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Role of Patents in Biosimilar Drug Development and Public Interest

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ABSTRACT

The innovation in the field of biotechnology has opened up new venues in the field of drug development like biosimilar drugs. The expiry of patents for many biopharmaceutical substances in various jurisdictions paved the way for the introduction of biosimilars in the market with reduced prices. The grant of patents for drugs as well as biopharmaceutical drugs act as an incentive for the developers to recoup their investment. But this has resulted in creating obstacle for access to medicine. The legislators have intervened in such situations by coming up with new statute for balancing public interest and interest of patent holders of these drugs. This paper explores whether patents on biologics facilitates competition or retard competition or it require any other mechanisms to balance the interest of patent holders and users/public interest. It explores how it has been regulated through legislative intervention in United States and protected public interest. In this context, examines the legislative attempts to protect public interest, by curbing anticompetitive practices of the patent holder in case of chemical drugs and bio pharmaceutical drugs, by exploring the Hatch Waxman Act and BPCIA of United States. It delves in to judicial decisions on patentability of biological materials and analyses its impact on biosimilar drugs. It also examines the challenges faced by the biosimilars in the Indian markets and the adequacy of the safety requirement of biosimilars in India.

Keywords: Biosimilars, Patents, Patentability, Public interest.

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INTRODUCTION

The grant of patent incentivises the inventor for his invention by granting monopoly over the invention. But expansion of patentable subject matter to life forms has created complexity in fixing patentability standards. This resulted in granting patents for all including gene. For example, the patent regime of United States has gone to an extreme extend by the US congressional intend of "anything made by the man under the sun is patentable". The *Chakraborty* case revolutionized biotech industry in United States and in the long run realized the abuse of patents in Myriad's case by preventing access to biological tools for diagnosis and research. The landmark decision of US Supreme Court in *Myriad* case invalidating isolated gene patents opened a new dawn in subject matter eligibility of biotechnology and in *Mayo* case by invalidating correlation method patents involving law of nature. Since the patent grant is not an absolute grant its validity can be challenged at any point. There should be a mechanism of balancing the interest of both users and owners. In United States for such a check and balance, Hatch-Waxman Act is one mechanism. The incentivising mechanism of innovators both generics and patented drug manufacturers continued by means of Biologics Price Competition and Innovation Act (hereafter BPCIA) and the Hatch-Waxman Amendments in the United States of America.

The growing biosimilar market offers huge potential for expansion for Pharmaceutical companies involved in manufacturing, research and development of drugs. In the light of expiry of patents of many biologics, there is great scope for generic pharmaceutical companies to come up with biosimilar drugs which are not like generic drugs. Thus, biosimilars drugs are different and more complicated than chemical drugs. Biopharmaceutical products are drugs made of biological materials like insulin, erthropoietin, chorionic gonadotropin, streptokinase, interferon, heparin. It is also called biological drugs or biologics in United States. Normally, drugs are chemical entities containing at least one active ingredient like paracetamol, imatinib, erlotinibetc. Biosimilars are biopharmaceuticals manufactured after the expiry of patents on biological material involved. Biosimilars should demonstrate that it is similar to the patented biological.

In US biopharmaceutical products are called biologics/ biological.

This scenario poses challenges due to the complexity of biological/biotechnology derived products as the generic approach is scientifically not appropriate for biosimilar products. In this context this paper examines how far the public interest is protected by way of exclusive marketing rights granted to developers and protection of its test data based on the Biologics Price Competition and Innovation Act (hereafter BPCIA) and the Hatch-Waxman Amendments in the United States of America. The intent of BPCIA is to incentivise biologics developers and facilitate further investment in this sector by granting data protection. Thus the first part of the paper delves on the EU and US approach on biosimilar drugs regulation, analysing positive and negative aspects of BPCIA and Hatch-Waxman Act. This issue is further exacerbated by judicial reasoning's based on a recent ruling from the U.S. Courts on biological materials related patents. The paper examines the provisions of the BPCIA and the surrounding uncertainties regarding the scope and type of data required by Food and Drug Administration agency (hereafter FDA), to support biosimilars applications. Also, to examine whether the patent drives innovation for biosimilars drugs or simply to dominate market by price differentiation.

European Union and United States Approach – Biosimilar Regulation

Biosimilars and generic drugs are versions of brand name drugs, normally they are manufactured after the expiry of patents, in case of biosimilars, biological entity and chemical entity, in case of generic medicines/non bio-pharmaceuticals. This makes generics much cheaper when compared to the patented drug. But generics should demonstrate bioequivalence to that of patented drug. This makes them to avoid repeating the costly clinical trials and thus able to come up with generics in cheaper price in the market.

But when it comes in case of biosimilars, they cannot be called as generics of the patented drug because unlike chemical compound, biosimilars are not the same biological product, but similar to it. So biosimilar manufacturers must demonstrate that the biosimilar is highly similar to the patented biological product or reference product (used in United States), except for minor differences in clinically inactive components. Biologics/biological product are one and the same. Biosimilar manufacturers must also demonstrate that there are no clinically meaningful differences between the biosimilar and the reference product in terms of safety and effectiveness. In biosimilars, bioequivalence is only the first step of clinical development because the pharmacodynamics may be different in spite of comparable kinetics unlike generics. Mainly, it has to demonstrate comparable exposure before entering further clinical testing for pharmacodynamics, safety and efficacy. [1] This makes biosimilars entirely different from generic medicines in terms of its procedure for approval. The most controversial issues with biosimilars are immunogenicity and extrapolation of therapeutic indications. Interchangeability and substitution are regulated by individual EU member states.[2] A originator/innovator drug/ reference drug can be substituted with a biosimilar drug in United States as well as in EU. Then it is called interchangeable product. In United States if biosimilar product meets additional requirements given in the Biologics Price Competition and Innovation Act then it can be called interchangeable product. The major requirements like comparability, interchangeable product are expected to produce the same clinical result in terms of safety and efficacy as the reference product in any given patient. The risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product will have to be evaluated so as to confer interchangeable product status.[3] Once such a biosimilar is approved as interchangeable by the FDA then the patient/pharmacist won't require the written prescription by the health care prescriber, subject to pharmacy laws. But FDA has said that while by law it could accept for filing and review an interchangeable biosimilar application, in practice it would not approve a biosimilar as interchangeable without some confirmatory market evidence. In this context, FDA suggested that perhaps five years of post-approval safety data would be sufficient for an applicant to submit a supplement to its previously approved biosimilar application, requesting a finding of interchangeability. So in the near future, most biosimilar litigation in the US will likely not involve an interchangeable biosimilar product.

EU became the first country to come up with guidelines for biosimilars approval to ensure its safety in 2001. The European Union (EU) was the first to come up with a formal approval of biosimilar pathway in 2001 and later amended to include similar biological medicinal products. In 2005 came up with first general biosimilar guidance. Sandoz's somatropin called Omnitrope in 2006 became the first formally approved biosimilar drug. In Europe, the opposition process to a patent granted by the European Patent Office (EPO) which called central is the most common approach for challenging the RBP's patents.ie., post grant opposition, within nine months after the patent is granted, which has public notice. It enables a biosimilar manufacturer to challenge a RBP's key patents in a single forum rather than multiple nation state patent courts. For example, oppositions were filed for epoetin (RBP Epogen [Amgen]), filgrastim (RBP Neupogen [Amgen]), infliximab RBP Remicade [Johnson and Johnson/Janssen]), insulin glargine (RBP Lantus [Sanofi]) and somatropin (RBP Gentropin® [Pfizer]).

EPO has 38 contracting states and provides unified patent prosecution and opposition with the option for national patents by applicant choice after prosecution. Oppositions may be filed by any public member(s) except the proprietor. It can be challenged based on some specific grounds. The outcomes may be retaining the validity, or invalidating the patent or the patent is maintained in amended form with a new published specification; decisions may be appealed within two months and countries may have conflicting rules whether they stay, i.e. halt further legal process, national patent infringement actions while an opposition and any associated appeal is pending. EU came up with specific biosimilar guidelines for similar biological medicinal products containing biotechnology derived protein as active substance as well as for monoclonal antibodies for the development and assessment of medicinal products. But still it faces challenges. The problem is to demonstrate comparable efficacy, an example of which is durable anti-viral effect in combination with inadequate immunogenicity data of a biosimilar interferon alfa candidate. So the demonstration of interchangeability according to stringent criteria will be a major challenge that may discourage biosimilar development. So immunogenicity of biosimilars must always be addressed in comparative studies. Another challenge is the lack of standardization of the assays and very few control sera are available which is creating a hurdle for immunogenicity comparative studies. The extrapolation of clinical efficacy and safety from one therapeutic indication for which the biosimilar was clinically studied, to other therapeutic indications should be done with caution with sufficient safety and efficacy data. Since there is a need to update the biosimilar guidelines due to newly developed background therapy as well as frequent updating, but that may create confusion too.

Biosimilar Patents in EU: Emerging issues

In EU there are no cases involving granting patents to biosimilars or any patent disputes on biosimilars presently existing, however, patent applications have been filed in EU. But the most important question will be how biosimilars will be satisfying the novelty and inventive step criteria. By drawing the analogy from decisions of biotechnology related patents any claim for the partial sequence which shows similar function of the patented sequence may hit novelty. This poses the question of how much percentage of difference/similarity when compared to identical sequence is required to satisfy the criteria of novelty. There are instances where noncoding sequence along with the partial sequence even though makes a structural difference may not cause any change in function, this shows instances of single change in sequences like Single nucleotide polymorphism may not satisfy inventive step criteria based on existing biotechnology patent decisions in Europe. Only if, the biosimilar manufacturer is able to show that the compound or sequence is having a better function/result ie., unexpected characteristics of a product or effects of novel process.[4] So granting novelty or inventive step especially for sequences related biological products are different, patent office's follows different ways. In EU Biotechnology patent directive expressly states isolated biological materials are patentable. The recent *Myriad* gene patent decision of European Court did not result in invalidation of BRCA patents. The reasoning given by the Court was that claims to human DNA encoding the BRCA1 gene and corresponding to the U.S. Patent No. 5,747,282 patent at issue in Myriad are obtained by technical processes are patent-eligible and do not fall within the category of alleged inventions that are excluded from protection as mere discoveries. The European Biotechnology patent directive clearly mentions that isolated gene are patent eligible. The Rule 29(2) of the EPC Implementing Regulations states that elements of the human body that are isolated or technically produced, including a sequence or partial sequence of a gene, can constitute inventions. This shows that in Europe there are less chances for controversies regarding biosimilar patenting issues. Biosimilars manufacturers can take patents for a new formulation, method of delivery, or dosage regimen for a known agent, etc. as well as follow on patents are having high potential value. But if the new changes differ substantially from the innovator drug them it cannot seek biosimilar approval. In case of follow on patents also separate clinical study data will be required. In EU already twenty-one biosimilars are in the market till now none of these have been withdrawn from the market for issues related to safety/efficacy. This reflects the effectiveness of the biosimilar guidelines in EU.

Biosimilars Patent Cooperation and Innovation Act (BPCIA) in United States and Public Interest

In United States biosimilar regulation was done through Biosimilars Patent Cooperation and Innovation Act (BPCIA) 2010 which is part of Ex US President Barak Obama's health care reforms provision included in the Patent Protection and Affordable Care Act, 2010. This is drawn similar to the Hatch Waxman Act for generic drugs. Here the generic manufacturers are given opportunity of challenge the patent on drugs by filing ANDA application which means generic manufacturer is going to infringe the patents. Based on this notice when the patent holder files a suit against the generic manufacturer for patent infringement and if the decision is not rendered by the court within thirty months ANDA applicant i.e., generic manufacturer will get 180 days exclusive marketing rights. Thus this provision acted as a tool for quality check of patents, conferring patent does not guarantees that it is 100% absolute. Thus facilities early entry of generics in the market at cheaper costs, thus protecting the public interest. It is in these lines BPCIA has been enacted, for early entry of biosimilars while considering the interests of patent holders

of the reference drug/original drug. Thus BPCIA facilitates competition between the original drug manufacturers with that of biosimilars.

Sandoz's filgrastim became the first approved biosimilar-Zarxio® in 2015.[5] While the EU's legal system is complicated because of multi-country patent litigation approach, the US biosimilar patent litigation has been complicated by biosimilar applicants and the reference biological product (RBP) applicants by choosing the nature of provisions under BPCIA beneficial for them.[6]

The EU and the US have similar regulatory standards for biosimilars that would enable a manufacturer to make a biosimilar product that could in theory satisfy both regulatory standards, assuming that the RBP is the same. In the EU, a biosimilar must demonstrate similar quality and biological activity and demonstrate no meaningful differences in terms of safety or efficacy between the biosimilar and the RBP. European Medical Agency develops product-specific guidances through a consultative process that establishes common comprehensive comparability and immunogenicity studies required for biosimilar applicants to demonstrate biosimilarity for approval. As part of these requirements, biosimilar applicants are expected to conduct a product-by-product analysis using state-of-the-art bioanalytics and manufacturing along with clinical and regulatory experiences to support biosimilarity. In United States, biosimilars must be highly similar to the RBP notwithstanding minor differences in clinically-inactive components. To demonstrate bio similarity, there must be no clinically meaningful differences in terms of safety, purity, or potency, essentially safety and efficacy. So far, US Food and Drug Administration (FDA) has come up with draft of product-specific guidances for biosimilars.[7]

In US biosimilar patent litigation is regulated through BPCIA provisions which mainly attempts to reduce litigation between the biosimilar applicant and RBP holder, by default exchange of information and there are at least two distinct phases of patent litigation.[8] This mechanism differs entirely from Hatch-Waxman patent litigation for small molecule drugs.[9] The intention of the legislation is to reduce maximum litigation as possible by voluntary exchange of information including the biosimilars application and information that describes the process(es) used to manufacture the biological product in the application and relevant patents as determined by the RBP holder and biosimilar applicant and limited rights are given if not participating in the voluntary exchanges. It means attracting the biosimilar applicant to prefer license from the original biologics manufacturer also, making these provisions as a tool for granting license in a reasonable terms between the parties. The Act also envisages multiple patent litigation 180 days prior to commercial product launch and post launch. The goals of the 180-day notification period for biosimilars is to satisfy its initial objective of settling disputes between parties, thus giving enough time for handling potential patent infringement and to ensure that there was sufficient time to file for injunction. But these provisions are making the applicant to wait till approval there by giving the RBP holder a sort of monopoly/exclusivity resulting in patent term extension. The other side is a patent infringement suit can be filed even after 180 days by the RBP holder thus delaying six months. This can be said to be a reason why there are only three biosimilars in US markets available when compared with the EU where twenty one biosimilars are in the market. The legal as well as regulatory hurdles with that of heavy expenses involved in pre marketing of the product as well as the post market commercialization will be huge are the compelling reasons for less biosimilar applicants in US. The protection for biologics, statutory exclusivity period of 12 years (despite the Obama Administration's attempts to limit this period to 7 years). The exclusivity period act as an incentive for the original biologics manufacturer after which biosimilar applicant can rely on the clinical data and non-clinical. Unique to the US, FDA may determine a biosimilar product is 'interchangeable' with the RBP. EU also has substitutive biosimilar provision. But till date no such interchangeable biosimilars products have been approved in both jurisdictions. The BPCIA tried to protect public interest by facilitating first filing for license of interchangeable biosimilars products by granting incentive of exclusive marketing rights for one year. So if biosimilar applicant goes further to get license for interchangeable biosimilar product he can avail this benefit. The first-filing biosimilar applicant has the benefit of first commercial marketing exclusivity for one year. The second interchangeable biosimilar product will get license only after if it satisfies the following conditions. (i) 12 months after first commercial marketing of the first-filed aBLA product interchangeable biosimilar product; (ii) 18 months after a "final court decision" in any litigation over patents that are the subject of the aBLA product are in favour of applicant, or the dismissal of such an action; (iii) 18 months after submitting aBLA to the biologic manufacturer and the biologic manufacturer fails to sue the biosimilar applicant; and (iv) 42 months after the approval of the aBLA product that is still the subject of litigation. The method seems to be more stringent so as to qualify for interchangeable product. The concerns are whether the investment on interchangeability is worth as far the acceptability of biosimilars in the market or is it worth to spend for its popularity/awareness on non-interchangeable product rather than on interchangeable biosimilars.

The recent litigation in biosimilars in United States shows the need to revisit the provisions of the BPCIA act so as to rectify the anomalies.[9] Around nine of the biosimilars

are under patent litigation in United States. Celltrion and Pfizer›s Inflectra (infliximab-dyyb), a biosimilar to Johnson and Johnson's Remicade (infliximab), which was approved has been challenged by Johnson and Johnson for patent infringement. So the lack of exclusivity period for the first noninterchangeable biosimilar potentially limits the incentives for early biosimilar entry unlike Hatch Waxman Act for generic medicines. Unlike the wide acceptance for the generics with much cheaper rate biosimilars are not gaining popularity, one reason being the cost itself, not a huge margin between original biologics manufacturer and the biosimilar manufacturer because of the extra expenses involved in proving comparability, safety and efficacy with that of reference biologics/original biologics. The study in US after three years of biosimilars entry in to US market reveals that only 12% of doctors are confidently recommending it out of 17% of doctors who supported biosimilars.[10]

In recent decision in Sandoz Inc.v.Amgen Inc.[11] the Supreme Court's decision added more clarity and more flexibility to biosimilar companies and filers of abbreviated Biologics License Applications ("aBLAs"), holding that (1) a reference product sponsor is not entitled to injunctive relief under federal law for an applicant's refusal to provide a copy of its aBLA and manufacturing information during the information exchange period contemplated by the BPCIA and (2) an applicant may provide statutory 180-day pre-launch notice of commercial marketing before its proposed biosimilar product is licensed by FDA, thus making it a non-mandatory provision. So in United States more experience has to be gained to study the impact of the BPCIA and further changes to be made in the light of upcoming litigation where court tries to clarify the same. The decisions in Myriad case[13] invalidating gene patents and Mayo's decision[12] of invalidating co relation patents will be added advantage for the biosimilar developer in United States giving access to biological product and an easier way for either infringement or challenging the validity of patents. Thus, patents for biologics have been used as a double edged sword for protecting the interest of the inventor at the same time using the provisions under BPCIA patents are subjected to challenge there by facilitating competition between original biologics and biosimilars.

Patentability challenge for Biologics and Biosimilars in United States

The recent judgments in Mayo and Myriad had created far reaching impact on patent eligibility. In *Mayo Collaborative Services v. Prometheus Labs, Inc*., the claims at issue were directed to a method of optimizing therapeutic efficacy of thiopurine drugs for treating autoimmune diseases by measuring the levels of certain metabolites in a patient's blood to determine whether the amount of drug should be increased or decreased. In holding the claims patent ineligible, the Supreme Court found that the claims merely "set forth laws of nature namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm" and failed to "do significantly more than simply describe these natural relations." Based on this decision many of the claims for method of treatment became ineligible. In *Endo Pharmaceuticals., Inc. v.* Actavis Inc[15]claims reciting a method of treating pain by administering to a patient oxymorphone dosed in accordance with the patient's creatinine clearance were directed to a law of nature and the administering step was insufficient to turn the natural law into a patentable application. The subject matter of the invention was "the reaction of the human body of a renally impaired individual to oxymorphone, which is unquestionably a natural law." Again claims for method of treating metabolic disease in patients intolerable to metformin therapy by administering a dipeptidyl peptidase-4 (DPP-4) inhibitor were held patent ineligible because they were "directed to an abstract idea of administering a drug to a targeted patient population," and the additional features recited in the claims were no more than "a well-understood, routine, conventional activity" and insufficient to "transform the abstract idea of administering DPP-IV inhibitor to a patent eligible subject matter."[13] However, in case of composition claims courts took a different view making it patent eligible. The claims directed to a composition comprising a specified amount of lisdexamfetamine having certain PK properties were held patent eligible.[14]Also claims directed to a controlled-release oxymorphone tablet having certain PK limitations were patent eligible.[15] Thus one can see the claims that are directed to a specific dosing regimen or indications or pharmacokinetic (PK) properties can easily be reduced to an abstract idea, a law of nature, or a natural phenomenon makes it ineligible patent subject matter. But claims for compositions or formulations becomes patent eligible.

In Association for Molecular Pathology v. Myriad Genetics, Inc.,[16] in which the court found claims directed to isolated DNA fragments derived from BRCA1 and BRCA2 genes patent ineligible, while those directed to cDNA fragments patent eligible. Though during isolation there will be mere changes in structure but that is not changing the natural functions of a gene as an information carrier. Thus the markedly different structure reasoning of the federal court has been rejected by the US Supreme Court. But in case of cDNA, i.e., complementary DNA it is it by human intervention how cDNA is synthesized, otherwise cDNA as such does not exists in the body. Thus the court tried to differentiate the human intervention involved in mere isolation as well as in creating cDNA. As far as biosimilars are concerned based on the above said decisions compositions and formulations may become patent eligible but claims relating to method of treatment/

dosage regimen becomes patent ineligible. The safer way is to go for process patents on the therapeutic applications of the biosimilar as there is a ban on patents on human organism incorporated by way of American Invent Act 2011.[17]

BIOSIMILARS IN INDIA- EMERGING CHALLENGES

The Indian biotech sector is divided into five major segments bio-pharma, bio-services, bio-agri, bio-industrial and bio-informatics.[21] The bio-pharmaceutical sector accounts for the largest share of the biotech industry with a share of 64% in total revenues in 2013, followed by bio-services (18%), bio-agri (14%), bio-industrial (3%) and bio-informatics (1%).It is the No. 1 producer of Hepatitis B recombinant vaccine.[18] Human health applications include therapeutics, diagnostics, pharmacogenetics to improve prescribing practices, functional foods and nutraceuticals and some medical devices. The shape of the future bioeconomy will depend on breakthroughs in basic and applied research in the biological sciences; but also on innovations in governance systems, regulations and business models.

India started producing the biosimilars from 2000. The 2017 report of Decision Resources Group's says 40 biosimilars are in pipeline when compared to EU. But according to experts the biosimilars available in India are non-innovator biologics because they are not meeting the standards of the International Guidelines for the biosimilar approval. Though India came up with the biosimilar guidelines in 2013 and again revised in 2016 which is in line with European medical Agency guidelines as well as that of WHO, the strict implementation and the rigorous standards of comparability with the originator drug is not going on. This has resulted in more number of biosimilars in India produced by Indian companies. Biocon and Mylan's fulphila (trastuzumab), a biosimilar of Neulasta indicated to minimise febrile neutropenia while cancer patients undergo chemotherapy, became the first biosimilar produced by an Indian company approved by US FDA in 2018.[19] Fulphila is currently under review in Australia and the European Union.

The price differentiation became a basis for its success in India when compared to the quality and safety that is mandated in countries like US and EU. The lethargic attitude of the implementers of the guidelines affects the quality of biosimilars making available to the patients of India. A recent example is the biosimilar launched by Mylan in 2014, Mylan launched Hertraz and Biocon launched CANmab similar biologic of Trastuzumab in India but without properly following the biosimilar guidelines. Same companies did not prefer to obtain approval of their Indian trastuzumab biosimilar in US rather a new biosimilar MYL-1401O fulfilling regulatory requirements of US-FDA was obtained in year 2017. This shows how the multinational companies are taking advantage of the situation by not selling their best products in Indian market. The Indian government started giving subsidies for the production of biosimilars in 2017. This shows that non-innovator biologic approved by RCGM and CDSCO in India are not effective and there is a need to review entire approval process of Similar Biologic.

The Delhi High Court decision in *Roche v Drug* controller general of India[20] where Biocon and Mylan were prevented from labelling their versions of the breast cancer therapy drug trastuzumab as "biosimilars" of Roche's Herceptin (sold in India under the brand names Herclon and Biceltis), for the use of language on the packaging and any use of data from Roche's own work on trastuzumab in product inserts. Roche argues

Table 1: Indian Companies Manufacturing Biosimilar Drugs in India.[39]

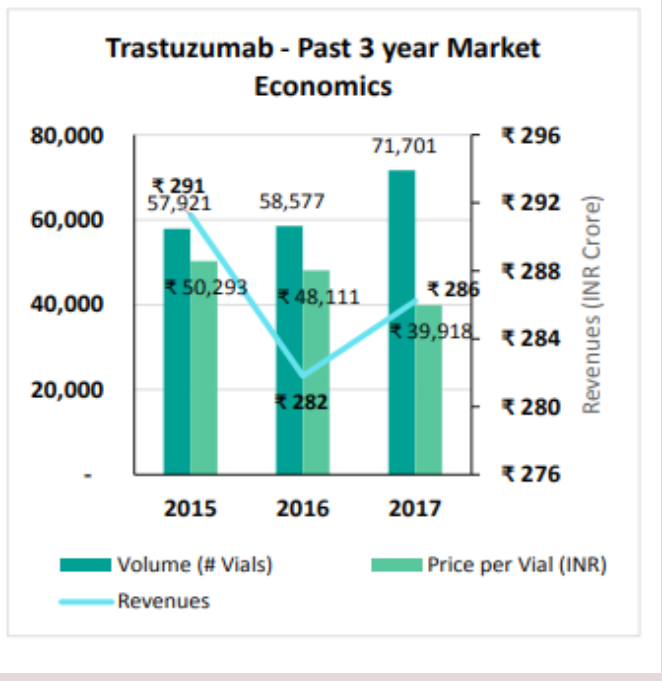
COMPANY(LOCATION)	BIOSIMILAR	PRODUCT DESCRIPTION
Dr. Reddy'sLab (Hyderabad)	Grafeel	Filgrastim(recombinant ranulocyte-macrophage colony-stimulating factor, G-CSF)
	Reditux	Biosimilar rituximab (mAb targeting CD20)
	Cresp	Darbepoetinalfa (recombinant erythropoietin)
Intas (Ahmedabad)	Epofit	Recombinant erythropoietin
	Neukine	Filgrastim (recombinant G-CSF)
	Neupeg	PEGylated G-CS
	Intalfa	Recombinant human interferon alpha-2b
ShanthaBiotech/Merieux Alliance (Hyderabad)	Shanferon	Recombinant interferon alpha-2b
	Shankinase	Recombinant streptokinase
	Shanpoietin	Recombinant erythropoietin
Reliance Life Sciences (Mumbai)	ReliPoietin	Recombinant erythropoietin
	ReliGrast	Recombinant G-CSF
	ReliFeron	Recombinant interferon alpha-2b
	MIRel	Recombinant reteplase (tissue plasminogen activator)
Wockhardt (Mumbai)	Wepox	Recombinant erythropoietin
	Wosulin	Recombinant insulin
Biocon (Bangalore)	Eripro	Recombinant human erythropoietin
	Biomab	Bioximilarnimotuzumab (humanized mAb targeting epidermal growth factor receptor)
	Nufil	Filgrastim, recombinant G-CSF
	Myokinase	Recombinant streptokinase biosimilar
	Insugen	Recombinant human insulin

Table 2: Current prices of selected blockbuster biologics and cost of manufacture for the active ingredient.[40]

Medicine	Example indication	Duration of treatment used for comparison (corresponding dosage in mg)	Lowest available price (USD)			Cost of manufacturing the active ingredient
			US	UK	INDIA	
Adalimumab	Rheumatoid arthritis	2-week cycle (40mg)	$707	$482	$385*	$1–12
Alemtuzumab	Relapsingremitting multiple sclerosis	2-year treatment course (96mg)	$122,477	$77,213	N	$2–29
Bevacizumab	Metastastic colorectal cancer	2-week cycle (700mg) $	$3,694	$2,216	$1,077*	$14–210
Etanercept	Rheumatoid arthritis	1 month of treatment (200mg)	$2,019	$3,526*	$639*	$4–60
Infliximab	Crohn's disease	1 maintenance dose (350mg)	$1,753*	$1,808*	$1,723*	$7–105
Ranibizumab	Wet agerelated macular degeneration	1 intravitreal injection (0.5mg)	$1,300	$229	$57*	$0.01–0.15
Rituximab	Non-Hodgkin's lymphoma	1 cycle (650mg)	$3,685	$1,400*	$711*	$13–195
Trastuzumab	HER2-positive breast cancer	3-week cycle (420mg)	$2,878	$1,172	$861*	$8–126

*Biosimilar

Table 3: Indian Biosimilars in Export Market.



Source: IPSOS data

Table 4: Indian Biosimilars Market in Europe.

Medicine Name	Active Substance	Marketing Authorisation Holder(Indian)	Authorisation Date
ACCOFIL	FILGRASTIM	INTAS PHARMACEUTICALS	18/9/2014
SEMGLEE	INSULIN GLARGINE	BIOCON/MYLAN	23/3/2018
PELGRAZ	PEGFILGRASTIM	INTAS PHARMASEUTICALS	21/9/2018

Table 5: Indian Biosimilars Market in United States.

Medicine Name	Active Substance	Marketing Authorisation Holder(Indian)	Authorisation Date
Fulphia	Pegfilgrastim	Biocon/Mylan	4/6/2018
Ogivri	Trastuzumab	Biocon/Mylan	1/12/2017

The data shows growing export market for Indian biosimilars in Europe and United States.

that what biocon is selling is not a biosimilar of their product Herceptin. They have not followed the thoroughly clinical and regulatory guidelines for biosimilar in India. So Biocon cannot sell their products as biosimilar of Roche and cannot use any details/data in their packing and results in passing off. The court agreeing with the contentions transgressed in to the power of drug controller and RCGM and CDSCO safety ensuring committees. Also for the allegation of usage of brand name, here Biocon was using its own Trade name and also it is clearly mentioned that it is manufactured by them and Biocon's product is certified by the drug controller. So there is no misrepresentation or confusion created as the consumers are doctors only as it is an intravenous drug. Also, if the issue is regarding the use of Herceptin brand name of Roche Biocon used it to mention biosimilar of Herceptin which is a fair use under Trademark. They failed to prove misrepresentation aspect. The Roche's action to prevent biocon from entering the market has been taken before Competition commission

Table 6: The Leading Players in the Segment and Their Target Markets

Company	Pipeline info	Target Markets	Stage of Development
Biocon	Adalimumab		Global Phase 3 completed
	Trastuzumab	USA, EU, Canada, Australia, EM	Approved in USA, under review in EU, Canada & Australia, Filed/Marketed in Emerging markets
	Pegfilgrastim	USA, EU, Canada, Australia, EM	Filing stage
	Bevacizumab	Marketed in India	Global phase three
	Filgrastim		Early Development
	Etanercept		Early Development
Intas Biologicals			5 biosimilars in the pipeline for India, and 5 for regulated markets of EU and USA
Dr. Reddys	Rituximab Pegfilgrastim Bevacizumab	EU and USA	Approval enabling studies initiated
ZydusCadila			8 biosimilars in the pipelines for regulated markets and India
Reliance Life Sciences			14 biosimilars in global pipeline
Lupin Pharma			5 biosimilars in global pipeline
Wockhardt			4 biosimilars in global pipeline

of India where they are denigrating the competitor's product in the Market which cannot be considered as a marketing strategy it will fall under anti-competitive practice.

Biologics Patents: Issues in India

India is among the top 12 biotech destinations in the world and ranks third in the Asia-Pacific region.[21] The Indian biotech industry holds about 2 per cent share of the global biotech industry.[22] The 2014 Indian Patent Office (IPO) annual report stated that approximately 43,000 patent applications were filed between April 2013 and March 2014. Over 2,300 of these are related to biotechnology and other related fields.[23] Although patent filing in India in general has increased in the last few years, biotechnology patent filing has decreased. This is consistent with the global trend. Among other things, it could be attributed to more stringent criteria for patentability and grant of patents in this domain. Since biosimilars are biological products, for its patenting one should know the patent jurisprudence for biotechnology related inventions in India.

Patents incentivize the inventor by granting exclusive rights and public through disclosure of the invention. Patentability i.e., both patent subject matter principle and standards of patentability act as the gatekeepers to maintain public domain to facilitate innovation while preserving the basic materials. TRIPS Agreement has provided flexibilities under Art. 27.3 which helps to keep natural phenomenon and laws of nature in the public domain. As far as Indian Patent is concerned by way of exclusions under section 3 where discoveries are not patentable made biological materials un patentable Exclusion of chemical process from the purview of product patent also kept biological materials as well as diagnostic kits outside the purview of subject matter even in 1970 Patent Act. After signing WTO, based on the TRIPs flexibilities Indian patent act expressly excludes diagnostic, surgical, prophylactic, curative method patents and method of treatment from the purview of patents. Also excludes plants and animals other than microorganism.[28] Thus it gives the impression that biological materials like gene are not patentable. As far as patent legislation is concerned, the Patents Act, 1970 does not specify which are patentable, but it illustrates subject matters that are not patentable. This is used as a major barrier for patenting products and also inventions related to biotech and pharma industry, the 2005 amendment was bought in to incorporate the product patenting as mandated by TRIPS, by one handle we recognised and incorporated, by another handle we raised the standard of patentability and exclusion of patentable subject matter. Even after repeated amendments even now the Patent Act of India is not addressing certain cardinal building blocks of biotech inventions. The Act is silent on terms like DNA, rDNA, genes etc which are crucial in determining the scope of biotech invention; however silence in this regard is giving the patent officer more flexibility. Indian patent law has provided exclusions in subject matter to keep life forms based discoveries as non-patentable which means natural products isolation will fall under mere discovery principle. The definitions in Patent Act for invention and inventive step draws to a very high standard of patentability. However the recent trends and the ground reality shows the fact that there is high monopolisation happening in agro and pharma

sector. Even after more than 12 year of product patenting, the core issue of product patents on seeds, plants and medicines remains the same and the threat of monopolies and protection of well-defined pubic interest and public domain in law still needs to be addressed. The lack of judicial decisions, as well as confusing biotechnology examination guidelines as well as careless patent grants on non-eligible matter in biotechnology also adds to the uncertainty.

The importance of this exclusionary category of subject matter is that it helps to keep this category in public domain, nobody can properties it and thereby protecting public interest. Patents for genetically modified gene sequence as well as for genetic technologies should be granted cautiously because these are upstream products used in experimentation, patents on upstream products will result in to preventing access to researchers, scientist and also for laboratories for diagnosis purpose. So, section three of Patent Act are taking care of human rights i.e Right to health. The provisions of compulsory license as well as research exceptions are provisions to ensure public access to affordable pharmaceuticals/ biomedical treatments and to encourage further research. The examinations guidelines which are not having any statutory back up should not dilute legislative intent. The economic growth should not neglect the social progress and human values so as to protect anything having some commercial value.[24]

The exclusions should be viewed as aspects of nature where no property rights can be claimed and should be viewed as tools of invention and innovation that should remain freely accessible in order to maximize technological advance.[25] Such gene patents prevent access to innovate further in genetic testing technologies itself. [26] As far as India is concerned, there is a need for having a clear policy on patenting of gene. In this context, the term microorganism has to be re-examined as viral sequences are of highly useful in developing vaccines. In some countries virus has been excluded from the microorganism. TRIPS does not expressly mandates to grant patents on gene, in such a situation there is no obligation on the part of India to grant gene patents. Adopting TRIPS provisions India has excluded medicinal, surgical, curative, diagnostic, therapeutic process for the treatment of human beings and animals from patentable subject matter. Also, the application of provisions of section 3(d) to the biotechnology patent applications provisions, is yet to be seen how India will treat such patent applications because of lack of case laws. There is a strong need for India to take a policy decision on gene patents keeping in view its importance in drugs and vaccine development, developing diagnosis tests and kits.

Patents, Biosimilars and Public interest

Patents are granted for a period of twenty years, this itself shows that public interest to be considered by restricting the monopoly to certain period. Biosimilars are able to manufacture because of this restricted monopoly, thus striking a balance between the owners and users interest. Thus able to make the same drug available at a cheaper affordable price. Countries adopt various mechanisms to protect public interest like subject matter exclusions, raising patentability standards, provisions on compulsory licensing, government use, experimentation exception and patent exhaustion principle. All these are keeping in mind the public interest. Thus Indian Patent Act is a big example for this. The exclusions of subject matter provisions as well as higher patentable standards ensure robust public domain for facilitating new inventions, thereby protecting public interest at large. This makes Indian Pharma companies to manufacture biosimilars early and became pioneers in biosimilars manufacturing than any other country, also able to come up with low cost biologics. Thus biosimilar production at lower cost is actually protecting our public interest especially for a country like India where medicines are not affordable for the substantial population. The on-going attempt to lobby through the Trans Pacific Partnership Agreement/ Free Trade agreements, where mandatory grant of patents on plants, animals, seed i.e., a back door entry of exceptions given under Art 27.3 of TRIPS as a patentable subject matter (which mandates patents on diagnostic methods too) should be strongly defeated.[27]

Biosimilars and Challenges in India

With lapse of the patents on biological product, it will made accessible for biosimilar product manufacturers so that one can expect cost reduction. Biosimilars are bigger and more intricate than the chemical drugs. As they are not the generics, the generic approach won't be suitable for the biosimilar product. Many of the biopharmaceuticals produced in India are non-innovator drugs which means not followed any standards of biosimilars so as to qualify that status. Biobetters are those where improvements on original non innovator biopharmaceutical drugs are made. Biobetters include structural changes, bi-functional targeting (with or without a biosimilar core) or an improved formulation that may result in an expected improvement in safety and/or efficacy.[33] They need not qualify to be biosimilars. Biosimilars are like original product yet not indistinguishable to the inventor product, prompting prerequisite of the comparability testing. The fertile area for biosimilars in India is the exclusion for biological materials from patenting. So more chances that in case of any suit against biosimilars they can challenge the patentability. As biosimilar maker needs to face extraordinary difficulties in the development, clinical improvement, manufacturing, duplication of pre-clinical and clinical studies, registration

and product marketing contrasted with customary generics, India needs to create particular regulations/guidelines administering biosimilar, with stringent administration. India's Central Drugs Standard Control Organization (CDSCO) published Proposed Revised Guidelines on Similar Biologics (2016) and compelling collaboration in the middle of originator and biosimilar producer.[28] India can become one of the key player/ maker of biosimilars by the accomplishment of biosimilar upon the satisfactory execution of the pharmacovigilance framework and administrative rule while India's pharmacovigilance framework is under upgradation.[35] Presently, we have pharma companies marketing biosimilar drugs as well as in collaboration with foreign companies for biosimilar development.[35] Recently, biopharma company Biocon had collaborated with the US pharma giant Mylan for development and commercialization of generic biologics. Dr Reddy's Laboratories had partnered with TR-Pharm, a start-up from Turkey, for three biosimilar products. Aurobindo had incurred Rs. 411.89 crore towards R&D expenses, which was around 3.5 per cent of its revenues during the last financial year. The development of biosimilars would be challenged by regulatory hurdles along with the cost associated with conducting clinical trials in various geographies along with patent infringement issues giving way for Indian companies to become key players on biosimilar drugs unlike United States situation.

The new biosimilar guidelines 2016 would be a relief for maker of these drugs as it specifically calls for calling for specific post marketing safety data "through a pre-defined single arm study of generally, more than 200 evaluable patients and compared to historical data of the Reference product. The study should be completed preferably within 2 years of the marketing permission/manufacturing license unless otherwise justified. [29]

Also the provisions like if a product is found to be similar "in pre-clinical, *in vitro* characterization having established PK [pharmacokinetic] methods and a PD [pharmacodynamic] that is surrogate of efficacy, the residual risk is significantly reduced in the Phase I study if equivalence is demonstrated for both PK and PD.[30] Phase III clinical trials of such a Similar Biologics product may be waived where considered necessary, an appropriate single arm study in at least 100 evaluable subjects may be carried out in the most sensitive indication to address any residual uncertainty.[38] Also the clinical safety and efficacy study can be waived, noting: "In case the safety and efficacy study is waived all the indications approved for reference product may be granted based on comparable quality, nonclinical as well as convincing PK/PD data.[31] Wherever the phase III trial is waived, the immunogenicity should have been gathered in the PK/PD study and will also need to be generated during post-approval Phase IV study. Thus the guidelines clearly clarify the approval process of Similar Biologics in India thereby ensuring that new, essential and affordable Similar Biologic drugs reach the Indian population at large making it tune with global standards.[32] Approximately 70 biosimilar products have been approved in India and, according to GaBI's list, more than 25 have been developed in India since 2000.[33] WHO has kicked off a pilot pre-qualification program for biologic and biosimilar drugs for 2 key biologic products – rituximab and trastuzumab, in order to facilitate affordable access of these critical drugs in low and middle income countries.[34] Thus proved to be a great boon for the Indian vaccine industry in creating a common platform for validation of products and procurement by multiple countries, a boost for Indian biosimilars to compete with others.

But the market penetration of Indian biosimilarseven in Indian market are very slow. The recent Biocon/Mylan biosimilars export to United States shows that quality wise product differentiation done for US and Indian markets calls for vigilance in Indian Authorities and also shows the need for strict quality assurance in Indian markets.

CONCLUSION

The expiry of patents of biological products is a big opportunity for Indian Pharma companies to dominate the biosimilars market globally. The Indian generic companies proved it in case of therapeutic drugs, now it is the time to prove for biosimilars too. The Indian Pharma companies should strictly comply with the biosimilar guidelines; also concerned authorities are having the very much duty to ensure the compliance of it. This will make Indian Pharma companies to compete globally. By providing access to original cell lines of the original drug manufacturer will facilitate to cut down the cost and reduce the prices of the biosimilars drastically. The experience of EU and United States and their success especially EU shows the strict measures they adopted for approval of biosimilars. The United States also shows how different strategies can be adopted to facilitate competition with original drug manufactures with that of biosimilars. In India there is a need to ensure that biosimilar guidelines are following thoroughly. In case of patents for biosimilars it shows the difference in various jurisdictions how patentability standards are applied and how inventive step will become a barrier to overcome the threshold. India being a country with weaker patent protection with biologics more opportunity for the pharma companies to come up with quality biosimilars in the market and dominate the globe by providing access to biosimilars at cheaper price.

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CONFLICT OF INTEREST

The author declare no conflict of interest.

ABBREVIATIONS

US: United States; EU: European Union; EPO: European Patent Office; **FDA:** Food and Drug Administration Agency; **BPCIA:** Biologics Price Competition and Innovation Act; **DNA:** Deoxyribonucleic acid; **RBP:** Reference Biological Product; **ANDA:** Abbreviated New Drug Application; **RCGM:** Review Committee on Genetic Manipulation; **CDSCO:** Central Drugs Standard Control Organisation; **cDNA:** Complementary Deoxyribonucleic acid; **aBLA:** Abbreviated Biologics License Applications.

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