, each of the ranks were converted into their respective relative ranks by multiplying the rank given to geography with the weight allocated to the respective parameter.

Relative rank of geography with respect to regulatory parameter = likert's scale rank given to geography* weight allocated to respective regulatory parameter

Example: rank on liket's scale for status of biosimilar substitutability in spain i.e.3* 15% (weight allocated to this parameter) = 3*15% or 0.15 = 0.45

9.6 Calculation of overall relative ranking of geography with respect to all seven regulatory parameters under consideration:

Overall relative rank of geography with respect to all seven regulatory parameters = addition of relative rankings of geography with respect to all seven regulatory parameters

Example: Addition of all seven relative ranks of spain of each of the parameter =

10. Review of literature as per the methodology

Brief description and scope of parameters

Those parameters that were most discussed in all the secondary research articles and were mentioned in a way such that they were found to be most influential in determining the launch of biosimilars in the respective geographical market were taken into consideration.

10.1 Existence of legislation for regulatory approval pathway for biosimilars:

Definition: Current status of biosimilar legislation in the relevant geography

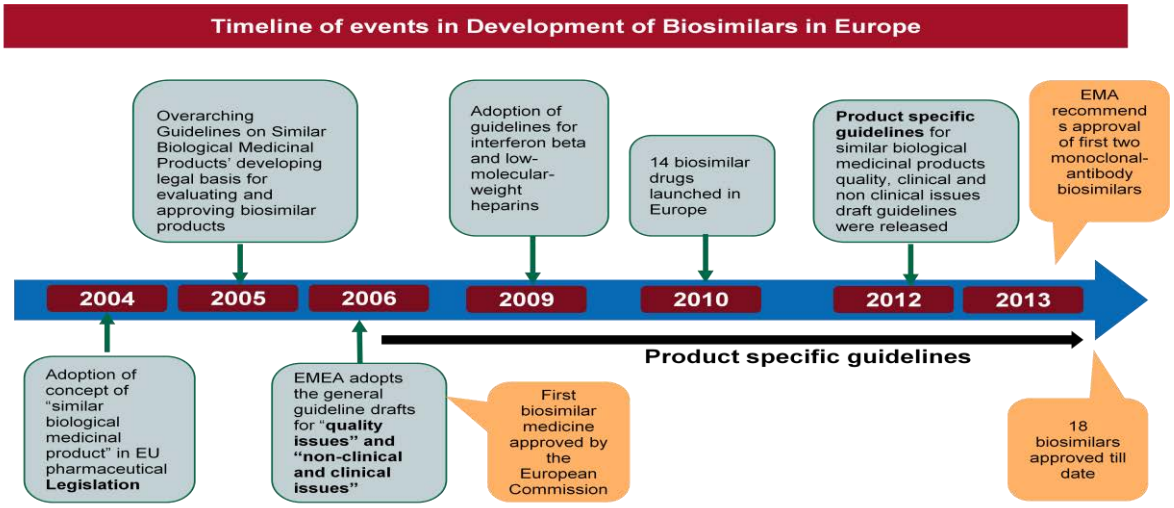
Comments: Existence of an approval pathway reduces regulatory confusion creating a more welcoming environment

This parameter has been taken into consideration because existence of defined legislation and associated guidelines in a geography for biosimilars and releasing them to all into the global industry market helps facilitating knowledge of exact legislative requirements for approval of biosimilars and ensures clarity in the mind of manufacturers to cause their biosimilar approved in other countries apart from their domestic geographies.

As is **Europe European Medicines Agency (EMA) is the key regulatory body for biosimilars**

- It is a decentralized agency responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union
- Under which lies two sub committees working party and CHMP

- EMA's Committee for Medicinal Products for Human Use (CHMP)
  - prepares scientific guidelines in consultation with regulatory authorities in the European Union (EU) Member States
  - substantiate data to claim similarity
  - addresses planning and conduct of comparability studies that forms basis for marketing authorization application



CHMP*- Committee for Medicinal Products for Human Use, EMA – European medicines agency

Sources: ipapharma.org, ema.europa.eu1, ema.europa.eu2, ema.europa.eu/ema/index

Key Developments:

In 2004 Adoption of concept of "similar biological medicinal product" in EU pharmaceutical Legislation

In 2005 Overarching Guidelines

In 2006 product specific guidelines also the general guideline for "quality issues" and "non-clinical and clinical issues" were adopted.

Along with EMA, the national regulatory authorities too exist for each of the five EU5 member states

Country (EU-5)	Name of Local Regulatory Body
Italy	The Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA)
Spain	The Spanish Agency for Medicines and Health Products (Agencia Española de Medicamentos y Productos Sanitarios, AEMPS)
Germany	The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM)
France	National Security Agency for Medicines and Health Products (ANSM)
U.K	Medicines and Healthcare products Regulatory Agency (MHRA).

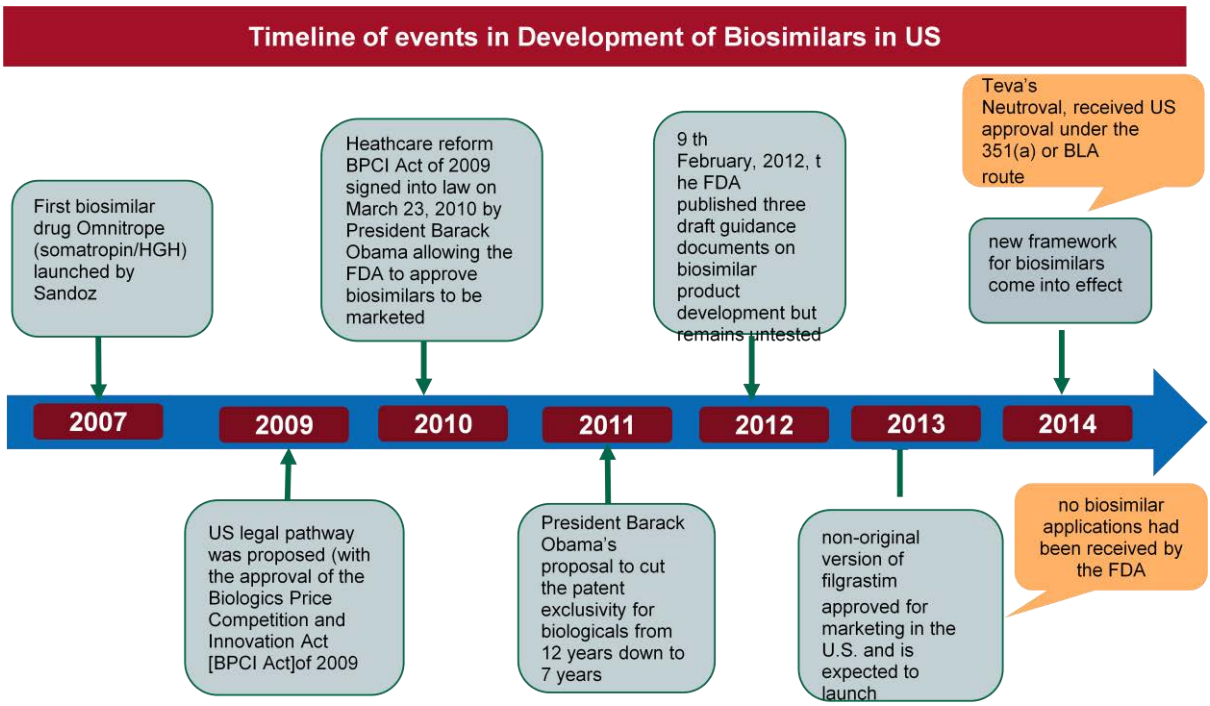
Source for data: ema.europa.eu/ema/index, gabionline/Italian-Medicines-Agency, gabionline/biosimilars-policies-in-Spain gabionline.net.Germany, pmlive.french, pharmalinkconsulting

In United States (U.S.) legal pathway for biosimilars was proposed (with the BPCI act of 2009 signed into law on Mar 23, 2010 by president) allowing the Food and Drug Administration (FDA) to approve biosimilars to be marketed). **USFDA** (Unites States food and drug administration) with CDER/CBER – is the key is key regulatory authority. Thereafter, in Feb 2012, the FDA published its three draft guidelines.

- FDA has established three committees to ensure consistency in regulatory approach
  - CDER/CBER biosimilars Implementation Committee:
    - developing initial interpretation of the statute

        - policy development
        - resource needs
    - CDER biosimilars Review Committee:
        - product-specific and scientific issues related to biosimilars within CDER
    - CBER biosimilars Review Committee:
        - Note: USFDA – United states food and drug administration, BPCI – Biologics price competition and innovation act, CBER – Center for biologics evaluation and research, CDER – center for drug evaluation and research, BRC – biosimilars review committee, US PHS – United states public health service act, US FD&C – United state food, drug and cosmetic act
        - Same as CDER BRC but it's for biologics rather than chemical drugs
- The FDA released three draft guidelines
    - First "scientific considerations in demonstrating biosimilarity to the reference product."
    - Second "quality considerations in demonstrating biosimilarity to the reference protein product."
    - Third "questions and answers regarding implementation of biologics price competition and innovation act of 2009."
- Additional FDA guidelines are Interchangeability, Non proprietary naming, Labeling, Sample retention, Quality attributes that shift over time, Product specific guidelines

FDA's CDER and CBER both have regulatory responsibility for therapeutic biological products; they consult with each other regularly and whenever necessary



Sources : imshealth, goldstandard, thomsonreuters, imshealth.com, gabionline

Note: USFDA – United states food and drug administration, BPCI – Biologics price competition and innovation act, CBER – Center for biologics evaluation and research, CDER – center for drug evaluation and research, BRC – biosimilars review committee, US PHS – United states public health service act, US FD&C – United state food, drug and cosmetic act

Sources: gabi-journal.net, safebiologics.org, biosimilarsnews, fda.gov

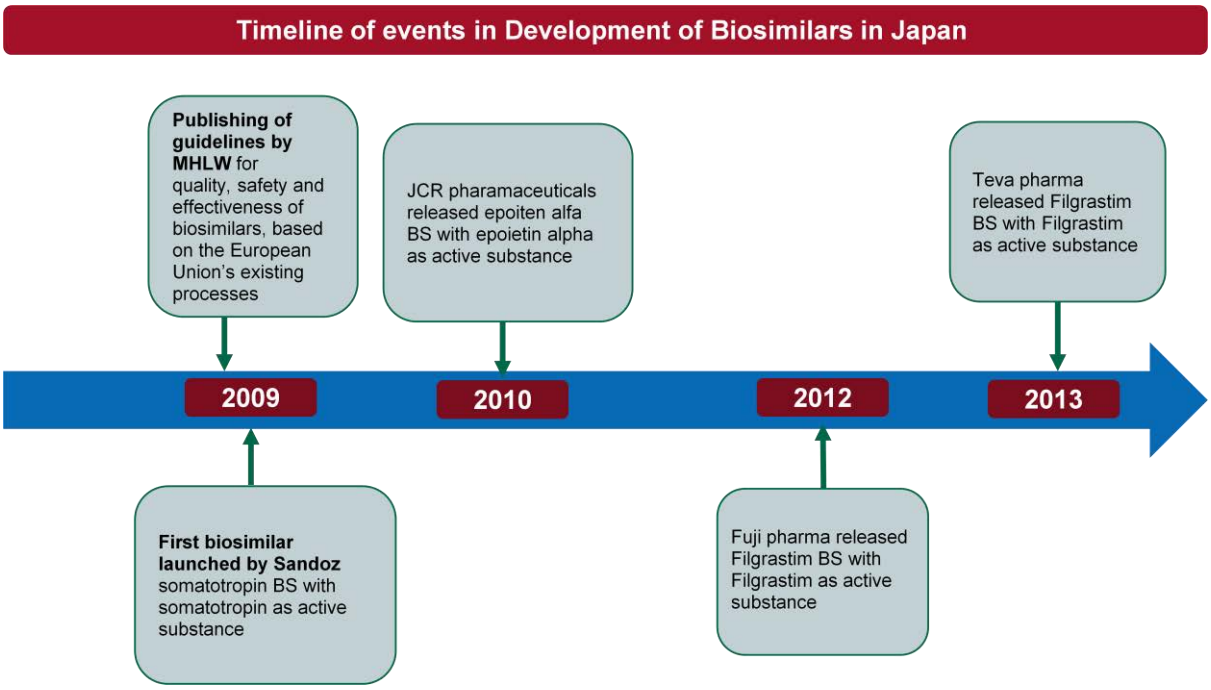
In Japan, biosimilars guidelines following the principles of the EU framework were established by Japan's **Ministry of Health, Labor and Welfare in March 2009**

- The guidelines cover
  - Manufacturing process
  - Characterization of quality attributes

- Clinical and non-clinical studies for biosimilars

- A guideline was published in 2009 by the Ministry of Health, Labor and Welfare (MHLW) on the quality, safety and efficacy of the biosimilars products.

- The guideline covers specific product categories (i.e., recombinant vaccines, PEGylated recombinant proteins and non-recombinant proteins that are highly purified and characterized) while excluding others (e.g., polyglycans and synthetic peptides).



Sources: [gabionline.net](), [gabionline.net/Japanese-guidelines]()

- Four biosimilars drugs have been approved in Japan till date

China (SFDA): "State Food and Drug Administration" (SFDA) in China had approved 40 biopharmaceutical products up until December 2011 the majority of which were domestic Biosimilars. Guidance for Review and Approval of Biosimilar Products guidelines was announced by DOH in 2008, and is mainly based on EMA guidelines with consideration of local regulatory environment. China has not established a regulatory pathway of its own for biosimilars development also there is no indication that China will establish a biosimilar regulatory pathway in the next five years making the registration process highly lengthy and costly.

The Chinese Revised Provisions for Drug Registrations require biosimilars to be treated as new biologic drugs and is required to complete a full clinical development program, and submission documents and timelines for biosimilars are the same as for all clinical trial applications

Typically, four phases of clinical trials are required for biologic drugs even if the innovator brand is marketed in China. The entire registration process typically takes six years or longer when accounting for both clinical trial application/new drug indication (CTA/IND) and new drug approval (NDA) time.

All pharmaceuticals go through the same centralized drug registration process for approval.

- Guidelines for Registration of Drugs (2010)
- Guidance for Review and Approval of Recombinant Protein Drugs (2002)
- Guidance for Review and Approval of Biosimilar Product (2008)
- Points to Consider for Common Technical Documents (CTD) in Review and Approval of Biosimilar Product (2010)

http://www.raps.org/focus-online/news/news-article-view/article/4511/regulatory-approval-of-biosimilars-a-global-perspective.aspx

Russia: There does not exist any dedicated regulatory authority for biosimilars. As on 31 may 2013 Russia has not yet developed a regulatory framework for biologicals or biosimilars. In fact, Russia has yet to define what a biosimilar is, and Russian Law does not yet recognize biosimilars as distinct products.

Director of The Ministry of Health of the Russian Federation's Department for State Control over Drug Circulation, confirmed that the definition of biosimilars was being introduced legislatively, and that standards and regulations were being discussed, with particular attention to interchangeability and the choice of reference drugs for comparative evaluation.

Russia does have some simple, non-innovator biologics (e.g., epoetin alfa, filgrastim, somatropin) that were not required to demonstrate comparable safety and efficacy to a previously approval biologic brand 1

Based on the above literature review for the parameter the below mentioned ranking on likert's scale have been allocated to study geographies:

Table 1 Ranking based on Existence of legislation for regulatory approval pathway for biosimilars

Spain	5
Italy	5
France	5
Germany	5
United Kingdom	5
United States	4
Japan	3
Russia	2
China	2

Low (1)				High (5)
1	**2**	**3**	**4**	**5**
No standard guidelines/pathway for the approval of biologics	No standard guidelines/pathway for the approval of biosimilars, but approval pathway/guidelines present for biologics	biosimilar guidelines adopted from EMEA by the regulatory authority without any changes in regulatory approval structure	Biosimilar guidelines adopted from EMEA by the regulatory authority, thereafter changes brought in regulatory approval structure by the authorities and created their own	EMEA guidelines followed for the approval of biosimilars

10.2 Reference Product Approval required in the Domestic Country:

Definition: Whether or not a regulatory agency requires that a biosimilar be compared to a locally licensed and sourced reference brand

Comments: Necessity of the approval of the reference product in the specific region for the approval of the biosimilar in the similar geography

In cases where the approval of the reference product is not required in the same geography, then whether the specific country is open for comparing non-innovators to biosimilars or biologics approved in the different geographies

In Europe Facilitating global development of biosimilars CHMP allows the applicant to use non-EEA authorized reference bio therapeutic product fulfilling certain conditions.

- **2006**: As per EMA's guidelines single reference medicinal product, authorized under EEA* fulfilling complete dossier requirements is recommended to be used as the reference bio therapeutic product for comparability programme for quality, safety and efficacy studies during the development of a biosimilars
- **2013**: CHMP released draft guidelines in 2013 with the aim of:
  - Facilitating the global development of biosimilars
  - To avoid unnecessary duplication of clinical trials as was under the existing policy.
- This allows an applicant to compare the biosimilars in certain clinical studies and in vivo non-clinical studies with reference bio therapeutic product batches sourced from outside the European Economic Area (EEA)
  - RBP* need to be representative of reference bio therapeutic product authorized under EEA
  - Approved by a regulatory authority with similar scientific and regulatory standards as EMA (i.e. ICH countries)
  - Applicant must provide adequate data or information to scientifically justify the relevance of these comparative data, establish an acceptable bridge to the EEA-authorized reference product
  - Include data from analytical studies, clinical PK and/or PD that compare all three products (the proposed biosimilars, the EEA-authorized reference bio therapeutic product and the non EEA-authorized reference bio therapeutic product).
  - All comparisons should meet the target acceptance criteria for analytical and PK/PD similarity which will be determined on a case-by-case/product-type basis, should be discussed upfront with the Regulatory Authorities.

Source for data: ema.europa.eu, ema.europa.eu/ema/index, ema.europa.eu/EEA, eu/commission, Gaskin_PPD_Biosimilars, processdevelopmentforum

EEA- European Economic Area, ICH-International Conference for Harmonization, RBP- Reference bio therapeutic product

In United States FDA draft guidance documents suggests Reference product should be approved and marketed in the US, non U.S. licensed products may be used in comparability studies if an appropriate bridge can be built to a U.S. licensed reference product2

- It is unclear as to what the bridging data should consists
- Projected barriers to acceptance of non-U.S licensed RBP:
  - FDA moving towards global harmonization of biosimilars approval process
  - Interchangeability currently not being considered by FDA
  - Marketing strategies for US biosimilars entrants have to take into account whether foreign derived clinical trial data will be discouraging factor in physician decision making in prescribing one biosimilars over another

Source for data: thomsonreuters.com

In Japan: Reference product must be approved in the target geography only.

The reference products should be drugs approved in Japan and be the same product throughout the development period of the biosimilar products

http://www.china-pharm.net/download/ispe2013web/pdf-download/1030-2e.pdf

Based on the above literature review for the parameter the below mentioned ranking on likert's scale have been allocated to study geographies:

Table 2 Ranking based on Reference Product Approval required in the Domestic Country

Spain	4
Italy	4
France	4
Germany	4
United Kingdom	4
United States	5
Japan	3
Russia	1
China	1

Low (1) High (5)

1	2	3	4	5
No information available on any such restriction	A biolosimilar is approved based using non-innovator biologics as reference product.	ONLY The reference product has to be approved in the target geography will be accepted as RBP	Reference product must be approved in the target geography but batches can be sourced from outside	If the reference product is not approved in the target geography it must be approved in another geography with similar standard or in any other geography with well established pathway

10.3 Status of Indication Extrapolation of Biosimilars:

Definition: Whether or not a regulatory agency allows for extrapolation to indications of the innovator drug for which biosimilar drug has not been tested

In Europe Extrapolation to multiple indications is acceptable (or not) is decided on a case-by-case basis by the CHMP/EMA

- Indication extrapolation is possible based on
  - Achievement of the overall evidence of comparability provided from the quality, non-clinical and clinical comparability exercise, this justifies acceptance of the new medicinal product as a biosimilars and it can then be cross-referred to the clinical data obtained through the extensive experience of the reference bio therapeutic product
  - Adequate scientific justification that includes at least one clinical study in the most sensitive patient population measuring the most sensitive clinical endpoint(s).
  - If pivotal evidence for comparability is based on pharmacodynamics, and for the claimed indications if different mechanisms of action are relevant (or uncertainty exists), then applicants should provide relevant data to support extrapolation to all claimed clinical indications.
  - Extrapolation is possible in case biosimilar has same mechanisms of action or the same receptor(s) are involved as RBP in all indications under consideration (Similar pharmacodynamic properties to RBP)
- Source for data: ec.europa.eu/enterprise, Instructions_Biosimilars

Celltrion's Remsima and Hospira's Inflectra, which contain the same substance, infliximab, and are biosimilar versions of Johnson & Johnson/Merck's Remicade they have the same indications as Remicade, extrapolation of indications is regarded by the EU authorities as acceptable even for complex molecules such as MAbs

Extrapolation of safety and efficacy data to other indications of the reference drug may be possible based on overall evidence of comparability, with adequate justification. One set of studies may be required, whereas for two very different indications, more than one set of studies will be required. In addition, immunogenicity studies should be conducted for each indication

In United States: Biosimilars, in contrast to small molecule chemical generics, cannot automatically claim all indications of the reference bio therapeutic product and any extrapolation of data requires scientific justification

- The FDA is allowing for indication extrapolation for biosimilars as long as the extrapolation is founded on scientific justification
- Following requirements needs to be fulfilled:
  - Similarity with the reference bio therapeutic product must be convincingly demonstrated, based on the totality of the evidence from a thorough comparability exercise
  - If clinical similarity can be shown in a key indication, extrapolation of efficacy and safety data to other indication of the reference bio therapeutic product may be possible, e.g. if the relevant mechanism of action and/or the receptor(s) involved in the extrapolated indications are the same

- The safety profile of the biosimilars must have been properly characterized and unacceptable immunogenicity excluded

The FDA is allowing for indication extrapolation for biosimilars as long as the extrapolation is founded on scientific justification

In Japan Indication extrapolation is permitted, as long as it is scientifically justified by the applicant and the MOA is the same in each indication3

No information for china and Russia

Based on the above literature review for the parameter the below mentioned ranking on likert's scale have been allocated to study geographies:

Table 3 Ranking based on Status of Indication Extrapolation of Biosimilars

Spain	5
Italy	5
France	5
Germany	5
United Kingdom	5
United States	4
Japan	3
Russia	2
China	2

Low (1) High (5)

1	2	3	4	5
Not Allowed	No information available**	Permitted if: 1. Quality and preclinical data are comparable 2. MOA is the same between indications 3. Post-marketing surveillance period for the reference product has expired	Permitted, provided there is scientific evidence irrespective of number of indications for which extrapolation is being done	Possible based on overall evidence of comparability, with adequate justification. One set of studies may be required, whereas for two very different indications, more than one set of studies will be required

10.4 Support offered by the government by means of its policies to Local/MNCs:

Definition: Whether or not a regulatory agency allows for extrapolation to indications of the innovator drug for which biosimilar drug has not been tested

Comments: Indication extrapolation allows for

In Europe some of the EU5 Countries like Germany and Italy have provisions for Prescription quotas, their more widespread use by sickness funds, prescribing encouraged by the health insurance funds, which engage with physicians by way of seminars and "Dear Doctor" letters to help build their confidence in the biosimilar concept, in combination with drug utilization studies.

Other indirect indications of government support are seen in following instances:

Indications:

- Allowing of Non-EEA reference product to be used in comparability exercise indicates government support with the aim of going global
- Pioneered in Formulating Abbreviated approval pathway for biosimilars and releasing them so as to be known to all biosimilars manufacturers across geographies so that no confusion exists in the mind of manufacturers to cause their biosimilar approved in other countries apart from their domestic geographies
- Allowing extrapolation of clinical data of Non -EEA registered reference product to Biosimilars being manufactured in domestic countries if reference product qualifies in the bridging studies

- Policy measures aiming at improving physician prescription behaviour may influence biosimilar uptake, i.e. prescription quotas, budget target, prescription conditions/guidelines (including prescribing by the international non proprietary name (INN) and official recommendations on switching and interchangeability policies)

Spain No evidence of government support Lack of reference pricing and automatic substitution4 but open for MNC's to enter

Italy: Includes prescription quota and prescription targets EU5 countries (Italy) set quotas for biosimilars. No details on quotas' level, setting (ambulatory or inpatient) or indications are provided. In the survey, the countries included (Germany and Italy) prescription targets for biosimilars4

France: No evidence of government support, Lack of reference pricing and automatic substitution4 but open for MNC's to enter

Germany: Includes prescription quota and prescription targets, EU5 countries (Germany and Italy) set quotas for biosimilars. No details on quotas' level, setting (ambulatory or inpatient) or indications are provided. In the survey, the countries included (Germany and Italy) prescription targets for biosimilars4

United Kingdom: No evidence of government support, Lack of reference pricing and automatic substitution4 but open for MNC's to enter.

In United States:

Following Indications suggests positivity of the government:

- Allowing of Non-EEA reference product to be used in comparability exercise indicates government support with the aim of going global

- Formulating Abbreviated approval pathway for biosimilars like EU and releasing them so as to be known to all biosimilars manufacturers across geographies so that no confusion exists in the mind of manufacturers to cause their biosimilar approved in other countries apart from their domestic geographies
- Allowing extrapolation of clinical data of Non -EEA registered reference product to Biosimilars being manufactured in domestic countries if reference product qualifies in the bridging studies4

In Japan: No evidence of government support, No data available on biosimilars

In Russia: Domestic regulations inclined towards giving high support to local companies

The Russian government is supporting development of local versions of both bevacizumab and alteplase suggesting a growing interest in the benefits that non-originator biologics can offer, but plans to implement a biosimilars pathway have not be announced1

Majority of biologics are procured by the government in large quantities and then distributed free at point of care in hospitals, it is unsurprising to hear Ivanov suggest that public healthcare officials are enthusiastic about efforts to substitute high cost imported products for cheaper, domestically produced biosimilars.

There is currently no firm regulatory framework for the approval of biosimilars (although discussions continue to take place) and interchangeability of products for originator brands occurs freely once a biosimilar is launched. "The government is required by law to accept the lowest tendered price for all drugs that are approved in Russia and, to control costs, the government does substitute lower cost generics or biosimilars for branded products," explains Ivanov.

http://www.firstwordpharma.com/node/1114074#axzz2ypWgn8uZ

In China: Domestic regulations providing support to the entry of MNCs in their market Government support available in the geography to help companies venturing into the biosimilar domain

China does not allow import or export of biological samples; all laboratory work must be done locally4

Based on the above literature review for the parameter the below mentioned ranking on likert's scale have been allocated to study geographies:

Table 4 Ranking based on Support by the government policies to local /MNC's

Spain	3
Italy	4
France	3
Germany	4
United Kingdom	3
United States	5
Japan	2
Russia	2
China	5

Low (1) High (5)

1	2	3	4	5
Domestic Regulations are not suppoting biosimilars at all	Domestic regulations inclined towards giving high support to local companies	No information available	Domestic regulations help in formulation of certain policies that helps increasing uptake of biosimilars in their respective markets	Domestic regulations help in formulation of certain policies that helps increasing uptake of biosimilars in their respective markets, also providing support to the entry of MNCs in their market

10.5 Status of Biosimilar Interchangeability:

Definition: Whether or not a regulatory body allows for interchangeability of a biosimilar for the originator product with reference to the prescribing physician

Comments: The regulatory bodies encouraging interchangeability with the prescribed biologics would result in increased opportunity for biosimilars

In Europe EMA allows interchangeability although at the discretion of the prescribing physician(as only those biosimilars which are prescribed by the physician(interchangeability) can be dispensed by the pharmacist) so physician informed consent is important as said by the national regulatory authority, since EMA has left it to the decision of national regulatory authority to decide upon interchangeability.

Neulasta and Granocyte are often perceived by physicians as interchangeable with Neupogen, making switching to biosimilar Neupogen less of a barrier to uptake interchangeability and/or substitution remain the responsibility of national regulatory authorities.

In United States: Only if assigned by FDA through appropriate data (i.e., from clinical Trial) or only after first year after launch.

The BPCI Act includes a further incentive for biosimilar product developers to invest in interchangeability studies

The U.S. is the only country to formally allow an "interchangeable" designation for biologic medicines. In Europe for example, the EMA does not make recommendations

on whether a biosimilar could be used interchangeably with its reference medicine, this is a matter for the national competent authorities[11]

http://www.amgen.com/science/substitution_interchangeability.html

In order to gain a label for interchangeability, applicants must demonstrate biosimilarity, then also that the product would be expected to produce the same clinical result as the reference product in any given patient.

In addition, the BPCI Act includes a further incentive for biosimilar product developers to invest in interchangeability studies. After the first biosimilar has been deemed interchangeable with a particular reference product, subsequent biosimilars will not be permitted to gain interchangeability until either 180 days after commercial launch, or 1 year later if launch required a successful patent infringement action. The exclusivity also expires 36 months after approval if launch has not occurred due to ongoing litigation, or 12 months after approval if the subsequent biosimilar applicant has not been sued.

Interchangeability with a reference product can be sought in an initial 351(k) application. However, the FDA has highlighted the difficulty of this approach compared to approval for biosimilarity first, particularly since the requirements for interchangeability have not yet been determined. In order to gain a label for interchangeability, applicants must demonstrate biosimilarity, then also that the product would be expected to produce the same clinical result as the reference product in any given patient.

The granularity of patient sub-groups required to demonstrate equivalence in any patient is not entirely clear. Data monitor believes that this will differ on a case-by-case basis, depending upon the variation observed between groups and the perceived risk of safety issues. The FDA has indicated that broader PPK studies should be considered for

biosimilarity approval where variability in PK could result in differences in safety and efficacy and the level of stringency is likely to be set somewhat higher for interchangeability5

The U.S. is the only country to formally allow an "interchangeable" designation for biologic medicines

- The BPCIA gives FDA the authority to designate biosimilars as interchangeable with the reference product
- The biosimilars may be substituted for the originator product by the pharmacist without the opinion of the prescribing physician.
- Conditions:
    - The biologic product is biosimilars to the reference product.
    - It can be expected to produce same clinical results as a reference bio therapeutic production any given patient.
    - For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of biological product and the reference bio therapeutic product is not greater than the risk of using reference bio therapeutic product without such alternation or switch

- Under the BPCI, biologics are separated into two distinct categories
    - products that are “biosimilars” to a reference product
    - products that are “interchangeable” with the reference product
    - In order to meet the higher standard of interchangeability, a sponsor must demonstrate that the biosimilars product can be expected to produce the

same clinical result as the reference bio therapeutic production any given patient, and, for a biological that is administered more than once, that the risk of alternating or switching between use of the biosimilars product and the reference bio therapeutic product is not greater than the risk of maintaining the patient on the reference product[12]

- Source for data: safebiologics.org, www.amgen, www.biosimilarsnews.com, uspharmacist.com

In Japan: Interchangeability is prohibited

- Japan does not allow biosimilars to be interchangeable with their reference bio therapeutic product and automatic substitution cannot apply to biosimilars.
- Additionally points out that substitution of a biosimilars with it reference or innovator product should be avoided throughout treatment.

In Russia: Yes, interchangeability of products for originator brands occurs freely once a biosimilar is launched.

The complexities of the Russian biosimilars market are abundant, suggesting that local expertise will be critical for success (Ivanov notes, for example, that there are numerous available biosimilars that have not undergone large-scale clinical testing). There is currently no firm regulatory framework for the approval of biosimilars (although discussions continue to take place) and interchangeability of products for originator brands occurs freely once a biosimilar is launched. "The government is required by law to accept the lowest tendered price for all drugs that are approved in Russia and, to

control costs, the government does substitute lower cost generics or biosimilars for branded products," explains Ivanov5

In China: Currently, no clinical studies have been undertaken to access clinical outcomes on repeated switches of a Biosimilar product and a reference product. Interchangeable clinical trials have to be executed and demonstrated, the same clinical result in any given patients, the risk in terms of safety is no more than that of using the reference product without a switch.

Based on the above literature review for the parameter the below mentioned ranking on likert's scale have been allocated to study geographies:

Table 5 Ranking based on Status of Biosimilar Interchangeability

Spain	4
Italy	4
France	4
Germany	4
United Kingdom	4
United States	5
Japan	1
Russia	5
China	2

1	2	3	4	5
Interchangeability not allowed	Not clearly mentioned	No information available	Interchangeability permitted by the national regulatory authority only on informed consent of physician	Interchangeability allowed

10.6 Status of Biosimilar Substitutability:

Definition; Whether or not a regulatory body allows for substitution of a biosimilar for the originator product by the pharmacist without reference to the prescribing physician

Comments; the regulatory bodies encouraging substitutability or interchangeability with the prescribed biologics would result in increased opportunity for biosimilars

In Europe: EMA does not allow, Across the EU, decisions on prescribing practices such as substitution is made at national level. I

In EU5 countries (egg: Italy, France and Germany), biologic medicines are specifically excluded from lists of products suitable for substitution

In other countries substitution is permitted only for INN-only prescriptions (egg: Sweden and UK) doctors routinely prescribe biologics by brand.

Spain: Automatic pharmacy substitution of biosimilars is not allowed without expressed permission from prescriber6

Italy: Automatic substitution (at pharmacy level) is prohibited (Substitution is allowed but on case to case basis at the discretion of Italian Medicines Agency (AIFA) depending upon clinical data and physician consent6

France: Automatic pharmacy substitution of biosimilars is not allowed biosimilars do not fall under generics so excluded from French substitution list

- Substitution right* and preference policies for biologicals/ biosimilars**Not yet allowed but the law has been adapted in January 2013 allow the possibility to create groups for substitution (known as group of similar biologicals that will be determined by the ANSM6

Germany: Automatic pharmacy substitution of biosimilars is not allowed

(Biologic medicines are specifically excluded from lists of products suitable for substitution)

Substitution right* and preference policies for biologicals/ biosimilars**: Not allowed in general but substitution is possible for specific groups of biosimilars (same producer)
Groups for substitution:

- Epoetin alfa: Abseamed, Binocrit, Epoetin alfa Hexal
- Epoetin zeta: Silapo, Retacrit.

United Kingdom: Automatic pharmacy substitution of biosimilars is not allowed

Without expressed permission from prescriber6

In United States: The biosimilars may be substituted for the originator product by the pharmacist without the opinion of the prescribing physician.

Under the BPCIA, an interchangeable product, by definition, "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."

Despite the apparent federal intent to freely substitute interchangeable biologicals, legislation was enacted in 5 states last year that requires the prescriber to be notified whenever a pharmacist substitutes a biosimilar product for the agent that was prescribed. In all, 28 bills related to biosimilars substitution were introduced in 18 states last year, said Jessica Mazer, assistant vice president for state affairs at the Pharmaceutical Care Management Association (PCMA).

Mazer said PCMA believes that if FDA classifies one biological as interchangeable with another, substitution should be allowed without the interference of "onerous" state requirements.

Bruce Leichner, senior vice president and general counsel for Momenta Pharmaceuticals, likewise urged FTC to "encourage FDA to adopt a preemption policy with respect to state substitution laws for biosimilars, because interchangeables are meant by statute to be substituted."

http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=4019

http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=4019#sthash.ZRg2lTHx.dpuf

In Japan: Automatic substitution is prohibited, cannot apply to biosimilars.

Additionally points out that substitution of a biosimilars with it reference or innovator product should be avoided throughout treatment6

http://www.china-pharm.net/download/ispe2013web/pdf-download/1030-2e.pdf

In Russia: Substitutability allowed, once approved, biosimilars are legally interchangeable with their branded biologic counterparts that also have received Russian regulatory approval6

In China: Not defined

Based on the above literature review for the parameter the below mentioned ranking on likert's scale have been allocated to study geographies:

Table 6 Ranking based on Status of Biosimilar Substitutability

Spain	3
Italy	3
France	3
Germany	3
United Kingdom	3
United States	4
Japan	1
Russia	5
China	2

Low (1) High (5)

1	2	3	4	5
Substitution not allowed	No information available	Substitution allowed for INN-only prescriptions or if prescribed by the physician himself	Substitutability permitted by the regulatory authority, but still the states seem to be passing bills to object it	Substitutability allowed

10.7 Domestic trial requirements:

Definition: Policies or government defined requirements of domestic biosimilar trials

Comments: No restriction by government in terms of local clinical trial location can turn out to be a positive opportunity for companies seeking to enter a particular geography

In Europe: Trial requirements are uniform across EU5 involving phase I (PK/PD), phase III clinical studies against relevant reference product7

Regardless of where they are conducted, all clinical trials included in applications for marketing authorisation in the EEA must be in accordance with:

the GCP Directive (Directive 2001/83/ECExternal link icon Annex I, as amended by Directive 2003/63/ECExternal link icon);

the ethical standards of the Clinical Trials Directive (Directive 2001/20/ECExternal link icon).

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016817.pdf

Require Phase I pharmaco-kinetic and pharmaco-dynamic trials and study in one representative indication for Phase III clinical studies against relevant reference products7

In United States: In its draft biosimilar question and answer document, the FDA stated that in order to demonstrate biosimilarity, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD)

study must include adequate direct comparisonwith the US-licensed reference product (FDA, 2012c).

Analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study must include adequate direct comparison with the US-licensed reference product (FDA, 2012c).

At least two clinical trials will usually be required for a biosimilar, one examining the PK and PD and the other evaluating efficacy and safety aspects, including immunogenicity

clinical data involving a non-US-licensed reference product can be used to support the biosimilar application if adequately justified with bridging studies

The FDA generally expects human clinical data in a biosimilar submission to include both PK and PD studies (where a relevant measure exists) against the reference product unless scientific justification is given to show that these studies are not necessary. At least two clinical trials will usually be required for a biosimilar, one examining the PK and PD and the other evaluating efficacy and safety aspects, including immunogenicity. As for other stages of the development pathway, clinical data involving a non-US-licensed reference product can be used to support the biosimilar application if adequately justified (see above). It is notable that this must already be considered for innovator product trials and the FDA follows international ICH guidance regarding bridging studies

Where possible, PK measures should be sensitive enough to detect clinically meaningful differences from the reference product – Broader PK studies (population pharmacokinetics [PPK]) should be considered where variability in PK could result in differences in safety and efficacy. Data monitor

In Japan: Non clinical Animal pike and pd studies; clinical pike and pd sudies; if required efficacy studies followed by post marketing surveillance

It is necessary to carry out comparability studies between the biosimilar and the reference product for pharmacokinetic, pharmacodynamic, efficacy and safety parameters.

Where comparability has been demonstrated through clinical pharmacokinetic, pharmacodynamic or pharmacokinetic/pharmacodynamic studies, further clinical studies may be reduced in some cases. In general, a well-designed crossover study should be considered in order to evaluate the comparability between the biosimilar and the reference product. However, a crossover study may not be suitable for long half-life products or products which may cause formation of antibodies7

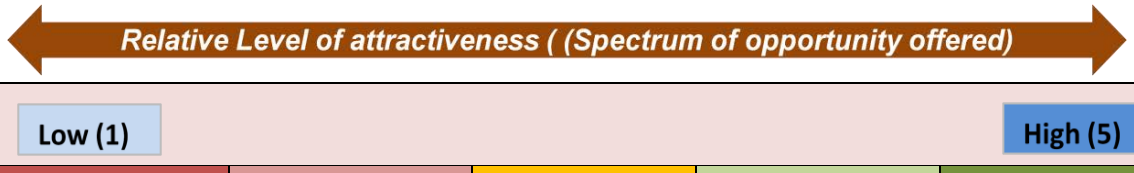
In Russia: Russian regulations require that a clinical trial is conducted in Russia; this requirement and the relatively large pharmaceutical market size are likely to be major contributing factors to the relatively high number of biosimilars trials that MNCs are conducting in the country7

In China: No information is available

Based on the above literature review for the parameter the below mentioned ranking on likert's scale have been allocated to study geographies:

Table 7 Ranking based on Domestic trial requirements

Spain	5
Italy	5
France	5
Germany	5
United Kingdom	5
United States	5
Japan	2
Russia	3
China	2



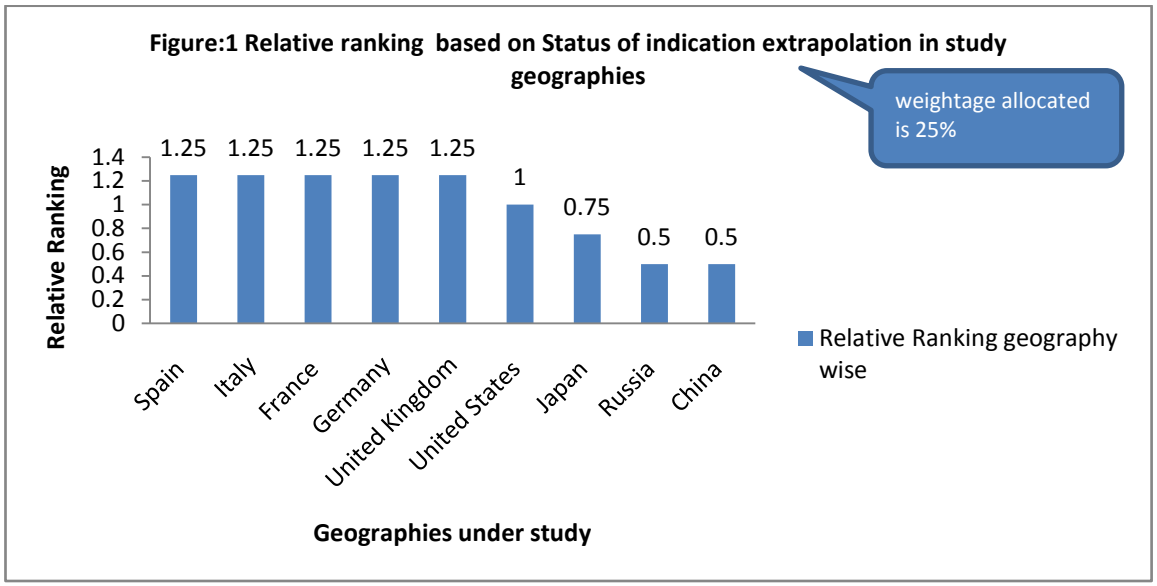
1	2	3	4	5
government has no comments on it	No information available	Government ask clinical trials to be conducted in their respective geography	government prefers conducting local trials however not mandatory	Government is flexible enough offers no restriction in terms of local clinical trial location

11. Findings

Relative ranking as per allocated weights to each of the regulatory parameters under study in each of the geographies:

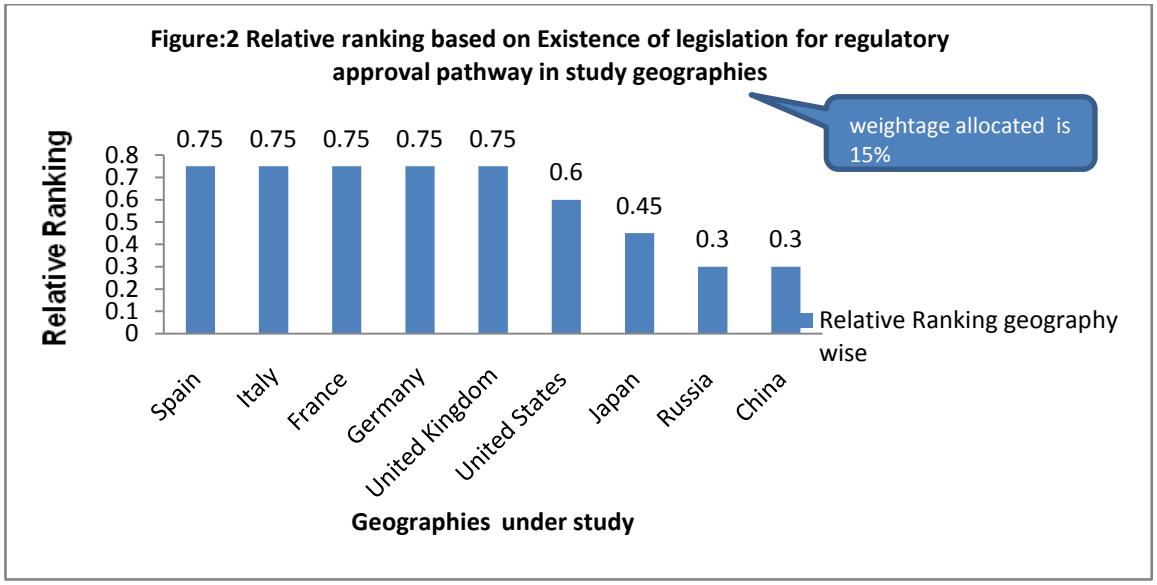
Parameters specific charts have been placed in descending order of weights allocated.

Figure 1 Relative ranking based on Status of indication extrapolation in study geographies



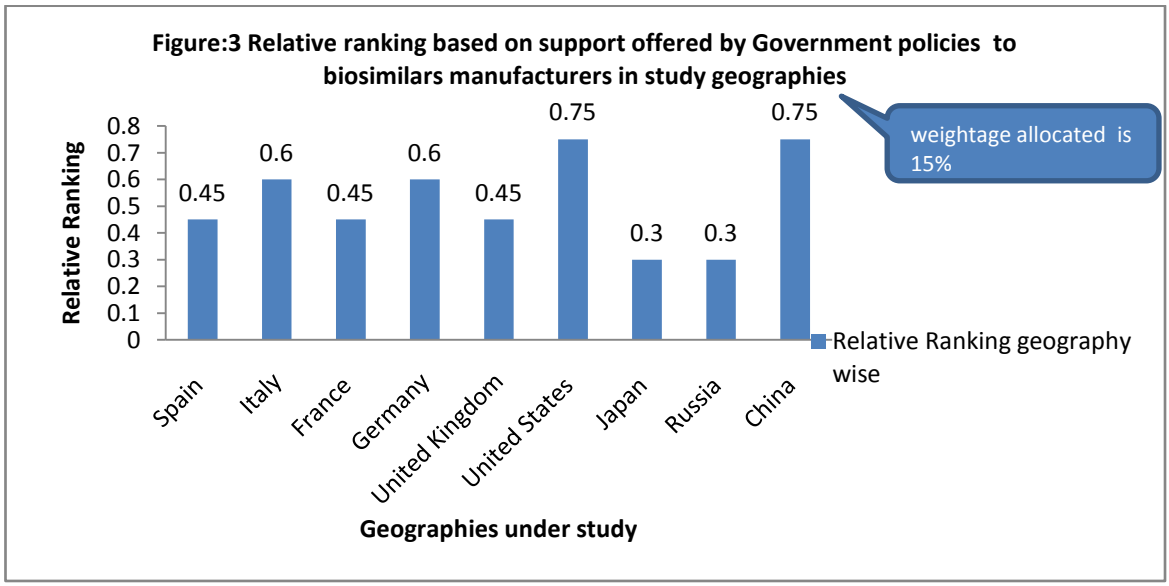
Interpretation: As seen in the chart Europe comprising of all EU5 countries which is already the biggest market for biosimilars till date shows the highest ranking that means it offers the least stringent regulation in terms of extrapolation of indication. So this means that study results of clinical studies carried out for one indication can be extrapolated for other indications of the same drug provided scientific justification is adequately provided.

Figure 2 Relative ranking based on Existence of legislation for regulatory approval pathway in study geographies



Interpretation: Here, all EU5 shows highest ranking than rest of the geographies thus indicating the presence of well established and clear cut regulatory approval guidelines.

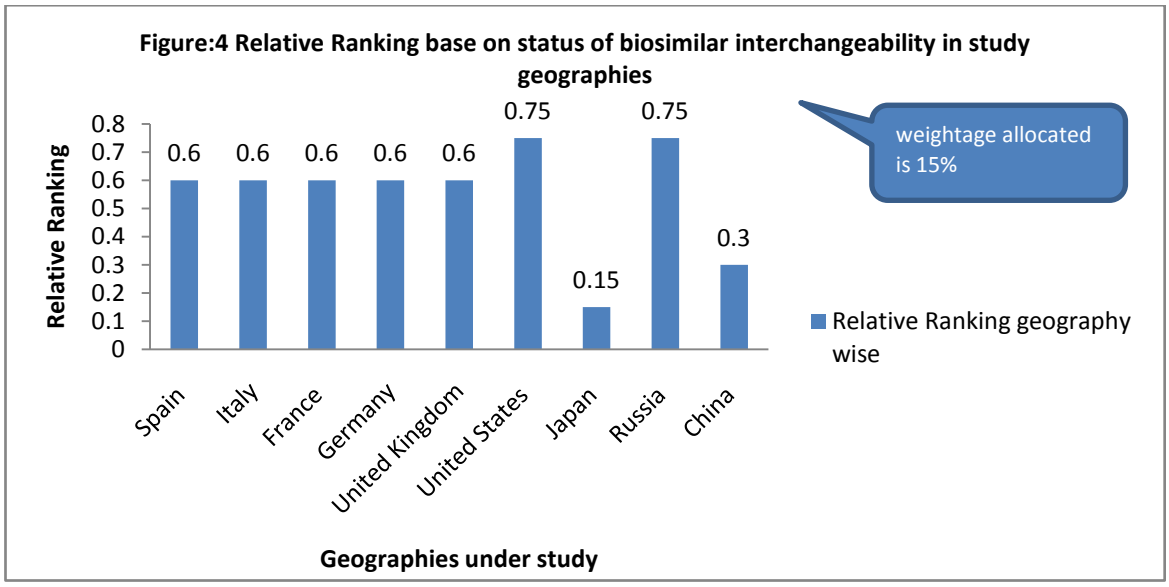
Figure 3 Relative ranking based on support offered by Government policies to biosimilars manufacturers in study geographies



Interpretation: In the above chart Unites States and China can be seen to achieve highest ranking because as per FDA the government in United States will offer high

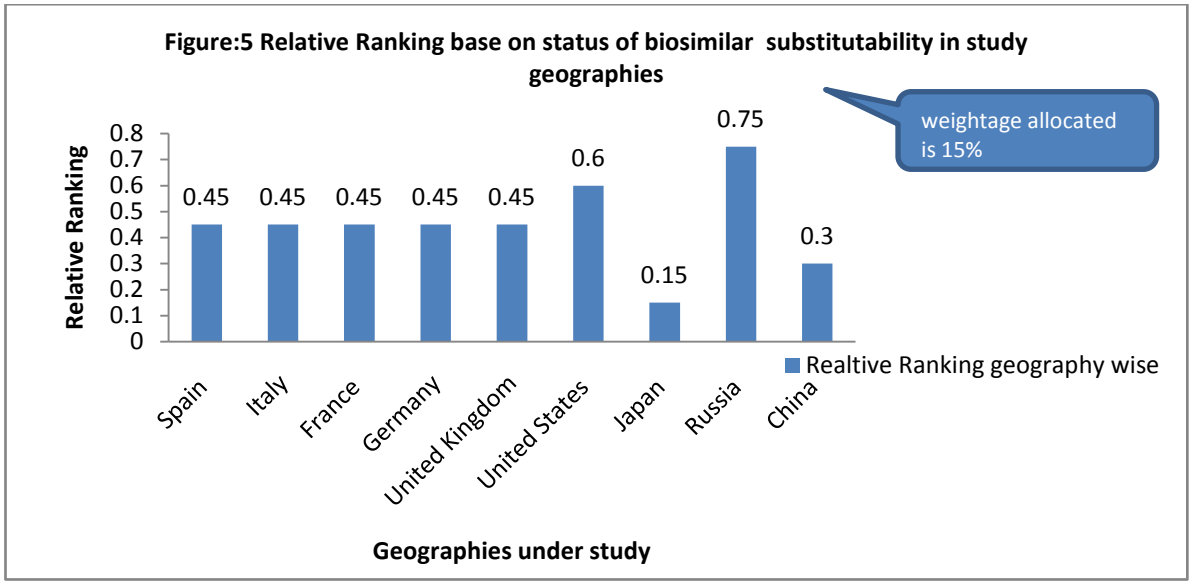
support to MNC'S entry into their biosimilar market in order to go global and develop them as biggest market for biosimilar in coming years by means of designing such supportive policies that are friendly to potential biosimilar entrants. Out of all EU5 government support is highly offered in Germany and Italy keeping prescription quotas, biosimilars under hospital prescribed drugs

Figure 4 Relative Ranking base on status of biosimilar interchangeability in study geographies



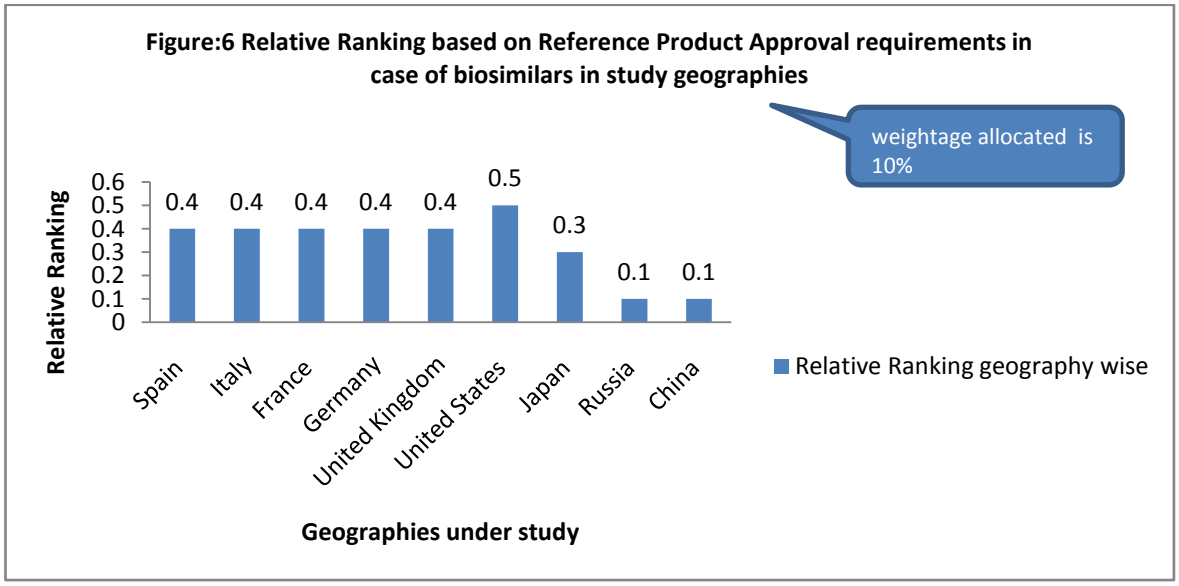
Interpretation: Interchangeability is very well accepted in United States and in Russia once when biosimilars will be launched it has been said that they will be freely deemed interchangeable with biologics so as a result these two geographies have got the highest ranking under these parameters. Europe experiences setback here since in EU5 interchangeability is not accepted but drugs can be interchanged under physician prescription.

Figure 5 Relative Ranking base on status of biosimilar substitutability in study geographies



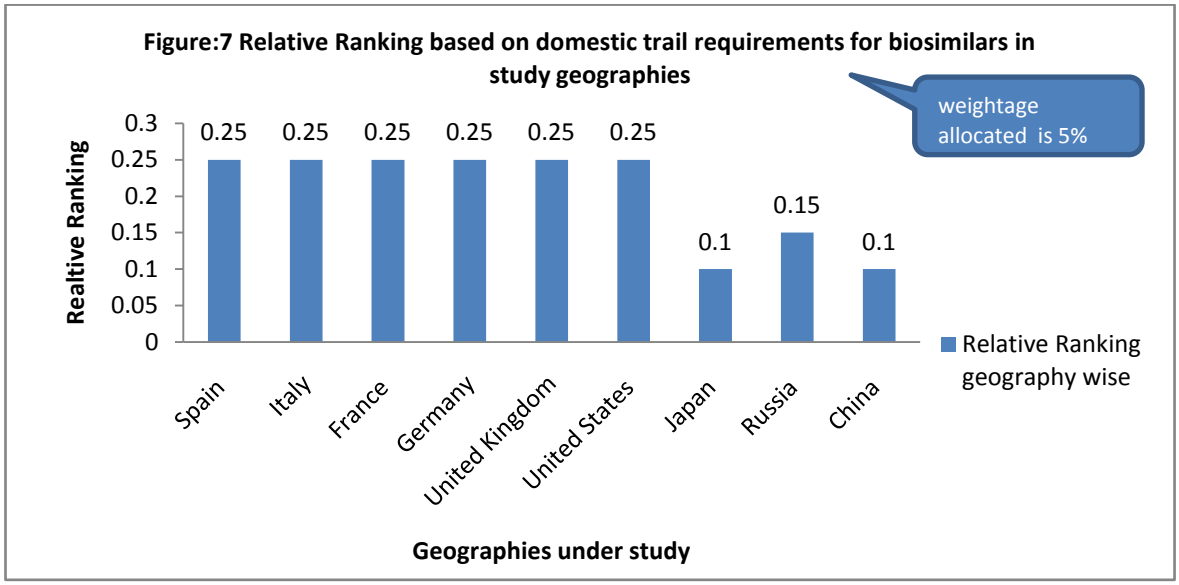
Interpretation: Substitutability is very well accepted in Russia once when biosimilars will be launched it has been said that they will be freely deemed substitutable with biologics so as a result these it has got the highest ranking under these parameters. Next highest rank is for United States where again substitution is acceptable, however in EU5 substitution is not accepted but drugs can be interchanged under physician prescription.

Figure 6 Relative Ranking based on Reference Product Approval requirements in case of biosimilars in study geographies



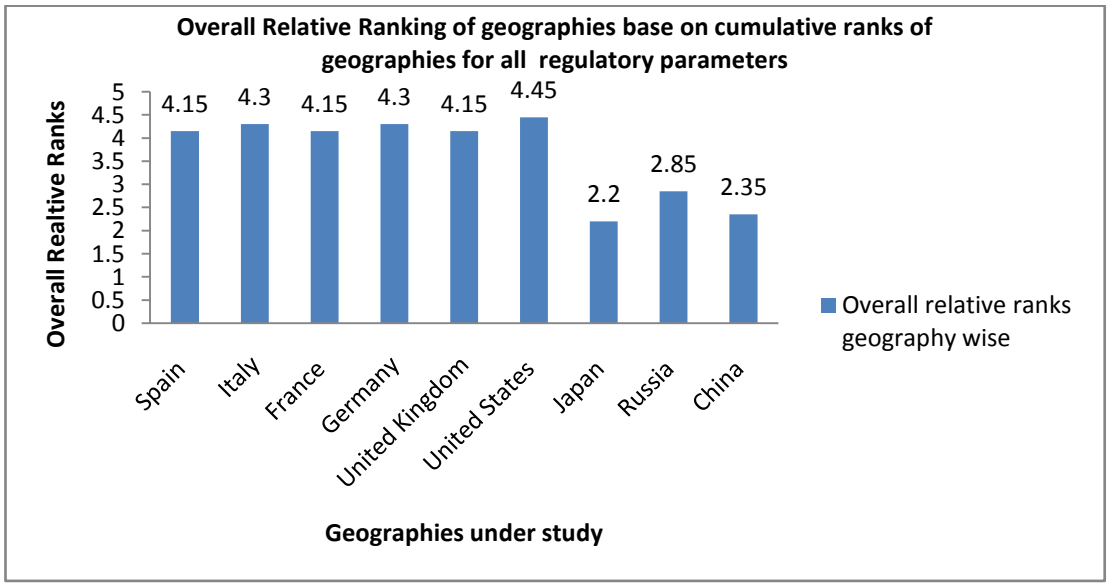
Interpretation: As seen in the chart reference product from other ICH countries or other countries has been proposed to be acceptable by United States this is in effort to go global for building upon their biosimilar market, next best supporting environment is being provided by EU5 reason for being next best is, only batches of reference product approved within their geography can be outsourced unlike U.S. where reference products approved in other similar geographies which follow similar regulatory framework for approval are as such accepted

Figure 7 Relative Ranking based on domestic trail requirements for biosimilars in study geographies



Interpretation: Domestic trial requirements are more or less same in EU5 and United States these two being ICH countries accept each other trial results so they have similar ranks however, the lowest ranking is for Japan and China due to data unavailability. In Russia the condition is strictly to conduct local trials so rank is low.

Figure 8 Overall Relative ranking of geographies base on cumulative ranks of geographies for all regulatory parameters



Interpretation: Overall relative ranking is a cumulative rank got by each geography by adding together individual relative ranks the geographies got for each of the parameter. As per table highest overall relative rank has been achieved by United States so can be considered most opportunistic and least Restrictive market next best market is offered by Germany and Italy due to high extent of government support by means of their policies.

12. Conclusion:

Based upon the study results the United States came out to be most opportunistic or in other way least restrictive market for biosimilar manufacturers because of certain parameters that are less restrictive in U.S. market such as the U.S. government in order to go global and establish themselves as a big biosimilar market has allowed use of reference product from other countries as it is provided their standards are almost same as FDA e.g. International Conference on Harmonization (ICH Countries) unlike Europe where only approved drugs in the country can be just outsourced in batches from other countries.

Allowing extrapolation of clinical data of Non -EEA registered reference product to Biosimilars being manufactured in domestic countries if reference product qualifies in the bridging studies

Other reasons for being at an upper edge to Europe is their regulation that formally announces and accepts “Interchangeability”(this term has been introduced by United States) and Substitution unlike in Europe where interchangeability is not accepted in real terms but as a consequence of physician prescription only then substitution can been carried out by pharmacist.

However, United States need to look up to Europe for creating more positive regulatory environment for biosimilars in terms of allowing for indication extrapolation as in U.S. extrapolation is permitted, provided there is scientific evidence irrespective of number of indications for which extrapolation is being done unlike Europe where extrapolation is permissible based on overall evidence of comparability, with adequate justification. One set of studies may be required, whereas for two very different indications, more than one set of studies will be required

Also, Europe's whose biosimilar legislation which is well established and accepted as a gold standard across the globe by all geographies entering in to biosimilar market space and even United States itself.

On comparing United States to other study geographies it has definitely got an upper edge over them in terms of regulatory scenario being offered by it such as government support being offered by it except for China where too government is highly supportive, also it is more flexible for allowing interchangeability and substitution however, interchangeability will be allowed in Russia as well once biosimilars are launched in their market. Lastly, in terms of existence of legislation which is better defined in U.S. than all other geographies and also reference product approval for which Japan is not at all flexible and for other two geographies data is not available.

13. Limitations: As the literature review was time limited and restricted to English language and to publically available secondary data and published documents, the results found may not be worth recommending or putting forth of any statements. It may be required to further research as the status of study parameters may change on an ongoing basis.

14. Disclaimer

Findings of this study is subject to change in case of change in status of any of the regulatory parameter under consideration in any of the geographies under study since the study is based on the publically available secondary data

15. Ethical considerations:

The following study being based on secondary/desk research will derive data from publically available data sources so there are no associated ethical considerations for the study.

16. References

1 http://thomsonreuters.com/products/ip-science/04_013/anoutlookonusbiosimilarcompetition-cwp-en.pdf
2 http://www.ema.europa.eu/ema/ , http://www.fda.gov/ , http://www.mhlw.go.jp/english/
3 http://www.gabionline.net/
4 ipapharma.org, ema.europa.eu1, ema.europa.eu2,ema.europa.eu/ema/index
5 thomsonreuters.com
6 http://www.china-pharm.net/download/ispe2013web/pdf-download/1030-2e.pdf
7 ema.europa.eu/ema/index, gabionline/Italian-Medicines-Agency, gabionline/biosimilars-policies-in-Spain gabionline.net.Germany, pmlive.french, pharmalinkconsulting
8 Source for data: bio-trends.com, www.gabionline,www.pmda.go, ec.europa.eu/enterprise,
9 Instructions_Biosimilars,
10 http://www.egagenerics.com/images/EGA%20Survey%20to%20MS%20on%20Biosimilars.pdf)
11 http://www.amgen.com/science/substitution_interchangeability.html
12 Source for data: safebiologics.org, www.amgen, www.biosimilarsnews.com, uspharmacist.com
13 source: Rovira, J., et. al. The impact of biosimilars' entry in the EU market. Granada (Spain) : Andalusian School of Public Health, 2011.
14 U.S. Food and Drug Administration. Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). 2012.
15 http://www.shearman.com/~/media/Files/NewsInsights/Publications/2014/02/FTCWorkshopSeekstoSparkBiosimilarsCompetitionAntitrust020614.pdf
16 http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=4019
17 See more at: http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=4019#sthash.ZRg2lTHx.dpuf

18 http://www.china-pharm.net/download/ispe2013web/pdf-download/1030-2e.pdf
19 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016817.pdf
20 **Parameter specific references**

1) Sources for parameter 1

1http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c

1http://www.pharmalinkconsulting.com/wp-content/uploads/2013/05/TOPRA-MAbs-Article-FINAL.pdf

http://www.gabionline.net/Reports/Biosimilar-policies-in-Spain

http://gabionline.net/Guidelines/Italian-Medicines-Agency-publishes-concept-paper-on-biosimilars

http://www.pmlive.com/pharma_news/new_french_regulatory_agency_ansm_afssaps_402076

http://gabionline.net/Biosimilars/General/Biosimilars-approved-and-marketed-in-Germany

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/%20HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm

http://www.raps.org/

http://www.hospira.com/

DR-Global Pipelines, Regulatory Pathways, and Key Stakeholder Perspectives of Biosimilars; March 2013

http://www.gabionline.net/Biosimilars/News/Russia-to-harmonize-biologicals-regulations

http://www.pmlive.com/pharma_intelligence/biosimilars_in_china_460090

http://www.pmlive.com/pharma_intelligence/biosimilars_in_china_460090

extra references

http://www.pharmachinaseminar.com/files/Biosimilars_in_China.pdf

file:///C:/Users/as8432/Downloads/Bettering_China%2527s_Biosimilars.pdf

http://www.raps.org/focus-online/news/news-article-view/article/4511/regulatory-approval-of-biosimilars-a-global-perspective.aspx

2) sources for parameter 2

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500142978.pdf

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/09/news_detail_001615.jsp&mid=WC0b01ac058004d5c1

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/landing/human_medicines_regulatory.jsp&mid=WC0b01ac058001ff89

http://thomsonreuters.com/products/ip-science/04_013/anoutlookonusbiosimilarcompetition-cwp-en.pdf

http://www.lifescienceleader.com/magazine/current-issue-3/item/4545-biosimilars-in-emerging-markets

https://www.google.co.in/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&cad=rja&ved=0CDkQFjAC&url=http%3A%2F%2Fwww.chinabiotoday.com%2Fdownloads%2F20130322%2Fdownload&ei=pXG5Us3BIo3JrQfcsoHgAw&usg=AFQjCNFLPQeRQ-8DoCI-AKFXm5zax-EGMQ&sig2=tCN5R8-YWZNedUL24A8CAA&bvm=bv.58187178,d.bmk

3) **sources for parameter 3**

http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf

C:\Users\as8432\Downloads\ZL101_00_002e_VV_Instructions_Biosimilars (1).pdf

bio-trends.com\News-and-Events\Press-Releases\Biologics-in-Immune-Infectious-Disease-092612

http://www.gabionline/

3.http://www.pmda.go/

3.http://www.healthtrustpg.com/biosimilars/pdf/ppd.pdf

3.http://www.pharmaphorum.com/articles/in-apac-the-biosimilar-market-is-set-to-grow

4) **sources of parameter 4**

4.http://www.egagenerics.com/images/EGA%20Survey%20to%20MS%20on%20Biosimilars.pdf)

4.http://www.firstwordpharma.com/node/1114074#axzz2ypWgn8Uz

4.http://www.healthtrustpg.com/biosimilars/pdf/ppd.pdf

5) **sources for parameter 5**

http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_market_012011_en.pdf

http://www.quintiles.com/library/experts/the-us-approval-pathway-for-biosimilar-products.pdf

269EEB673D&ei=OXr7UuiyDIK8rAeD6IG4BQ&usg=AFQjCNHLmGkHnwvqiExgriGrRFENzkRKtA&sig2=Hlc-TuA_JyXOS5z2tm5_jA&bvm=bv.61190604,d.bmk

http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_market_012011_en.pdf

http://www.amgen.com/pdfs/misc/Biologics_and_Biosimilars_Overview.pdf

http://www.gabionline.net/Reports/Biosimilar-policies-in-Spain

http://safebiologics.org/info-center.php

http://www.amgen/

http://www.biosimilarsnews.com/

http://www.uspharmacist.com/content/s/253/c/41438/

http://www.amgen.com/science/substitution_interchangeability.html

http://www.firstwordpharma.com/node/1114074?tsid=33#axzz2ypWgn8uZ.http://www.patentdocs.org/2014/03/china-pharmaceutical-regulatory-law-boot-camp.html

http://www.ibef.org/download/Biosimilars-in-India-30312.pdf

http://www.ipapharma.org/pt/Jan2013/11-14.pdf

6) **sources for parameter 6**

.http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_market_012011_en.pdf

http://www.quintiles.com/library/experts/the-us-approval-pathway-for-biosimilar-products.pdf

269EEB673D&ei=OXr7UuiyDIK8rAeD6IG4BQ&usg=AFQjCNHLmGkHnwvqiExgriGrRFENzkRKtA&sig2=Hlc-TuA_JyXOS5z2tm5_jA&bvm=bv.61190604,d.bmk

http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_market_012011_en.pdf

http://www.amgen.com/pdfs/misc/Biologics_and_Biosimilars_Overview.pdf

http://www.gabionline.net/Reports/Biosimilar-policies-in-Spain

http://gabionline.net/Reports/Biosimilars-policies-in-Italy

http://www.china-pharm.net/download/ispe2013web/pdf-download/1030-2e.pdf

http://www.ashp.org/menu/News/PharmacyNews/NewsArticle.aspx?id=4019#sthash.ZRg2lTHx.dpuf

http://www.china-pharm.net/download/ispe2013web/pdf-download/1030-2e.pdf

http://www.china-pharm.net/download/ispe2013web/pdf-download/1030-2e.pdf

7) **sources for parameter 7**

All the info has been derived from ZS Subscribed datasources the name of which cannot be shared.

ANNEXURE

Regulatory Setting*	Parameters	Defination	Comments	Relative Level of attractiveness ((Spectrum of opportunity offered) Low (1)				High (5)
				1	2	3	4	5
Regulatory Environrnent	Approval Pathway of Biosimilars	Current status of biosimilar legislation in the relevant geography	Existence of an approval pathway reduces regulatory confusion creating a more welcoming environment	No standard guidelines/pathway for the approval of biologics	No standard guidelines/pathway for the approval of biosimilars, but approval pathway/guidelines present for biologics	Biosimilar guidelines adopted from EMEA by the regulatory authority without any changes in regulatory approval structure	Biosimilar guidelines adopted from EMEA by the regulatory authority, thereafter changes brought in regulatory approval structure by the authorities and created their own	EMEA guidelines followed for the approval of biosimilars
	Reference Product Approval in the Domestic Country	Whether or not a regulatory agency requires that a biosimilar be compared to a locally licensed and sourced reference brand	Necessity of the approval of the reference product in the specific region for the approval the biosimilar in the similar geography In cases where the approval of the reference	No information available on any such restriction	A biolosimilar is approved based using non-innovator biologics as reference product.	ONLY The reference product has to be approved in the target geography will be accepted as RBP	Reference product must be approved in the target geography but batches can be sourced from outside	If the reference product is not approved in the target geography it must be approved in another geography with similar standard or in any other

			product is not required in the same geography, then whether the specific country is open for comparing non-innovators to biosimilars or biologics approved in the different geographies					geography with well established pathway
	Status of Indication Extrapolation of Biosimilars	Whether or not a regulatory agency allows for extrapolation to indications of the innovator drug for which biosimilar drug has not been tested	Indication extrapolation allows for	Not Allowed	No information available**	Permitted if: 1. Quality and preclinical data are comparable 2. MOA is the same between indications 3. Post-marketing surveillance period for the reference product has expired	Permitted, provided there is scientific evidence irrespective of number of indications for which extrapolation is being done	Possible based on overall evidence of comparability, with adequate justification. One set of studies may be required, whereas for two very different indications, more than one set of studies will be required
	Parameters	**Defination**	**Comments**	**1**	**2**	**3**	**4**	**5**

	Government Investment/ Push for Biosimilar Development or to encourage uptake	Government support to the domestic firms versus the MNCs for manufacturing, marketing the biosimilars	Government biosimilar support can include: tax exemptions; and funds for MNCs venturing in to this arena	Domestic Regulations are not supporting biosimilars at all	Domestic regulations inclined towards giving high support to local companies	No information available	Domestic regulations help in formulation of certain policies that helps increasing uptake of biosimilars in their respective markets	Domestic regulations help in formulation of certain policies that helps increasing uptake of biosimilars in their respective markets, also providing support to the entry of MNCs in their market
	Status of Biosimilar Substitutability	Whether or not a regulatory body allows for substitution of a biosimilar for the originator product by the pharmacist without reference to the prescribing physician	The regulatory bodies encouraging substitutability or interchangeability with the prescribed biologics would result in increased opportunity for biosimilars	Substitution not allowed	No information available	Substitution allowed for INN-only prescriptions or if prescribed by the physician himself with his informed consent	Substitutability permitted by the regulatory authority, but still the states seem to be not accepting it and is passing bills to object it	Substitutability allowed

	Status of Biosimilar interchangeability	Whether or not a regulatory body allows for interchangeability of a biosimilar for the originator product with reference to the prescribing physician	The regulatory bodies encouraging interchangeability with the prescribed biologics would result in increased opportunity for biosimilars	Interchangeability not allowed	Not clearly mentioned	No information available	Interchangeability permitted by the national regulatory authority only if, informed consent of physician is there	Interchangeability allowed
	Domestic Trial Requirement	Policies or government defined requirements of domestic biosimilar trials Example: In South Korea, the government does not require the trials to be conducted in their own country for the approval of the biosimilar	No restriction by government in terms of local clinical trial location can turn out to be a positive opportunity for companies seeking to enter a particular geography	government has no comments on it	No information available	Government ask clinical trials to be conducted in their respective geography	government prefers conducting local trials however not mandatory	Government is flexible enough offers no restriction in terms of local clinical trial location