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Review article

Biosimilars and Regulations: A Review

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ABSTRACT:

Currently, all biologics in India, including innovative and bioequivalent biologics (also known as similar biologics in India), are approved as new drugs. Recently in 2012, the Department of Biotechnology (DBT) and Central Drugs Standard Control Organization (CDSCO) issued the "guidelines on similar biologics". The guidance outlined an abridged procedure for the regulatory requirements for marketing authorization of similar biologics in India. Due to limited R&D capabilities, most domestic companies manufacture simple biologics. However,

companies have increasingly begun to shift their focus to the development of both novel and copy versions of monoclonal antibodies and second-generation biologics, which though more expensive and complex to develop can be priced at a premium, and compete in a much less crowded market than that faced by first-generation biologics.

A number of factors facilitate the development and uptake of Biosimilars in India. Poor patent enforcement in India provides opportunities for domestic biologics manufacturers, while publicprivate sector partnerships promote biologics development. Since there are less stringent regulatory requirements and low R&D costs, domestic biologics are priced much lower in India compared to originators, further driving uptake, as well as offering huge potential for contract manufacturing of biosimilars and for exports. Domestic companies are also entering into partnerships to facilitate development of biologics for the Indian and global market.

However, despite the low price of Biosimilars compared to originator brands, the domestic market is restricted by limited health insurance coverage and therefore poor access to biologic drugs. Also, issues regarding the quality and safety of some domestically manufactured biologics remain a concern among patients and physicians.

KEYWORDS: Biosimilars; Biologics; Regulations; Similar biologic.

INTRODUCTION

While biosimilar approval pathways are well placed in Europe, the US, and Japan, as well as in a number of other markets; in India the approved pathway is still very young and evolving. Currently, all biologics in India including innovative and bioequivalent biologics (also known as similar biologics in India) are approved as new drugs.

Similar biologics in India are defined as: "A biological product/drug produced by genetic engineering techniques and claimed to be 'similar' in terms of quality, safety, and efficacy to a reference innovator product, which has been granted a marketing authorization in India by a competent authority on the basis of a complete dossier, and with a history of safe use in India.

However, biologic products where the reference innovator product is not authorized in India will be considered on a case-by-case basis if such products have been granted marketing approval in countries with well-established regulatory systems (such as the US Food and Drug Administration and European Medicines Agency), and have been available for a minimum of 4 years".

A number of factors facilitate the development and uptake of Biosimilars in India. Poor patent enforcement in the country provides opportunities for domestic biologics manufacturers, while public-private sector partnerships promote Biosimilars development. Since there are less stringent regulatory requirements and low R&D costs, domestic biologics are priced much lower in India

compared to originators, further driving uptake, as well as offering huge potential for contract manufacturing of biosimilars and for exports. Domestic companies are also entering into partnerships to facilitate development of biologics for the Indian and global market. However, despite the low price of Biosimilars compared to originator brands, the domestic market is restricted by limited health insurance coverage and therefore poor access to biologic drugs. Also, issues regarding the quality and safety of some domestically manufactured Biosimilars remain a concern among patients and physicians.

The total biotechnology industry in India including biopharma, bioservices, agriculture biotechnology, industrial biotechnology, and bioinformatics generated sales of \$4bn in 2010–11. Of this total, the Indian biologics market alone generated over \$444m, demonstrating growth of 35% over the previous year¹. Today there are more than 20 biologic molecules and 50 brands approved for marketing in the Indian market, of which domestic companies have the capabilities to manufacture approximately 75%. In 2010, human insulin and analogue products generated over \$173m, while filgrastim and erythropoietin drugs generated \$4m and \$23m, respectively^{1,2}. These three molecules represented nearly half of the domestic biologics market by value. Due to limited R&D capabilities in terms of finance and expertise, most domestic biopharmaceutical companies manufacture simple Biosimilars, and as a result the simple biologic market is highly competitive, resulting in significant downward pressure on pricing. For example, there were 15 versions of erythropoietin products marketed in India by the end of 2010. However, manufacturers are now developing more complicated second-generation Biosimilars such as PEGylated versions of erythropoietin and filgrastim and monoclonal antibodies (MAbs), which though more expensive and complex to develop, can be priced at a premium, and compete in a much less crowded market than that faced by first-generation biologics³.

The Indian biologics industry is making rapid progress and is well positioned to capitalize on the emerging global biosimilars opportunity. Indian companies such as Biocon, Dr. Reddy's, IntasBiopharma, Reliance Life Sciences, and ZydusCadila have developed advanced capabilities to manufacture novel and Biosimilars such as insulins, darbepoetinalfa, PEGylated filgrastim, and

MAbs⁴⁻⁵. Also, many Indian biologics manufacturers are actively entering into partnership agreements with global players to overcome regulatory hurdles and to position themselves in the emerging biosimilars market⁴⁻⁵.

INDIA - BIOLOGIC REGULATORY OVERVIEW:

The "Guidelines on Similar Biologics" prepared by Central Drugs Standard Control Organization (CDSCO) and the Department of Biotechnology (DBT) lay down the regulatory pathway for a similar biologic claiming to be similar to an already authorized reference biologic. The guidelines address the regulatory pathway regarding manufacturing process and quality aspects for similar biologics. These guidelines also address the pre-market regulatory requirements including comparability exercise for quality, preclinical and clinical studies and post market regulatory requirements for similar biologics⁶⁻⁷.

The CDSCO is the national regulatory authority in India that evaluates safety, efficacy and quality of drugs in the country. The DBT through Review Committee on Genetic Manipulation (RCGM) is responsible for overseeing the development and preclinical evaluation of recombinant biologics. Presently, several organizations are actively engaged in manufacturing and marketing similar biologics in India. So far, these similar biologics were approved by RCGM and CDSCO using an abbreviated version of the pathway applicable to new drugs on a case by case basis. Since there are several such products under development in India, both regulatory agencies considered the need to publish a clear regulatory pathway outlining the requirements to ensure comparable safety, efficacy and quality of a similar biologic to an authorized reference biologic. Based on demonstration of similarity in the comparative assessment, a similar biologic may require reduced preclinical and clinical data package as part of submission for market authorization. The objective of this document is to provide guidelines to applicants to enable them to understand and comply with the regulatory requirements for the authorization of similar biologics in India.

The regulatory frameworks in developed nations are as detailed below in Table1. A comparative overview of the biosimilar guidelines across markets are detailed in Table 2.

Table 1. Biosimilar Approval Pathways.⁸⁻¹³

Country	Inception	Approval Pathway
Argentina	July 2008	Registration and registry modification of biological medicinal products
Australia	June 2006	CHMP/437/04 Guidelines on Similar Biological Products
Brazil	December 2010	Resolution No.55/2010 regulates all biological products
Canada	March 2010	Guidance for Sponsors: Information and Submission requirements for Subsequent Entry Biologics
China	-	All biologics, original or Biosimilars undergo the same pathway
Colombia	-	License for Manufacturing Facilities of Biological Products
EU	October 2005	CHMP/437/04 Guidelines on Similar Biological Medicinal Products
EU	November 2010	Guidelines on similar biological medicinal products containing monoclonal antibodies
India	July 2011	Department of Biotechnology issues draft guidelines for preclinical evaluation of similar biologics(biosimilars)
Japan	March 2009	Guidance issued by Japan's Ministry of Health, Labor and Welfare
Malaysia	July 2008	Guidance Document for Registration of Biosimilars in Malaysia
Mexico	June 2009	Article 222 of the General Health Law
Russia	-	Biosimilars are subjected to the same regulations as generics
Saudi Arabia	December 2010	Guidelines on Biosimilars version 1:1
Singapore	April 2010	Appendix 17 of the Guidance on Medicinal Product Registration in Singapore
South Korea	2009	Guidelines(Similar to European biosimilar guidelines) Improvement to the initial guidelines expected to be implemented during 2011
Taiwan	November 2008	Review Criteria for Registration and Market Approval of Pharmaceuticals Registration and Market Approval of Biological Products
Turkey	August 2008	Instruction Manual on Biosimilar Medical Products
US	March 2010	Law No. 11-148. The Approval Pathway For Biosimilar Biologic Products
Venezuela	August 2000	SRPB-R Guidelines application for Health registry of DNA recombinant products, monoclonal and therapeutic antibodies

Table 2. A comparative overview of biosimilar guidelines across the globe.^{10, 14-17}

Criteria	EU and Australia	US	Japan	South Korea	India	China
Biosimilar Pathway status	Pathway established	Pathway not established	Pathway established	Pathway established	Draft preclinical pathway issued; similar biologics currently approved as new drugs	No pathway; Biosimilars approved as new drugs
Clinical Trials	Mandatory but extent negotiable	Mandatory but extent negotiable	Phase I studies mandatory, Phase III studies may be abbreviated in some situations	Phase I studies mandatory, Phase III studies may be abbreviated in some situations	Only preclinical studies and Phase III trials are mandatory	Mandatory: Phase I-III studies for Biosimilars with a reference product not marketed in China. Phase III studies for Biosimilars with a reference

Reference product	Reference product should be approved and marketed in EU/Australia	Reference product should be approved and marketed in US	Reference product should be approved and marketed in Japan	Reference product should be approved and marketed in South Korea	Not defined	product marketed in China Not defined
Interchangeability	Decision at country level	Yes if assigned by FDA through appropriate data or only after first year after launch. Substitution decision made at the state level	Automatic substitution and interchangeability is forbidden	Not defined	Not defined	Not defined
Formulation	Same strength and route of administration, otherwise further studies required	Same strength and route of administration	Safety is primary concern, exact copy of identity not required	Dosage, form and strength must be the same	Same strength and route of administration	Not defined
Drug Name	Either brand name or INN plus company name	Not defined	Format=[INN name] BS injectable [company name]	Not defined	Not defined	Unique brand names used
Market exclusively for biosimilar products	No exclusivity	6 months to 1year exclusivity for first biosimilar	No exclusivity	No exclusivity	No exclusivity	No exclusivity
Post-marketing Surveillance	Mandatory alongside risk management plan	Only one bill requires mandatory post-marketing trials	Plan must be created to trace adverse events and submit a drug safety report	Pharmacovigilance plan must be submitted	Not defined	No requirement

FDA= Food and Drug Administration; INN= international non- proprietary name

APPLICABLE REGULATIONS AND GUIDELINES

The similar biologics are regulated as per the Drugs and Cosmetics Act, 1940, the Drugs and Cosmetics Rules, 1945 (as amended from time to time) and Rules for the manufacture, use, import, export and storage of hazardous microorganisms/genetically engineered organisms or cells, 1989(Rules, 1989) notified under the Environment (Protection) Act, 1986.

Various applicable guidelines are as follows:

- Recombinant DNA Safety Guidelines, 1990
 - Guidelines for generating preclinical and clinical data for rDNA vaccines, diagnostics and other biologicals, 1999
- CDSCO guidance for industry, 2008:
- Submission of Clinical Trial Application for Evaluating Safety and Efficacy
 - Requirements for permission of New Drugs Approval

- Post approval changes in biological products: Quality, Safety and Efficacy Documents
- Preparation of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products
- Guidelines and Handbook for Institutional Biosafety Committees (IBSCs), 2011.

COMPETENT AUTHORITIES

Central authorities such as the Drug Controller General of India (DCGI) and the Central Drug Standard Control Organization (CDSCO), as well as state authorities including drug regulatory agencies, are involved in the approval of

pharmaceuticals in India¹⁸. However, biologics manufacturers also need to obtain additional approval from regulatory authorities – including the Recombinant DNA Advisory Committee (RDAC), the Genetic Engineering Approval Council (GEAC), the Review Committee on Genetic Manipulation (RCGM), the Institutional Biosafety Committees (IBSCs), the State Biosafety Coordination Committees (SBCCs), and the District Level Committees (DLCs) – for the DCGI to grant permission for import of genetically modified organisms (GMOs) for research, conduction of preclinical research and clinical trials, and finally marketing approval (Table 3).

Table 3. Regulatory bodies and authorities that govern approval and safety of biologics in India.¹⁹⁻²³

Key regulatory function	Biosafety (evaluating pre-clinical and toxicological data and manufacturing process)	Examines environmental risk benefits and accords approval for environmental release	Drugs (biologics) Industrial policy/ import and export of biologic materials and Intellectual property	Market authorization of new drugs, clinical trials approval and monitoring of drug manufacturing	Pharmaceutical (Biologics) Pricing
Ministry	Ministry of Science and Technology	Ministry of Environment and Forest	Ministry of Commerce & Industry	Ministry of Health & Family Welfare	Ministry of Chemicals and Fertilizers
Department/ Divisions				<ul style="list-style-type: none"> • Department of Ayurveda, Yoga and Naturopathy, Unani, Siddha, Homeopathy (AYUSH) 	
Attached offices	<ul style="list-style-type: none"> • Department of Biotechnology 	<ul style="list-style-type: none"> • Conservation and survey division 	<ul style="list-style-type: none"> • Department of Commerce • Department of Industrial Policy and Promotion 	<ul style="list-style-type: none"> • Department of Family Welfare • Department of Health • Department of Health Research 	<ul style="list-style-type: none"> • Department of Pharmaceuticals
Subordinate offices				<ul style="list-style-type: none"> • Directorate General of Health Services (DGHS) 	
Committee (s)	<ul style="list-style-type: none"> • Recombinant DNA Advisory Committee (RDAC) • Institutional Biosafety Committees (IBSC) • Review Committee on Genetic 	<ul style="list-style-type: none"> • Genetic Engineering Approval Committee (GEAC) • State Biotechnology Coordination Committee (SBCC) • District Level 	<ul style="list-style-type: none"> • Directorate General of Foreign Trade (DGFT) 	<ul style="list-style-type: none"> • Central Drugs Standard Control Organization (CDSCO)- Headed by Drugs Controller General of India (DCGI) 	<ul style="list-style-type: none"> • National Pharmaceutical Pricing Authority (NPPA)

	Manipulation (RCGM)	Committee (DLC)			
Policy/Rules administered	Environment(Protection) act (EPA), 1986 Rules, 1989 of EPA		Industrial and Export and Import(EXIM) Policies	Drugs and Cosmetics Act, 1940- Rules 1945- Schedule Y	Pharmaceutical Policy, 2002

Key requirements as per the “Guidelines for Preclinical Evaluation of Similar Biologics in India” are listed below:

The similar biologic should demonstrate its similarity to the reference innovator product. The similar biologic production process should have consistency in production process to the reference innovator product. The similar biologic manufacturer should identify if there are any significant differences in quality, safety, and efficacy compared to the reference product and their potential impact on the similarity. If the differences are significant then more extensive evaluation is required to prove similarity. Where the reference product is approved for the treatment of multiple indications, then the similar biologic needs to justify its efficacy and safety for each of the indications it is to be approved for.

SELECTION OF INNOVATOR REFERENCE PRODUCT

Reference biologic which is authorized using complete dossier is critical for the development of similar biologic. The rationale for the choice of the reference biologic should be provided by the manufacturer of the similar biologic in the submissions to the DBT and CDSCO.

The reference biologic has to be used in all the comparability exercise with respect to quality, preclinical and clinical considerations. The following factors should be considered for selection of the reference biologic:

- The reference biologic should be licensed in India and should be innovator product. The reference biologic should be licensed based on a full safety, efficacy and quality data. Therefore another similar biologic cannot be considered as a choice for reference biologic.
- In case the reference biologic is not marketed in India, the reference biologic should have been licensed and widely marketed for 4 years post approval in innovator jurisdiction in a country with well-established regulatory framework. In case no medicine or only palliative therapy is available or in national healthcare emergency,

this period of 4 years may be reduced or waived off.

- The same reference biologic should be used throughout the studies supporting the safety, efficacy and quality of the product (i.e. in the development programme for the similar biologic)
- The dosage form, strength and route of administration of the similar biologic should be the same as that of the reference biologic.
- The active substance (active ingredient) of the reference biologic and that of the similar biologic must be shown to be similar. The acceptance of an innovator product as a reference biologic for evaluation of similar biologic does not imply approval for its use in India.
- Data Requirements for Similar Biologic Approval.
- The abridged preclinical guidelines rely on the fact that a similar biologic can demonstrate comparability with the designated reference product, as well as ensuring that a consistent manufacturing and purification process can be established. In order to achieve this, the following is required by the DBT:
 - Manufacturing process considerations – Ideally the similar biologic products are expected to be expressed and produced in the same host cell type as the reference product. The similar biologic manufacturer should provide complete description of the entire manufacturing process including molecular biology details, details of the fermentation process, and details of the downstream process for purification of the product.
 - Product characterization–To establish the similarity of the proposed similar biologic and the reference product in terms of composition, size, structure, and bioactivity, through comparative studies using physicochemical and biological assays. To address any concern regarding any contaminants in the similar biologic, characterization studies should also be undertaken on nucleic acid/protein content, host cell proteins, endotoxins, and viral validation.
 - Pharmacological characterization–Includes analysis of data regarding the route of

administration, absorption and elimination rates, bioequivalence range of the similar biologic with that of the reference drug, therapeutic index, the dose-response curves, tissue specific localization, and details of the formulation.

- Stability studies–Real-time studies should be conducted for stability data relating to shelf life and storage conditions of the test product. Other useful tools such as stress stability tests should be used to establish direct comparison between the similar biologic and reference innovator product.
- Preclinical evaluation using *in vitro* and *in vivo* studies–The requirements of the preclinical studies will vary depending on the therapeutic index of the product, the type of the product, and the number of indications applied for by the manufacturer.
- Immune responses in animals–Antibody response to the product in mice and reaction of test serum samples to host cell proteins should be compared between the similar biologic and the reference drug. The immune toxicity of the similar biologic should be evaluated through immunogenicity testing and evaluation of histopathology observation and human lymphocyte proliferation assays.

BIOLOGIC DRUG APPROVAL

As per guidelines for similar biologics in India, all biologics are approved as branded medicines, defined as medicines which contain one or more ingredients marketed under brand names given to them by their manufacturers in India. However, this differs from Western countries where brand-name medicines refer to new drugs developed by the innovator patent-holding companies²⁴.

An application for grant of permission to import a new drug or grant of approval to manufacture the new drug and its formulations should be made in Form 44 to the Drug Controller General of India (DCGI). The importer/manufacturer of the new drug is also required to provide the details of confirmatory clinical trials (Phase III) in India as required under Appendix I, Item 7 of the Schedule Y amendment of the Drugs and Cosmetics Act (first passed in 1940). If the drug is already approved/marketed in other countries, Phase III data should generally be obtained for statistically significant no of patients distributed in three to four centers in India to confirm the efficacy and safety of the drug in Indian patients when used as recommended in the product monograph²⁵.

However, following the government's liberalization of clinical trials procedures by making amendments to Schedule Y of the Drugs and Cosmetics Act, Phase II and Phase III clinical trials of drugs in India can be held concurrently with equivalent trials abroad, thereby reducing time to market²⁶, while Phase I clinical trials are usually not required for Biosimilars provided that pharmacoequivalence to the reference product can be proved²⁷. The DCGI also has the discretionary power of granting permission without confirmatory trials provided that the new drug has been approved and marketed for several years in other countries and that there is adequate published evidence regarding the safety of the drug²⁸.

Figure 1 provides the general approval procedure for biologics in India. Following approval, both the DCGI and the GEAC may impose conditions of surveillance on biologic products during marketing to monitor their clinical safety, requiring the manufacturer to provide periodic safety update reports (PSURs) for the first 4 years after the product reaches market. PSURs should be submitted every 6 months for the first 2 years and on a yearly basis for the subsequent 2 years. However, the DCGI may extend the period further if it deems it necessary²⁹.

INDIA:- DRIVERS AND RESISTORS OF BIOLOGIC UPTAKE

A number of factors facilitate the development and uptake of Biosimilars in India. Poor patent enforcement in India provides opportunities for domestic biologics manufacturers, while publicprivate sector partnerships promote copy biologic development. Since there are less stringent regulatory requirements and low R&D costs, domestic biologics are priced much lower in India compared to originators, further driving uptake, as well as offering huge potential for contract manufacturing of biosimilars and for exports. Domestic companies are also entering into partnerships to facilitate development of biologics for the Indian and global market.

However, despite the low price of Biosimilars compared to originator brands, the domestic market is restricted by limited health insurance coverage and therefore poor access to biologic drugs. Also, issues regarding the quality and safety of some domestically manufactured Biosimilars remain a concern among patients and physicians.

Table 4 illustrates some of the major factors influencing the Biosimilars industry in India.

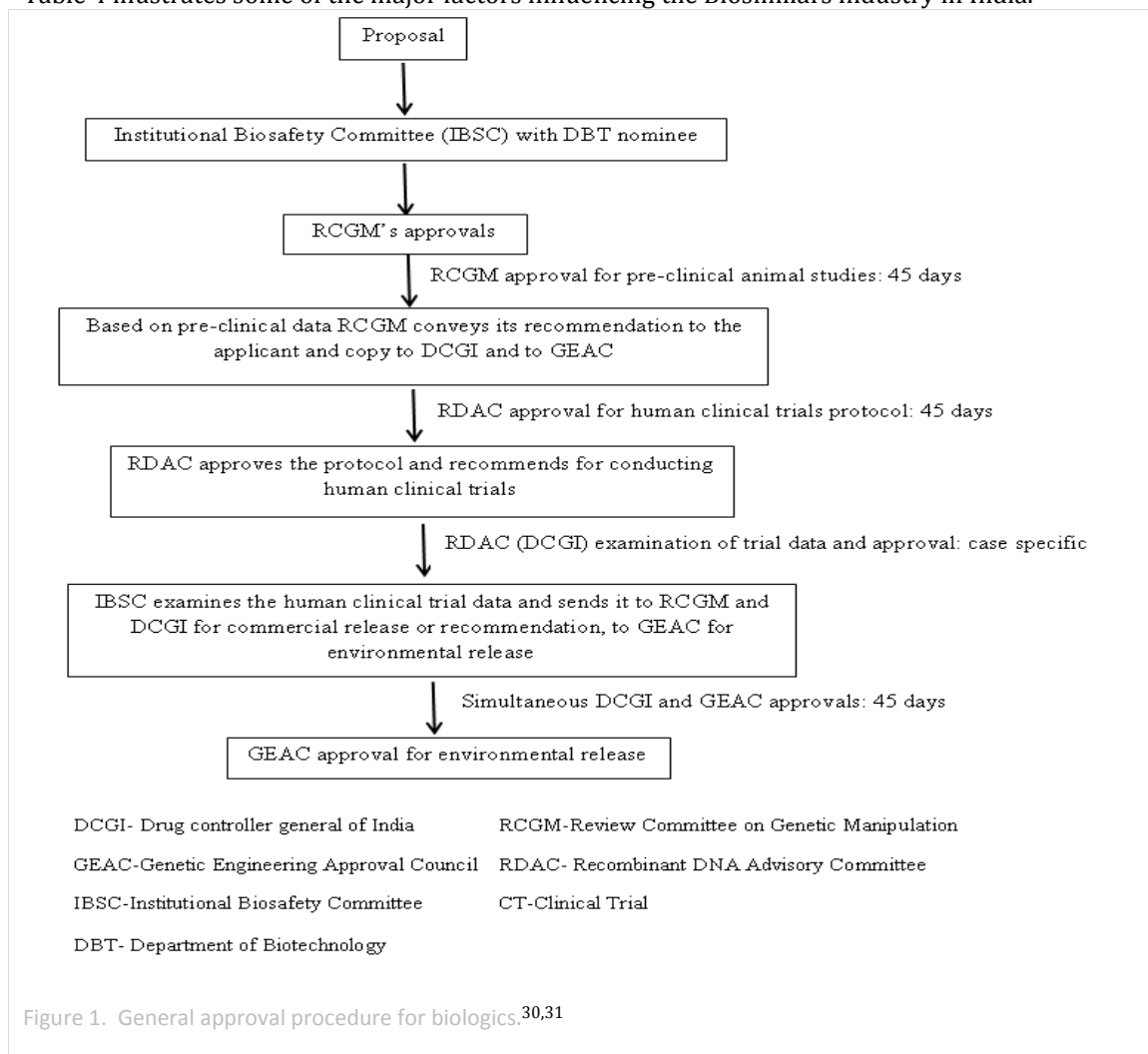


Table 4. Drivers of biologic uptake in India.

Drivers of the Indian Biosimilars market	Resistors to growth in the Indian Biosimilars market
<ul style="list-style-type: none"> • Poor patient enforcement in India provides opportunities for domestic biologics manufactures • Less stringent regulatory requirements and low R&D costs promotes Biosimilars development • Domestic biologics are priced much lower in India compared to originators • Domestic companies enter partnerships to facilitate development of biologics for the Indian and global market • Public- private sector partnership drive biotech development in India 	<ul style="list-style-type: none"> • Low levels of health insurance limit access to biologic drugs • Safety concerns over domestically manufactured biologics might impede their uptake

POOR PATENT ENFORCEMENT IN INDIA PROVIDES OPPORTUNITIES FOR DOMESTIC BIOLOGICS MANUFACTURERS

While India is improving its intellectual property and patent laws, issues of poor enforcement remain. This has enabled many Indian domestic companies to develop and obtain approval for domestically manufactured Biosimilars, which dominate the Indian biologics market.

Currently there are copy biologic versions of five of the top 10 branded biologics currently available in India; with a further three copy biologic versions of such brands in development (Table 5).

Table 5. Status of Biosimilars for top 10 biologics, 2010.

Brand Name	Generic Name	Company	2010 Global sales (\$m)	Status of copy biologic in India
Enbrel	etanercept	Amgen	7,270	Phase III studies being initiated
Humira	adalimumab	Abbott	6,716	n/a
Remicade	infliximab	Johnson & Johnson	6,514	n/a
Avastin	bevacizumab	Roche	6,214	Undergoing preclinical studies
Rituxan	rituximab	Roche	6,113	Launched in 2007
Herceptin	trastuzumab	Roche	5,221	Phase III studies being initiated
Lantus	insulin glargine	Sanofi	4,658	Launched in 2009
Epogen	epotinalfa	Amgen	4,584	Launched in 2001
Neulasta	pegfilgrastim	Amgen	3,558	Launched in 2007
Aranesp	Darbeoetinalfa	Amgen	2,973	Launched in 2010

n/a = not applicable

LESS STRINGENT REGULATORY REQUIREMENTS AND LOW R&D COSTS PROMOTE BIOSIMILARS DEVELOPMENT

In India, Phase I-II clinical trials are not required for copy biologic drugs if pharmacoequivalence can be proved against the reference product²⁷, while Phase III clinical trials can be performed on as few as 100 Indian patients¹².

Consequently, while biosimilar development takes approximately 8 years in the EU, it only takes 3–5 years in India for a copy biologic. Furthermore, approval of Biosimilars in other semi-regulated markets in South Asia, South East Asia, and Latin America often only takes an additional 6–10 months for drugs already approved by the Drug Controller General of India (DCGI) (Figure 2)³².

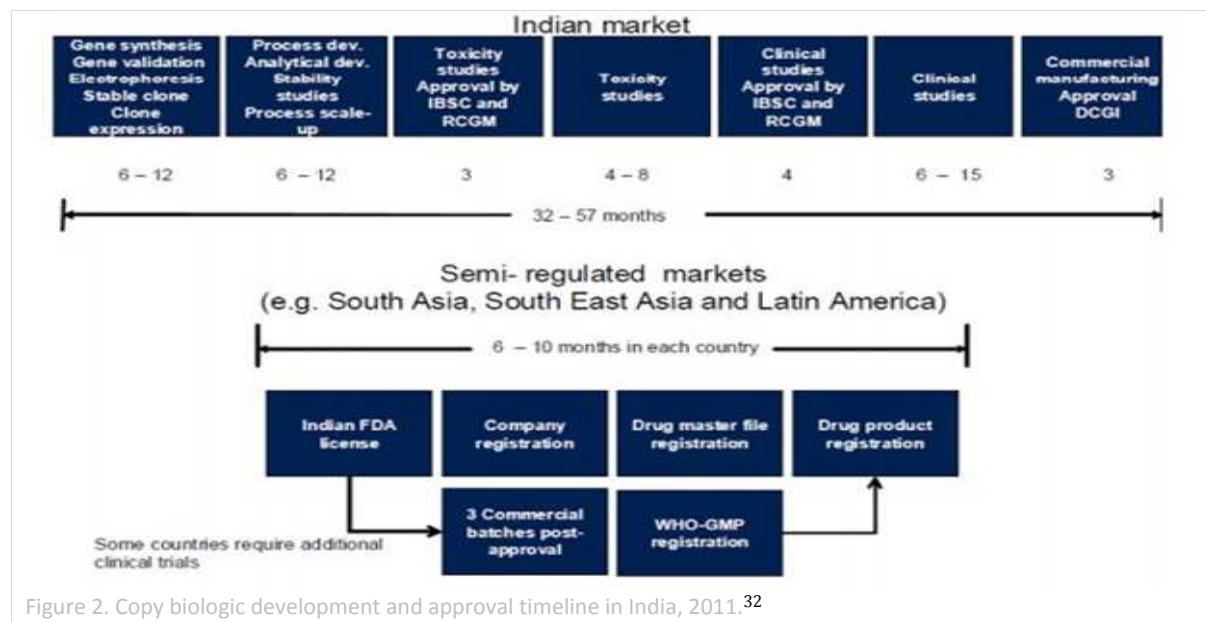


Figure 2. Copy biologic development and approval timeline in India, 2011.³²

In terms of cost, it is estimated that development of a biosimilar in a developed market ranges from \$100m to \$200m.³³ However, as a result of the lower cost of recruiting patients, labor and service fees, as well as less stringent regulatory approval

criteria, development of biologics in India is 90% lower than in the EU³⁴, equating to \$10m–20m. Large pools of treatment-naïve patients also allow for rapid clinical trial application and therefore additional cost savings compared to in developed markets³⁵. The cost advantage of manufacturing Biosimilars in India also offers huge potential for

contract manufacturing of biosimilars and for exports.

However, despite the low cost development of Biosimilars in India compared to innovative products, some companies are looking for even more attractive markets to perform biosimilar development. For example, India-based Biocon is to open a manufacturing facility in Malaysia by 2012 at a cost of \$161m.³⁶ The new facility is to focus primarily on the production of biosimilar products, making use of tax benefits and developed infrastructure which will assist in the growth of Biocon's Asia market.

DOMESTIC BIOLOGICS ARE PRICED MUCH LOWER IN INDIA COMPARED TO ORIGINATORS

With low development and manufacturing costs, domestic biologic players are able to sell their products at a discount of 12% to 74% compared to

the original biologic drug being sold in the Indian market (Table 6). Such discounting has at times forced manufacturers of originator brands to reduce their price in order to retain their market share. For example, when Reditux (rituximab; Dr. Reddy's) was launched in 2007, the price difference between it and Rituxan (rituximab; Roche) was 50%.³⁷ In response, Roche lowered the price of Rituxan while promoting its brand through various schemes in order to help maintain market share²⁷.

Such aggressive discounting also acts as a deterrent for international biosimilars players looking to launch biosimilars in India, since biosimilars in the EU and Japan are generally priced only 20–30% cheaper than referenced brands.

Table 6 provides the copy biologic price difference compared to reference/innovator brand for key molecules.

Table 6. The copy biologic price difference compared to reference/innovator brand for key molecules.

Biologic	Discount to reference biologic (%)	Average discount to brands (%)
Epoetin	12-40	25
Filgrastim	16-29	23
Pegfilgrastim	36-74	55
interferon alfa-2a	16-56	36
interferon alfa-2b	44-55	49
Rituximab	38-47	42
insulin glargine	38-43	40

DOMESTIC COMPANIES ENTER PARTNERSHIPS TO FACILITATE BIOLOGIC DEVELOPMENT FOR THE INDIAN AND GLOBAL MARKET

Given the commercial opportunity, both domestic and foreign companies are looking to either enter or bolster their position in the biologics market. However, companies may lack the credentials required to successfully develop, manufacture, and commercialize biologics, and therefore look towards partnership agreements as a solution. Such collaborations are mutually beneficial, often providing the source company with the resources

and experience to commercialize its products, while granting the partnering company rapid entry to the biologics arena, where early market entry will be important in the race to establish market share.

Biologics partnership deals typically have one or more of the following goals:

- Market access in emerging or developed markets
- Diversifying into or enhancing existing biosimilar portfolios
- Accessing expertise in biosimilar development, manufacturing, and/or commercialization
- Reducing development and manufacturing costs.

Table 7. A numbers of key deals entered into during 2009–11 involving Indian companies.

Source/Target	Partner/Acquirer	Product(s)	Nature of deal	Deal summary	Date
NeuClone	Lupin	Chinese hamster	Partnership	NuClone to provide an exclusive proprietary mammalian Chinese	June 2011

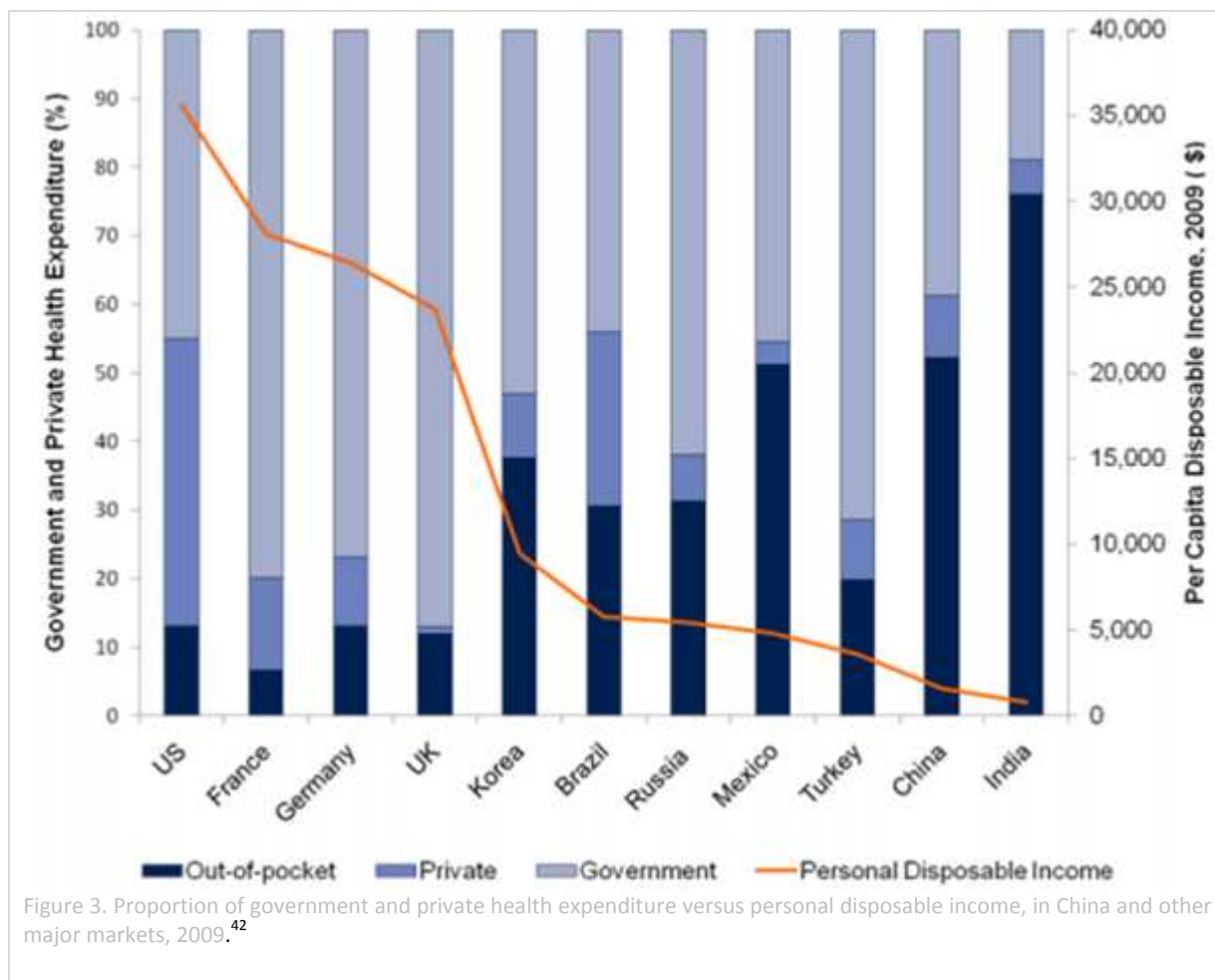
		ovary cell line		hamster ovary cell lines	
Inbiopro Solutions	Strides Arco Lab	Biosimilars	Majority acquisition	Strides partnered with Inbiopro to commercialize its biosimilars pipeline products	December 2010
Biocon	Pfizer	Insulin and analogues	Partnership	Biocon entered into an exclusive agreement with Pfizer to commercialize several of Biocon's insulin product globally	October 2010
Orf Genetics	DM Corporation	Human Recombinant therapeutic proteins and biosimilars	Joint venture	Joint venture to develop and market human recombinant therapeutic proteins and biosimilars	September 2010
Biomab	Cipla	Monoclonal antibodies	Minority acquisition	Acquisition of 25% stake in Biomab, a biotech company in Hong Kong, for around \$25m	June 2010
Mab Pharm	Cipla	Monoclonal antibodies	Minority acquisition	Acquisition of 40% stake in Indian biosimilar company Mab Pharm, for around \$40m	June 2010
Pfenex	Ranbaxy	Expression technology	Development agreement	Development of biosimilars using Pfenex expression technology platform	March 2010
Biovel Life Sciences	Ranbaxy	Biosimilars	Majority acquisition	Ranbaxy acquired product rights and manufacturing facility in Bangalore, India from Biovel Life Sciences	January 2010
Shantha Biotechnics	Sanofi	Biosimilars	Majority acquisition	Acquisition valued at €550m (\$767m). In addition to vaccine expertise, Shantha Biotechnics is a leading biosimilar company in India, with a portfolio which includes epoetin alfa and interferon alpha-2b	July 2009
Biocon	Mylan	Monoclonal antibodies	Partnership	Partnership for the development of complex biosimilars including monoclonal antibodies	June 2009
IntasBiopharma	Apotex	GCSF and PEG-GCSF	Partnership	Agreement to develop biosimilar products including a biosimilar version of pegfilgrastim	June 2011

GCSF = granulocyte colony-stimulating factor

RESISTORS TO OF BIOLOGIC UPTAKE IN INDIA LOW LEVELS OF HEALTH INSURANCE LIMIT ACCESS TO BIOLOGIC DRUGS

The domestic biologics market in India is in its infancy, largely due to the limited affordability despite the low price of Biosimilars versus their reference products. This is largely due to the fact

that only 11% of the population in 2007 was covered by health insurance, with the majority of healthcare cost met out of pocket (Figure 3).³⁸ Consequently, affordability is a key challenge in India for Biosimilars manufacturers because even the discounted price of Biosimilars compared to originator brands is not affordable to the majority of patients³⁹.



Furthermore, India's National Pharmaceutical Pricing Authority (NPPA) allowed domestic companies Wockhardt and Biocon to increase the prices of their insulin products Wosulin (Wockhardt) and Insugen (Biocon) by 18% in March 2011.⁴⁰ The NPPA claimed that this was to reflect rising input costs, although it has also been reported that it also stated that the move would help give local manufacturers the same opportunities as manufacturers outside of the country⁴¹. Although the domestic insulin formulations are still expected to be less costly than imported versions, the price hike may make access to the drugs more difficult.

SAFETY CONCERNS OVER DOMESTICALLY MANUFACTURED BIOLOGICS MIGHT IMPEDE THEIR UPTAKE

Some physicians remain skeptical with regards to the safety and efficacy of Biosimilars and are slow to adopt these drugs. There are also instances of physicians actively seeking the withdrawal of a

number of domestically manufactured insulin's from the market, due to the risk of adverse effect. A recent paper published by a Dr. SR Joshi states that there have been several accidents with copy biologic insulin's in India, leading to the withdrawal of several batches⁴³. Although the cost savings offered by Biosimilars compared to originator brands is appealing to patients, physicians, insurance providers, and governments, there are concerns regarding the safety, efficacy, and quality of these products because of the lack of stringent evaluation guidelines by the Indian drug regulatory system⁴⁴.

Further causes for concern have been the noticeable differences in the potency between several Indiaproduced Biosimilars compared to their reference products⁴⁵. Also, to stave off potential competition from the Indian Biosimilars, originator companies have proactively conducted studies comparing their drugs. For example, a study by BoehringerIngelheim revealed that the India-registered Elaxim (tenecteplase; Emcure)

was not copy biologic to Metalyse (tenecteplase; BoehringerIngelheim). The study also concluded that the differences in manufacturing process introduced impurities that affect the potency and efficacy of the copy biologic⁴⁶. Similarly, Roche conducted studies comparing its Rituxan (rituximab) with Reditux (rituximab; Dr. Reddy's) and highlighted numerous differences including a much higher level of remaining host cell proteins in Reditux compared to Rituxan, as well as differences in glycosylation⁴⁷. However, it is not clear as to whether this represents a failing of the Indian registration system or a failing of the acceptable level of difference between originator and biosimilar products⁴⁸.

BIOSIMILARITY ACROSS THE GLOBE

US Food and Drug Administration (FDA) published draft biosimilars guidelines in February 2012.⁴⁹⁻⁵⁰ Although details are lacking in a number of areas such as interchangeability, the guidance sets out the agency's broad views and gives developers greater certainty for the initiation of development programs. The guidelines generally indicate a stepwise risk-based approach in which requirements at each stage will depend upon the degree to which concerns have been alleviated. Differentiation from a reference product is permitted, but should be sufficiently justified. The key findings of the 2012 guidelines are below:

- In the US, the US Food and Drug Administration (FDA) defines biosimilarity as being "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and as "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency."
- In February 2012, the FDA issued three draft documents covering scientific and quality considerations for demonstrating biosimilarity to a reference product in order to gain approval using the biosimilar (351(k)) pathway.
- The agency intends to use a risk-based, "totality-of-the-evidence" approach to assess biosimilarity, which is in keeping with how it reviews small molecule or innovator biologic products. Most notably, this is stated as meaning that minor differences in formulation or structure will be acceptable providing that sufficient justification is given.
- In order to gain FDA approval, biosimilarity must be demonstrated against a single reference

product that has been approved in the US. However, under certain circumstances, animal or clinical study data from comparison to a non-US licensed product can be used to support the application, if sufficient justification is given.

- A biosimilar is typically expected to have the same primary amino acid sequence as its reference product; however, this is not mandatory. Minor modifications that are unlikely to have an effect on safety, purity, or potency may be acceptable where sufficiently justified by the applicant.
- Biosimilar applications in the US should generally include comparative analytical studies, animal studies, and human clinical studies (including immunogenicity and pharmacokinetic and/or pharmacodynamic studies). A high level of similarity between a biosimilar and its reference product demonstrated in analytical work can be used as justification for more selective or targeted approaches in subsequent animal or clinical studies.
- The initial guidance focuses on general therapeutic protein products, rather than addressing specific aspects such as for biosimilar monoclonal antibodies (MAbs), which are considered more complex and pose further issues. Guidance states that the agency should be consulted on whether an application is appropriate if a product cannot be adequately characterized with state-of-the-art technology.
- The FDA is continuing to review interchangeability requirements and, as such, this is not covered by these initial draft guidelines, although a requirement to show no greater safety risk or diminished efficacy from switching between the biosimilar and reference product is stated.
- Approval of a biosimilar for one indication can potentially be extrapolated to additional indications of the reference product if sufficient scientific justification is given to support biosimilarity in each case.
- Biosimilars receiving the approval of the FDA can be approved as non-interchangeable or interchangeable.
- Post-marketing safety monitoring should take into account safety or effectiveness concerns associated with the use of the reference product and be capable of differentiating between adverse events relating to each product.

OTHER BIOSIMILARS REGULATORY ISSUES

- The FDA submitted proposals for biosimilar user fees in January 2012. These are set as the same

for innovator products overall, but with a proportion brought upfront by initial and annual development fees.

- With the Prescription Drug User Fee Act (PDUFA) IV due to end in September 2012, the PDUFA V will need to be implemented by this time.
- The FDA aims to review submitted biosimilar applications within a 10-month timeframe.
- EU Biosimilar Regulatory Developments
- The European Medicines Agency (EMA) issued a concept paper in November 2011 regarding the updating of existing overview biosimilars guidelines that have been in place since October 2005.
- The EMA is due to release final guidance on MAB biosimilars in April 2012, and draft guidelines on low molecular weight heparins and analog insulin in May or June 2012.
- The EMA issued draft guidelines for biosimilar interferon beta products for public consultation in January 2012, and this consultation period will close in May 2012 (EMA, 2012). The guidelines provide requirements for non-clinical studies, clinical studies, pharmacovigilance, and extrapolation.
- In Germany, reference pricing has encouraged payers towards biosimilars by imposing higher patient co-payments for products which extend beyond this reimbursement limit. From July 2012 the reference prices for biosimilars are set to be reduced.
- In March 2012, the Belgium government announced it was to create a target for biosimilar uptake.
- Rest of World Biosimilar Regulatory Developments
- The Iranian pharmaceutical market has traditionally seen high generic penetration following a governmental policy known as the National Drug Policy (NDP) that requires drugs to be manufactured domestically where possible. A total of 24 biosimilar products are expected to have entered the Iranian market by the end of 2012.

REFERENCES:

1. BioSpectrum ABLE Biotech Industry Survey. The eighth survey of Indian biotech industry. 2010. [Accessed on 05 Apr 2015] Available from <http://www.ableindia.org/html/resources/eighth_biospectrum_June_10.pdf.
2. Sheppard A. Modified Biologics: the global outlook Biosimilars, A presentation at Biosimilar Asia

Conference 2011, 24-26 May 2011, Grand Hyatt Shanghai, China.

3. Biospectrum- Erythropoietin. 2005. [Accessed on 06 Apr 2015] Available from <<http://biospectrumindia.ciol.com/content/BioBusiness/10509062.asp>.
4. Business Standard. Angel Broking - Cadila Healthcare - 3QFY2011. 2011. [Accessed on 07 Apr 2015] Available from http://www.business-standard.com/content/research_pdf/cadila_210111_01.pdf.
5. Desai JP. Bridges to Bloom: The Future of Indian Biosimilars" by Universal Consulting India (Pvt) Ltd., September 2009. [Accessed on 08 Apr 2015] Accessed from <http://www.universalconsulting.com/pdf/The%20Future%20of%20Indian%20Biosimilars.pdf>.
6. CDSCO. Draft guidance on approval of clinical trials and new drugs. 2011. [Accessed on 07 Apr 2015] http://cdsco.nic.in/Guidance_for_New_Drug_Approval-23.07.2011.pdf
7. Shirodkar SN. DBT completes draft guidelines on preclinical trial data for similar biologics. 2011 [Accessed on 08 Apr 2015] Available from <http://www.pharmabiz.com/PrintArticle.aspx?aid=63640&sid=1>
8. EGA. Global Development, The Way Forward The EGA's Perspective. 2010a. [Accessed on 08 Apr 2015] Available from: http://www.egagenerics.com/doc/ega_biosimilars_Schwarzenberger_090424.pdf.
9. EGA. 8th EGA Annual International Symposium On Biosimilar Medicines. 2010b. [Accessed on 08 Apr 2015] Available from: <http://www.egagenerics.com/bio-articles.htm>.
10. Chen H. Requirements For China To Globalize Success Seen In Domestic Biosimilars Market. 2009. [Accessed on 08 Apr 2015] Available from: <http://www.genengnews.com/analysis-and-insight/requirements-for-china-to-globalize-success-seen-in-domestic-biosimilars-market/59580243>
11. Alexander J. Expert Panel to Recommend Regulatory Guidelines for Biosimilars Soon. 2011. [Accessed on 06 Apr 2015] Available from: <http://www.pharmabiz.com/NewsDetails.aspx?aid=60815&sid=1>.
12. Diccio R. Developing Biosimilars in Regulated/Semi-Regulated and Unregulated Markets, A presentation at Informa Life Sciences Biosimilars Conference 2010, June 2010.
13. GaBi. EMA to Revise Overarching Biosimilar Guidelines. 2012. [Accessed on 08 Apr 2015] Available from: <http://gabionline.net/Guidelines/EMA-to-revise-overarching-biosimilar-guidelines>
14. Kubrekar V. Innovations in drug delivery for biologics to enhance efficacy, A presentation at the Biosimilars India Conference 2011, 14-15 July 2011 Mumbai, India.
15. Tessensohn JA, Yamamoto S. Patent term extensions for biologic innovators in Japan. *Nat Biotechnol.* 2011; 29(1):34-7.
16. Nomura. Coming of age: generic-centered players flourishing and preparing to go global. 2011 [Accessed

- on 08 Apr 2015] Available from
http://www.nomura.com/europe/resources/upload/Korean_biopharmaceuticals.pdf.
17. Department of Biotechnology. Guidelines on similar biologics. 2012. [Accessed on 08 Apr 2015] Accessed from
http://www.igmoris.nic.in/Files2/Guidelines_SimilarBiologics.pdf.
18. Controller General of India. [Accessed on 08 Apr 2015] Available from
http://igmoris.nic.in/clinical_trials.asp
19. Clinical Trials Registry – India. Search for trials. 2011. [Accessed on 08 Apr 2015] Available from
<http://ctri.nic.in/ClinicalTrials/pubview.php>.
20. Department of Industrial Policy & Promotion. Industrial Policy – Industrial licensing. 2011. [Accessed on 08 Apr 2015] Available from
http://dipp.nic.in/inv_opp/manul.pdf.
21. Government of India. Web directory–Union government ministries. 2011. [Accessed on 08 Apr 2015] Available from
http://goidirectory.nic.in/union_categories.php?ct=E002.
22. Ministry of Chemicals & Fertilizers. Pharmaceutical policy - 2002. [Accessed on 08 Apr 2015] Available from
<http://chemicals.nic.in/pharma4.htm>.
23. Ministry of Environment & Forests. Rules for the manufacture, use, import, export and storage of hazardous microorganisms genetically engineered organisms or cells. 1989. [Accessed on 08 Apr 2015] Available from
<http://envfor.nic.in/legis/hsm/hsm3.html>.
24. Parliamentary Standing Committee - 45th report. Issues relating to availability of generic, Generic-branded and branded medicines, their formulation and therapeutic efficacy and effectiveness. 2010. [Accessed on 05 Apr 2015] Available from
<http://164.100.47.5/newcommittee/reports/EnglishCommittees/Committee%20on%20Health%20and%20Family%20Welfare/45th%20report.pdf>.
25. Ministry of Health and Family Welfare. Drugs and Cosmetics rules 1988 (eighth amendment). 1988. [Accessed on 05 Apr 2015] Available from
http://dbtbiosafety.nic.in/act/_Annex-7.htm.
26. Tharu R. Clinical Trials in India - Boon or Bane? 2008. [Accessed on 05 Apr 2015] Available from:
<http://www.medindia.net/news/healthwatch/clinical-trials-in-india-boon-or-bane414191.htm#ixzz3YIVgw7wi>.
27. Ariyanchira S. The Opportunity for India in The Global Biosimilars Market. 2010. [Accessed on 05 Apr 2015] Available from:
<http://www.pharmaphorum.com/2010/06/21/the-opportunity-for-india-in-the-global-biosimilarsmarket/>
28. CDSCO. Import or manufacture of a new drug for clinical trials or marketing. 2010. [Accessed on 05 Apr 2015] Available from
http://cdsco.nic.in/html/Sec_122_A.htm
29. Ministry of Health & Family Welfare. Schedule Y - Requirements and guidelines for permission of import and / or manufacture of new drugs for sale or to undertake clinical trials. 2005. [Accessed on 05 Apr 2015] Available from
http://dbtbiosafety.nic.in/act/Schedule_Y.pdf
30. Tripathi KK. General approval procedures for biotech medicines - Regulatory approaches and criteria for approvals of biotech medicines in India. 2009. [Accessed on 08 Apr 2015] Accessed from
<http://www.grips.ac.jp/docs/tripathi.pdf>.
31. Ministry of Environment & Forests. Notification regarding adoption of the recommendations of the task force on r-pharma under the chairmanship of Dr. R A Mashelkar, DG-CSIR with effect from 1.4.2006. 2006. [Accessed on 08 Apr 2015] Available from
http://envfor.nic.in/divisions/csurv/geac/rpharma_tf.pdf.
32. Subramaniam KV. India as a global leader in biosimilars, A presentation at the Biosimilars India Conference 2011, 14-15 July 2011 Mumbai, India.
33. Arnun PV. Opportunities in the Biosimilars Market. 2010. [Accessed on 05 Apr 2015] Available from:
<http://pharmtech.findpharma.com/pharmtech/Ingredients/Opportunities-in-the-BiosimilarsMarket/ArticleStandard/Article/detail/660530>
34. Bourgoin A. What you need to know about the follow-on biologic market in the US: Implications, strategies and impact - competitive landscape. 2011. [Accessed on 05 Apr 2015] Available from
<http://thomsonreuters.com/content/science/pdf/ls/newport-biologics.pdf>
35. The New Trends of Drug Development Outsourcing in China and India. 2012. [Accessed on 06 Apr 2015] Available from:
http://www.researchandmarkets.com/reports/2238850/the_new_trends_of_drug_development_outsourcing_in#pos-0
36. Ghangurde A. Biocon plans biosimilars R&D and production unit in Malaysia. 2010. [Accessed on 05 Apr 2015] Available from
<http://www.scripintelligence.com/business/Biocon-plans-biosimilars-RandD-and-production-unit-in-Malaysia-305021>.
37. Gale J, Bhattacharjee A. Dr. Reddy's is developing eight more drugs. 2007. [Accessed on 06 Apr 2015] Available from
http://www.bloomberg.com/apps/news?pid=newsarchive&sid=an605eC_iu.c&refer=home
38. Bhattacharjya AS, Sapra PK. Health Insurance In China And India: Segmented Roles For Public And Private Financing. Health Aff 2008; 27(4):1005-1015.
39. Tandon VR, Mahajan A, Khajuria V, Kapoor V. Biologics and challenges ahead for the physicians. JIACM 2006; 7(4): 334-43.
40. Dey S. 1 insulin price cap for all brands. 2012. [Accessed on 06 Apr 2015] Available from:
http://www.business-standard.com/article/companies/1-insulin-price-cap-for-all-brands-112112100017_1.html.
41. WHOSIS. Global Health Observatory. 2010. [Accessed on 08 Apr 2015] Available from:
<http://apps.who.int/ghodata/>.
42. Joshi SR. Biosimilar peptides: Need for pharmacovigilance. J Assoc Physicians India. 2011 Apr; 59 Suppl: 44-7.

43. Joshi SR. Biosimilar insulins: Are they really 'similar'? 2009. [Accessed on 06 Apr 2015] Available from http://www.japi.org/february_2009/biosimilar_insulins.html.
44. Mody, Goradia, Gupta. How Similar Are Biosimilars In India? 2010. [Accessed on 06 Apr 2015] Available from: http://www.pharmafocusasia.com/research_development/blind-comparative-study.html.
45. Werner R. How biosimilar drugs compare to the original substance - International experts workshop on early treatment strategies for AMI. 2009. Kuala Lumpur. [Accessed on 06 Apr 2015] Available from http://www.metalyse.com/img/download/mi_news_kualalumpur2009.pdf.
46. Yang P. Roche – an innovator's perspective and position on biosimilars. 2009. [Accessed on 06 Apr 2015] Available from < www.roche.com/irp101005.pdf
47. Patwardhan A. Dr. Reddy's Position on Biosimilars, A presentation at the FDA Part 15 Public Hearing, November 2010.
48. Kliche W. There Is No Biosimilar To Metalyse, A presentation at Informa Life Sciences Biosimilars Conference, 2010, June 2010.
49. FDA. Guidance for Industry: Quality Consideration in Demonstrating Biosimilarity to a Reference Protein Product. 2012a. [Accessed on 08 Apr 2015] Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf>.
50. FDA. Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. 2012b. [Accessed on 08 Apr 2015] Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>.

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