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

A secondary/desk research

Study conducted at ZS Associates
India Private Limited
New Delhi (Global Headquarters)

Worked in Knowledge Management Team under
Business Consulting Track
As Knowledge Management Associate - Intern

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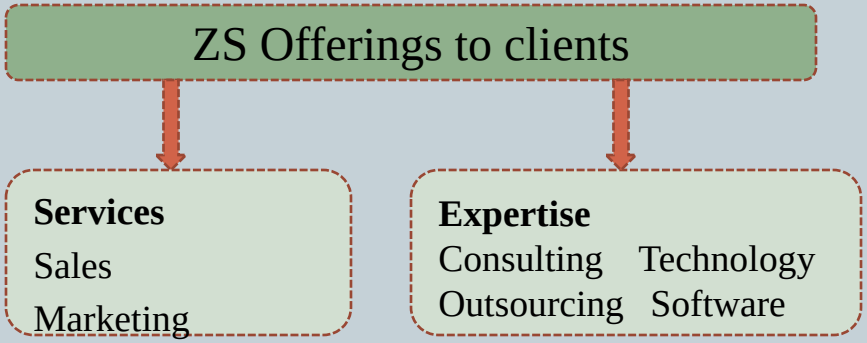
Introduction

- Its a global leader in sales and marketing consulting.
- Majority of clients are top pharmaceutical companies which alone constitutes 85% of total clientele rest 25 % is constituted by medical devices and priority industries.



- Role of ZS for clients
  - Help clients gain market share at lower cost by creating data-driven strategies that they can implement rapidly
  - Providing marketing- and sales-related services like

Customer insight	Product development	Sales and marketing strategies	Sales compensation planning	Plan administration

Biosimilars – An Overview

- **By U.S. FDA**
  - A biosimilars is a biological product that is highly similar to a U.S. licensed reference biological product not withstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference bio therapeutic production terms of the safety, purity, and potency of the product (Source: fda.gov)

Terminology used	Geographies
Biosimilars	Europe and Australia
Follow on proteins/Biologics	US and Japan
Subsequent entry Biologics	Canada
Similar Biologics	Asia excluding Japan

2004 - Adoption of concept of "similar biological medicinal product" in EU pharmaceutical Legislation
2006 - First biosimilars medicine approved by the European Commission
2014 - 18 biosimilars approved till date

2009- US legal pathway was proposed (with the approval of BPCI act
2010 - BPCI act of 2009 was signed into law
2012 - FDA published three draft guidance

2009- Publishing of guidelines by MHLW for quality, safety and effectiveness of biosimilars, based on the European Union's existing processes
2014 – 4 biosimilars launched till date

USFDA – United states food and drug administration, BPCI – Biologics price competition and innovation act,
MHLW – Ministry of Health, Labour and Welfare

Key terms discussed in study

- A **Reference Biotherapeutic Product (RBP)** is used as the reference product for head-to-head comparability studies in order to show similarity in terms of quality, safety and efficacy. Only an originator product that was licensed on the basis of a full registration dossier can serve as a RBP

- **Interchangeability** is where a biosimilars deemed interchangeable with reference product, that are judged to be similar in terms of clinical result in any given patient, show no increased risk in terms of safety or diminished efficacy and can be exchanged one with another without a significant risk of an adverse health outcome

- **Substitution (Automatic substitution in U.S.)** : The practice by which a product other than the one specified on the prescription is dispensed to the patient by the pharmacist, without prior informed consent of treating physician
  - A variation of substitution is practiced in some countries where, if the physician prescribes by international non-proprietary name (INN), the pharmacist may dispense any product with the same active ingredient**.**
- **Extrapolation of indications:** The decision whether to extend the efficacy and safety data from an indication (a medical condition, disorder or disease) for which the biosimilar has been clinically tested to other conditions for which the reference bio therapeutic product being used is approved, is known as " Indication Extrapolation".
- **Biosimilarity** means that the biological product is highly similar to the reference bio therapeutic product not withstanding minor differences in clinically inactive components, with no clinically meaningful differences in terms of the safety, purity, and potency of product

Key Regulatory authorities (Geography wise)

- European Medicines Agency is the key regulatory body for biosimilars and CHMP prepares scientific guidelines in consultation with regulatory authorities in the European Union (EU) Member States
- National regulatory bodies are

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).

In china: SFDA (State Food and Drug Administration)

- The U.S. FDA was authorized to approve follow-on biologics by the BPCI Act passed by the U.S. Congress in 2010, and had issued a draft guidance in 2012

  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:

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**

In Russia: No defined body exists

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

Business Question and Rationale of study

- Finding out the most opportunistic /least restrictive market for biosimilars from perspective of biosimilar specific regulatory environment that exists in study geographies
- Factors that led to the need to raise this question:
  - Undergo stringent regulatory approval process before they can be brought into the market
  - Regulations offers entry barrier for new players willing to enter this market space
  - Established pharmaceutical manufacturers first need to know the suitable markets based on regulatory setting that exists

- **<u>Rationale of the study:</u>**

  - Study involves finding out the most opportunistic markets depending upon secondary data.
  - Opportunity assessment will help pharma MNC'S to decide upon in which geographies they should investment for biosimilars depending upon favourability of market from regulatory perspective.
  - Study determines the analysis by ranking seven major markets on the Likert's scale taking specific regulatory parameter into consideration 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.

Research Questions and Objectives

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

- **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.

- **Objectives:**
  - 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).
  - To determine and pick up those biosimilar regulatory parameters that has greatest influence in determining the regulatory scenario in these geographies.
  - To determine compliance of geographies under consideration to the study parameters and allotting the ranks accordingly.
  - To determine the most opportunistic geography/geographies as a biosimilar market from regulatory environment perspective based on overall rankings.

Study design and **Methodology:**

- Type of study: **Exploratory Secondary/Desk Research**
- Geographies under study
  - EU5 (United Kingdom, France, Germany, Spain, and Italy)
  - United States of America
  - Japan
  - Pharmerging markets (China, Russia)
- Data (information) collected: Recording of regulatory scenario in study geographies with respect to regulatory parameters under consideration.
- Data collection tools: ZS Specific data sources and publically available secondary data sources have been deployed to derive data.

- **Methodology**
  - **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:
    - Discussions based on the market trends seen for biosimilars uptake
    - The projected potential markets based on forecasted sales in the geographies
    - Taking into consideration the regulatory setting and environment existing for biosimilars already launched in the market in the geographies.

Literature Review and parameters

- **Literature Review:**
  - ZS specific Data sources* are searched 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.

- **Deciding upon the parameters:** 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

Listing parameters &Ranking of geography

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

- 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.
- **Likert's scale** was used as a tool to rank the variations in regulatory scenario with respect to above seven parameters
- On 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
- 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)***

Allocating weights to regulatory parameters and Calculation of relative ranks and overall ranks of geographies

Regulatory parameter	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%

Calculation of relative ranking:

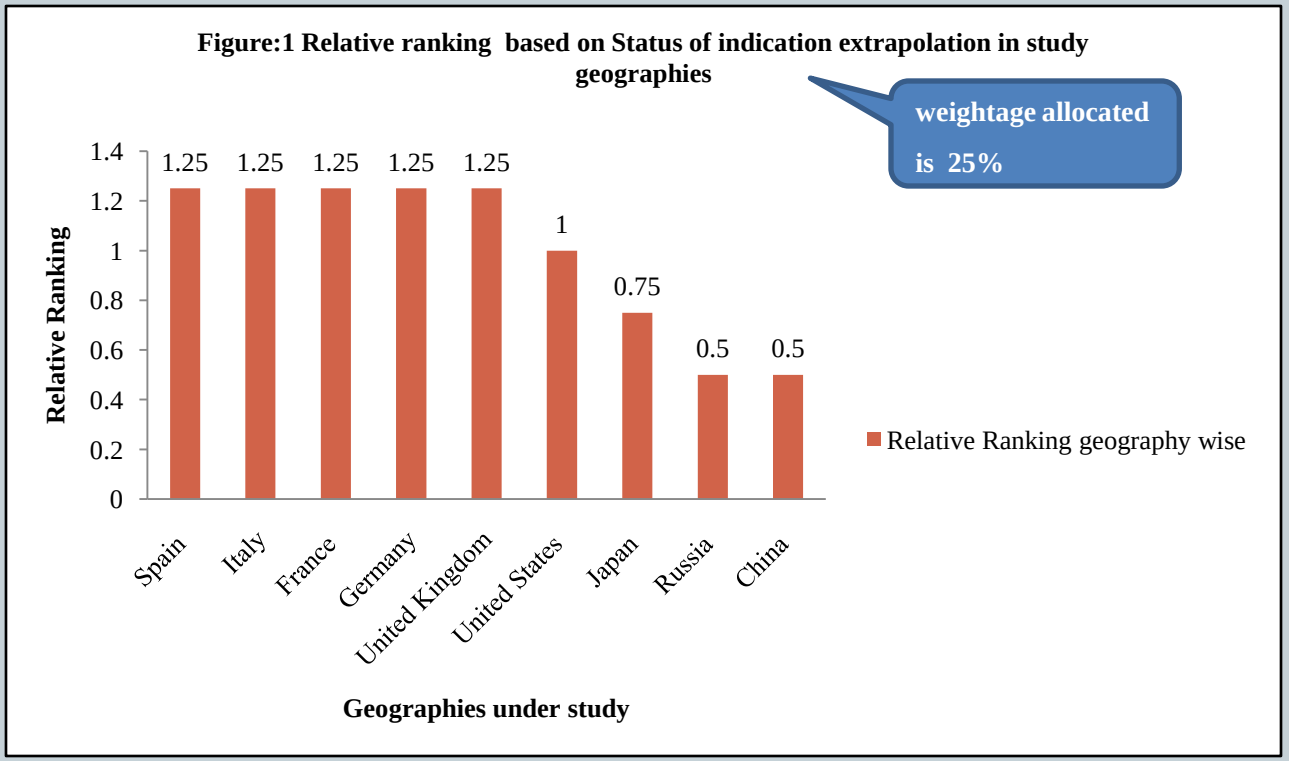
- Relative rank of geography with respect to regulatory parameter = likert's scale rank given to geography* weight allocated to respective regulatory parameter
- Example: rank on liket's scale for status of biosimilar substitutability in Spain i.e. 3*15% (weight allocated to this parameter) = 3*15% or 0.15 = 0.45

Calculation of overall relative ranking of geography

- 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 = (1.25+0.75+0.45+0.6+0.45+0.4+0.25) = 4.15 out of 5

Findings

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



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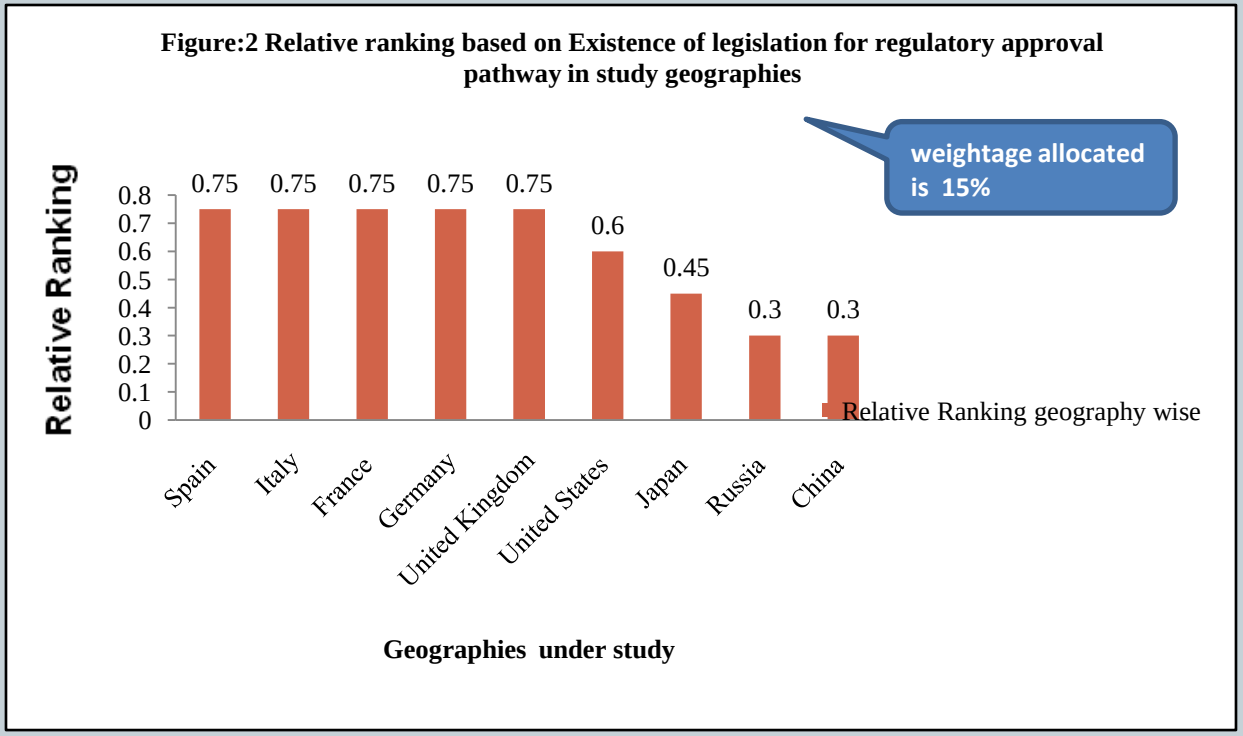
- **Figure 2 Relative ranking based on Existence of legislation for regulatory approval pathway in study geographies**



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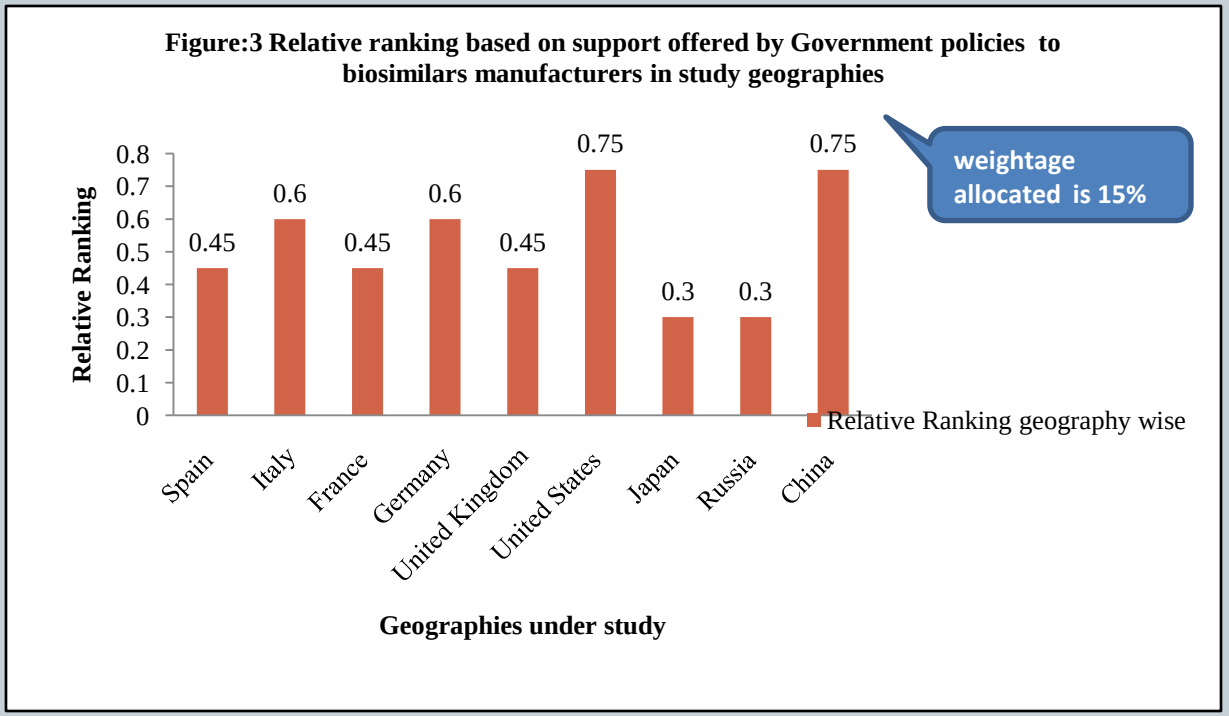
- **Figure 3 Relative ranking based on support offered by Government policies to biosimilars manufacturers in study geographies**



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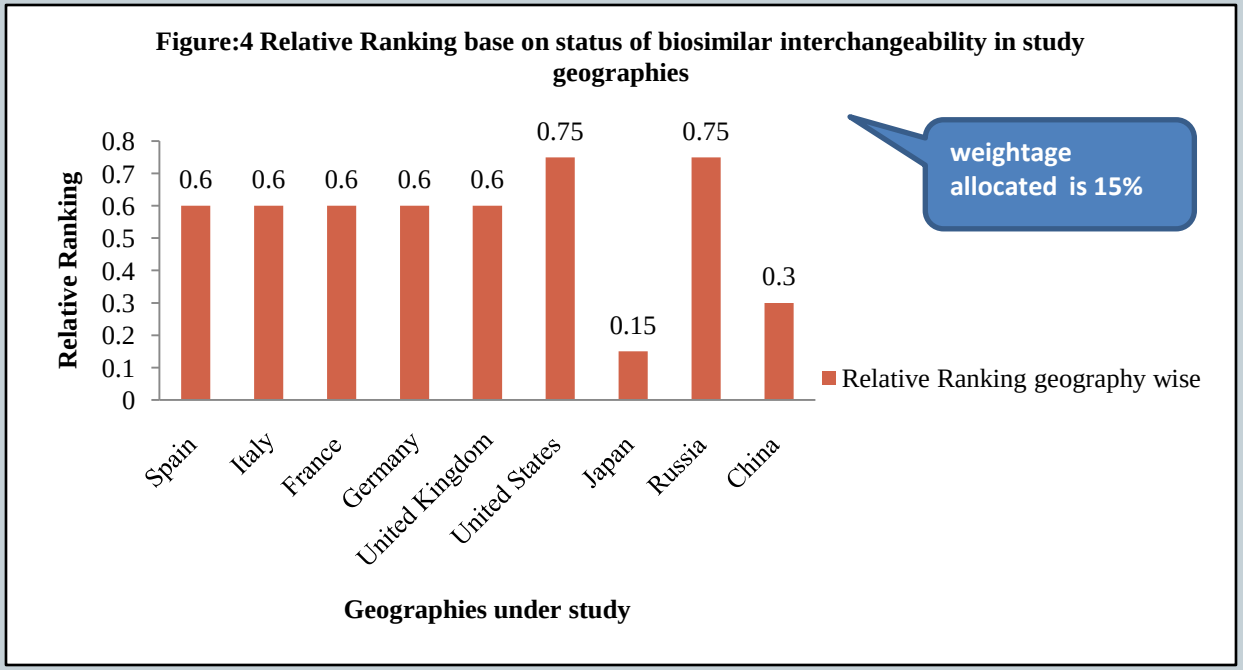
- **Figure 4 Relative Ranking base on status of biosimilar interchangeability in study geographies**



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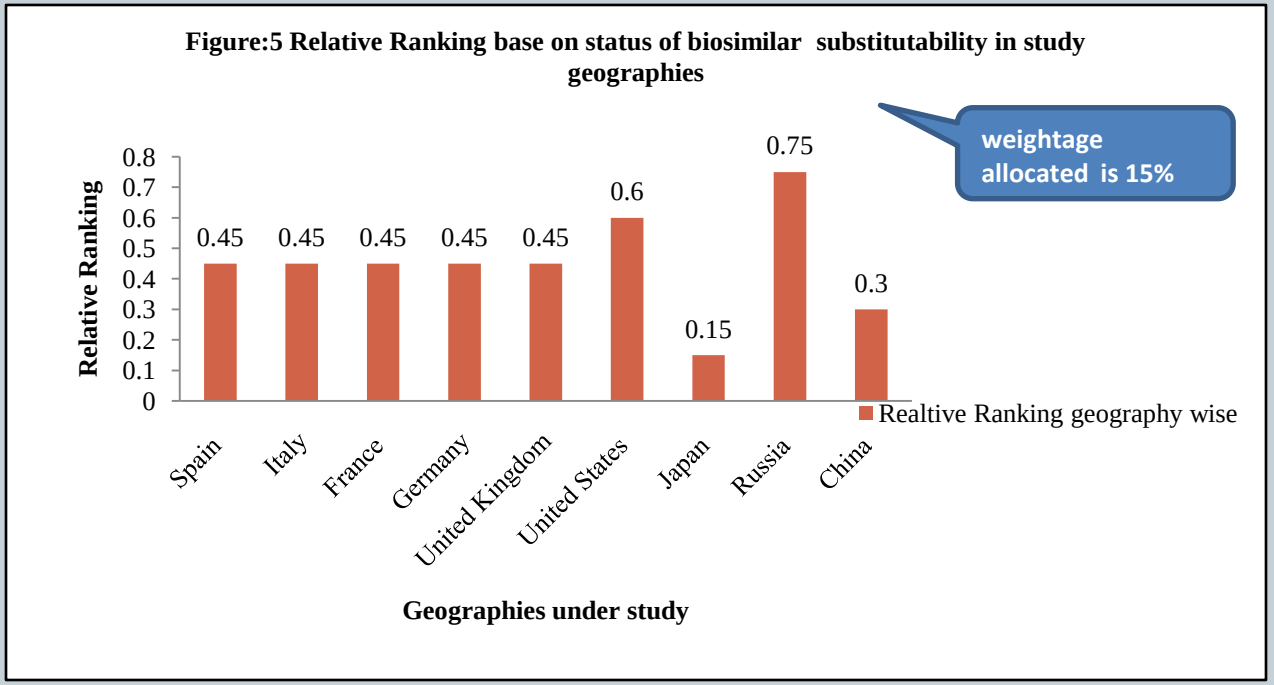
- **Figure 5 Relative Ranking base on status of biosimilar substitutability in study geographies**



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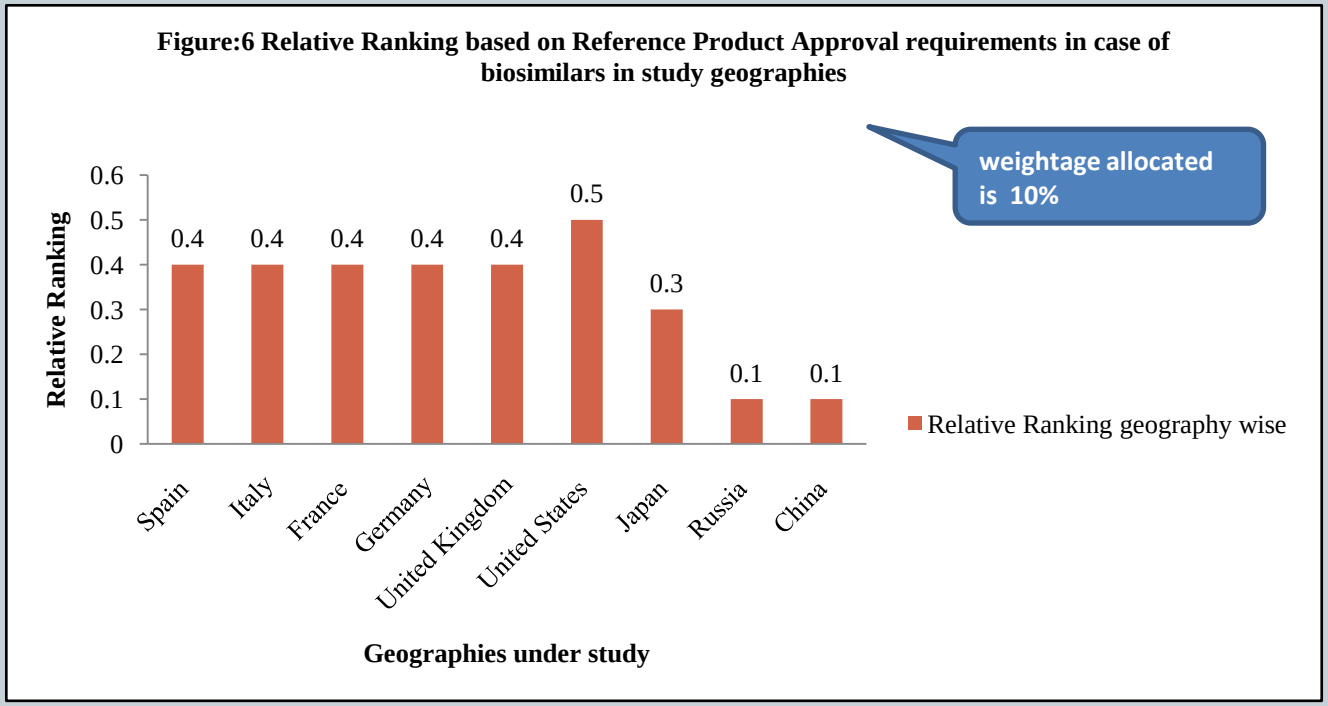
- **Figure 6 Relative Ranking based on Reference Product Approval requirements in case of biosimilars in study geographies**



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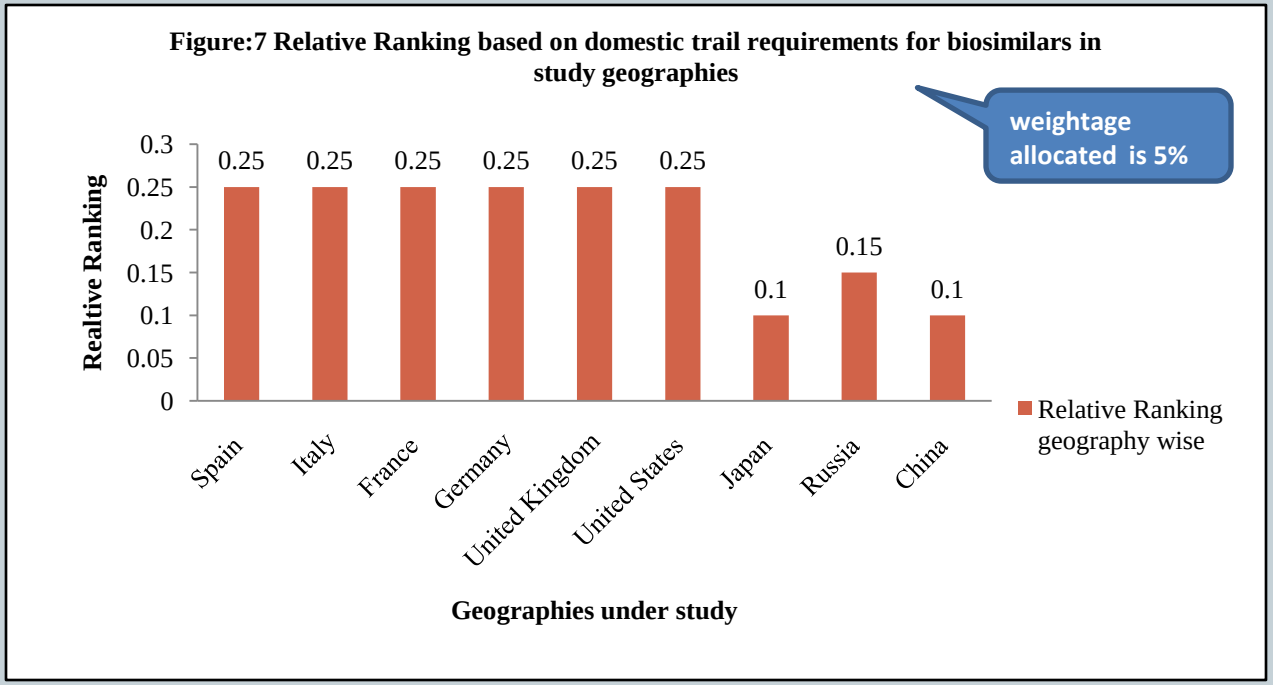
- **Figure 7 Relative Ranking based on domestic trail requirements for biosimilars in study geographies**



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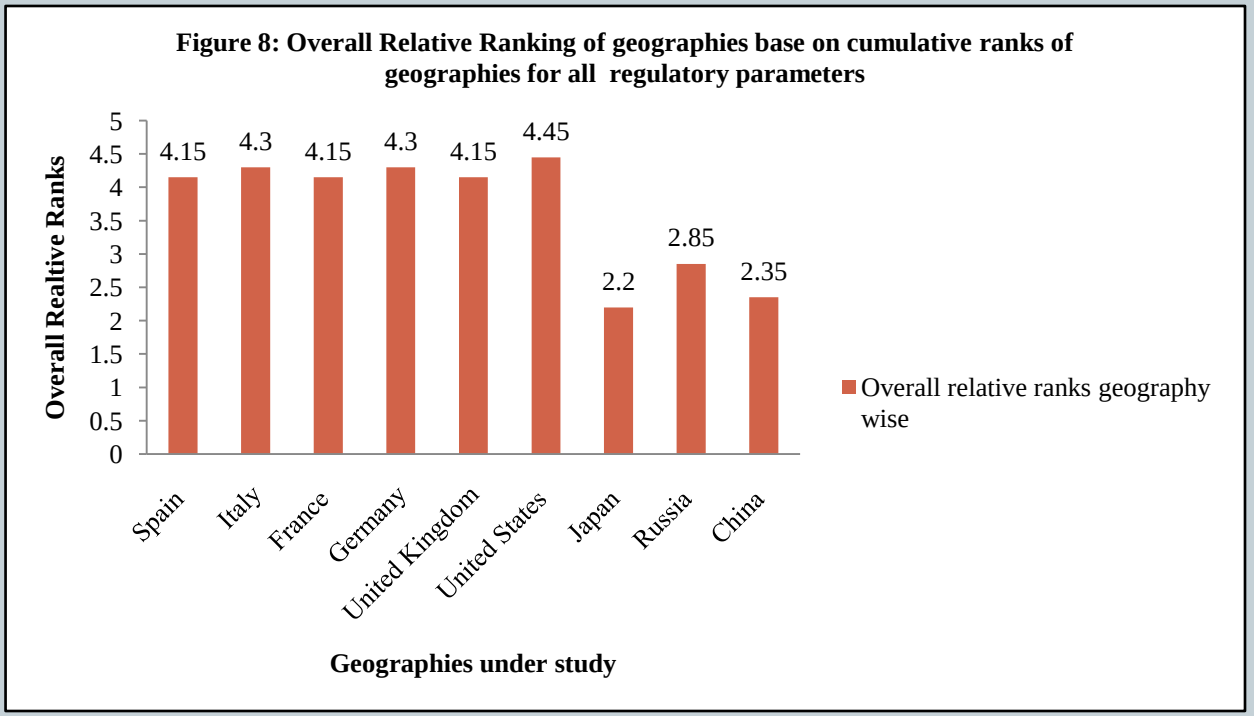
- **Figure 8 Overall Relative Ranking of geographies base on cumulative ranks of geographies for all regulatory parameters**



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
- 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 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
  - Regulation that formally announces and accepts "Interchangeability"(this term has been introduced by United States) and Substitution
- **Lagging areas**
  - In U.S. extrapolation is permitted, provided there is scientific evidence irrespective of number of indications for which extrapolation is being done in comparison to 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
  - 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.

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- Comparison with other geographies U.S. is superior in terms of
  - Regulatory scenario being offered by it such as government support being offered except for China where too government is highly supportive
  - Allows interchangeability and substitution.
  - Existence of legislation which is better defined in U.S. than other geographies
  - Reference product approval for which Japan is not at all flexible.
- Limitations of study
  - 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 sufficient enough to declare any concrete statements for the opportunity offered by the geographies. Further research may be required to give suggestions as the status of study parameters may change on an ongoing basis.
- **Ethical considerations:**
  - The following study being based on secondary/desk research has derived data from publically available data sources so there are no associated ethical considerations for the study.

Disclaimer

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- 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 that keeps getting updated

Open for Questions?????