Online Available at www.thepharmaresearch.info

THE PHARMA RESEARCH, A JOURNAL

The Pharma Research (T. Ph. Res.), (2010), 3; 157-171.
Published on- 15 June 2010

ISSN 0975-8216

Original Article

BIOSIMILARS, A REVIEW

Yashpal Sangwan*[1], Pawan Jalwal[2], Anju Jangra[2], Lalita Dahiya[2], Rajiv Saroha[1]

Affiliated to:
[1]P.D.M. College of Pharmacy, Safidon, Deptt. of Pharmacy, Kurushestra University, Kurushestra
[2]Faculty of Pharmaceutical Sciences, Shri baba Mastnath Institute of Pharmaceutical Sciences & Research, Asthal Bohr, Rohtak (124021)

ABSTRACT

Biosimilars* or *Follow-on biologics are terms used to describe officially approved new versions of innovator biopharmaceuticals, following patent expiry. The term "biosimilar medicine" comes from European Union (EU) legislation governing the approval process, but these products are also known as "Similar biological medicinal products", "follow-on biologics", "biogenerics" in United State (US) and other countries such as India, Japan etc. The chief industry body responsible for the regulation of pharmaceuticals is the European Medicines Agency (the "EMEA") (although the European Commission ("EC") has the final say on all pharmaceutical approvals). At the time Sandoz applied for registration of Omnitrope, the EU was undergoing significant changes in its regulatory environment for *follow-on biologic (FOBs)* which were termed as "biosimilars" in the EU. Two biosimilar somatropins, Omnitrope and Valtropin (marketed by Sandoz and Biopartners, respectively) have been approved by the EMEA.

Europe and the US are estimated to have a market size of above $16 billion by 2012 for biosimilars. Indian companies also have initiated to take part for biosimilars market. Several Indian companies including Dr Reddy's Laboratories, Wockhardt, Intas Biopharmaceuticals and Biocon are working on several biosimilar drugs.

Researchers at Reliance Life Science are also working on novel therapeutics for treatment of cancer, infectious diseases, inflammatory disorders, ocular disorders and neurodegenerative disorders, based on most advanced drug research platforms such as small interference RNA (siRNA) and monoclonal antibodies Reliance Life Sciences, which launched three biosimilars, or reverse-engineered versions of biotech drugs last year, which may launch four more such drugs in near future.

Keywords: Biosimilars, Follow-on Biologics, FOBs

***Corresponding author:**
Email: sangwan.yashpal@gmail.com

1.0 INTRODUCTION

Biosimilars or *Follow-on biologics* are terms used to describe officially approved new versions of innovator biopharmaceuticals, following patent expiry. The term “biosimilar medicine” comes from European Union (EU) legislation governing the approval process, but these products are also known as “Similar biological medicinal products”, “follow-on biologics”, “biogenerics” in United State (US) and other countries such as India, Japan etc . The situation in the United States is much less clear than in Europe. Generic drugs are drugs manufactured and marketed without a brand name.

In practice, generics are often marketed as equivalents to branded drugs. Generic drugs are generally much cheaper than their branded counterparts for a number of reasons. First, drug development is extremely time consuming and costly. On average, brand-name drug companies spend about $ 800 million to discover, develop, and produce a new drug. They then have to charge fairly high prices to recoup their investment and actually make a profit. Generic manufacturers, however, don't have to spend nearly so much on drug development. To gain Food and Drug Administration (FDA) approval, all a company has to do is prove that its version of a drug is chemically equivalent to the original. If the chemical makeup is the same, it's assumed that the research and clinical trials are as applicable to the generic version as they were to the original. Also, generics manufacturers benefit from advertising for branded drugs, lowering their own marketing expenses. Commonly, generic drugs in the United States are approved under section 505(j) of the Federal Food, Drug and Cosmetic Act (FFDCA)[1].

The EU has a centralized pharmaceutical approval process amongst member countries. The chief industry body responsible for the regulation of pharmaceuticals is the European Medicines Agency (the "EMEA") (although the European Commission ("EC") has the final say on all pharmaceutical approvals). At the time Sandoz applied for registration of Omnitrope, the EU was undergoing significant changes in its regulatory environment for *follow-on biologic (FOBs)* which were termed as "biosimilars" in the EU. Particularly relevant were the amendments to Directive 2001/83/EC in 2004, the primary Directive for the regulation of pharmaceuticals. Prior to the implementation of these amendments, Sandoz's Omnitrope received an unfavorable assessment from the EMEA. The amended Directive 2001/83/EC now permits the registration of "similar biological medicinal products", recognizing the need for an approval mechanism for FOBs. The EMEA has now granted Sandoz a favorable assessment for

Omnitrope and on 18 April 2006 the EC gave Sandoz the green signal for marketing approval [2].

1.1 Requirements for generic drug manufacturing:

Requirements for generic drug manufacturing include that a generic drug must meet several specified criteria to be approved for market release. Firstly, it has to contain the same active ingredient as the innovator drug and be administered by the same route. It must also have the same formulation, potency and conditions of use[3]. In the past, medicines have been almost exclusively low molecular weight compounds. Such chemical compounds (such as statins, angiotensin-converting enzyme inhibitors) are relatively easy to synthesize and precise copies of defined quality can be produced in a consistent manner. This reliability of synthetic method is reflected in the regulatory requirements for generics manufacturers. They only need to demonstrate that their compound is physicochemically identical to the original drug and 'bioequivalent' (has the same pharmacokinetic profile) in a limited clinical study for the relevant indication.

A number of biotechnology based products are currently marketed including insulin, growth hormones, interferon-b and factor VIII. These recombinant proteins are large molecules, produced from genetically modified cell lines, and extracted through complex and lengthy purification procedures. Because of the variability inherent in such processes, identical copies of original brands cannot be manufactured and, therefore, 'biogenerics' cannot exist. Instead, the term 'biosimilars' has been coined to describe these off patent copies of therapeutic proteins.

1.2 Regulatory approval

Limited documentation is required to obtain marketing authorization for a conventional small-molecule generic drug. In general, it is sufficient to show pharmaceutical equivalence and bioequivalence of a generic drug compared with the original product in a small study of volunteers, via an abridged procedure. However, this approach cannot be extrapolated to the majority of biopharmaceuticals because current analytical methods are inadequate to fully characterize these complex proteins. The amount of data required for market approval of biosimilars will be more than for a typical generic drug application but less than for a full new biopharmaceutical application[4].

1.3 Current biosimilars

Because of the benefits and potential risks associated with biopharmaceuticals and biosimilars, it is important that clinicians familiarize themselves with the relevant literature on the safety and efficacy of these agents in

various patient populations. The EMEA provides information on the approval process for human medicines [the European Public Assessment Report (EPAR)], including a scientific discussion on the clinical data submitted for approval. Generally, the EPARs for biosimilars have stated that the biosimilar received approval because it was shown to have a comparable quality, safety and efficacy profile to the reference product[5-11]. Despite the comparability of these biosimilars to the reference products, clinicians should be aware of some of the issues that emerged during the development and approval of these products, which highlight the challenges of biosimilars.

Two biosimilar somatropins, Omnitrope and Valtropin (marketed by Sandoz and Biopartners, respectively) have been approved by the EMEA. Omnitrope is a biosimilar version of the reference product, Genotropin (manufactured by Pfizer). Like Genotropin Omnitrope is a recombinant form of human somatropin that is manufactured with rDNA technology in *E. coli*. The comparability of Omnitrope to Genotropin was demonstrated in a randomized controlled trial in 89 children with a lack of growth hormone, with an additional safety study performed in 51 children[5]. During the development of Omnitrope, an immunogenicity issue emerged with an early version of the product. Up to 60% of patients enrolled in two clinical studies developed anti-growth hormone Abs, which did not appear to affect growth rate. The cause of immunogenicity was linked to excess host cell protein contamination, which was resolved by the manufacturer with additional purification steps[12].

Valtropin, a biosimilar version of Humatrope manufactured by BioPartner, was shown to have similar efficacy and safety to the reference product in a 12-month randomized controlled trial involving 149 children lacking growth hormone[6,13]. Clinicians should be aware that while these products have comparable active substances, Humatrope is synthesized in *E. coli* and Valtropin is synthesized in the yeast *Saccharomyces cerevisiae*. Five biosimilar Recombinant Human Erythropoietin (rHuEPOs) that are manufactured by two companies have been approved by the EMEA. Abseamed, Binocrit® and Epoetin alfaHEXAL are epoetin alfa products and are biosimilar versions of the reference product Eprex, all produced by Rentschler Biotechnologie GmbH but marketed by three different companies. The approval of these biosimilar epoetin alfa products was based on the demonstration of comparability with Eprex in quality, safety and efficacy. Comparability exercises demonstrated that although the active substance of the biosimilars was representative of the active substance isolated from Eprex by immunoaffinity chromatography[14-16], there was a

difference in glycosylation levels. The biosimilars contained higher levels of high-mannose-type structures, but this difference was not thought to be clinically significant. Comparable safety and efficacy between these three biosimilar epoetin alfa products and Eprex was demonstrated in a randomized controlled trial involving 479 haemodialysis patients with renal anaemia. Although the regulatory guidelines for biosimilar Recombinant Human Erythropoietin (rHuEPO) developed by the EMEA recommend that comparable efficacy and safety are demonstrated with two randomized trials in the nephrology setting[17], the biosimilar epoetins alfa products were approved based on a single nephrology trial. Data from a study involving 114 cancer patients receiving chemotherapy were also submitted for approval but this study was not adequately powered to demonstrate therapeutic equivalence to the reference product. Biosimilar epoetin alfa was approved for indications in cancer patients and patients planning to undergo surgery (for autologous blood transfusions) via data extrapolation—without a full dossier of clinical data for the indication. (For a more detailed review of biosimilar epoetin alfa,) Two additional biosimilar versions of Eprex, Retacrit and Silapo, are manufactured by Norbitec GmbH. Although this biosimilar manufacturer also used Eprex as a reference product, the international nonproprietary name (INN) for these products is epoetin zeta rather than epoetins alfa to the active substance of epoetin zeta was shown to be a representative of the active substance found in Eprex, and the protein structures were comparable. However, differences were noted for the glycosylation profile with respect to glycoforms without an *O*-glycan chain and variants of sialic acid, and a different immunogenicity profile was observed in dogs[18-19].

The comparability of epoetin zeta to Eprex was demonstrated in two randomized clinical trials, a correction phase study and a maintenance phase study, involving 922 haemodialysis patients with renal anaemia. The correction phase study demonstrated comparability between epoetin zeta and Eprex for mean haemoglobin levels over the evaluation period. However, comparability was not demonstrated for mean dosage during the evaluation period. Similar results were reported in the maintenance phase study, suggesting a possible difference in the bioactivity of epoetin zeta and Eprex[18-19]. Data were also presented from a study involving 261 cancer patients receiving chemotherapy, but this study was not designed to demonstrate therapeutic equivalence between products in this patient population. Like biosimilar epoetin alfa, epoetins zeta was approved for indications in renal anaemia, chemotherapy-induced anaemia, and for pre-donation of blood prior to surgery for autologous

transfusion[20-21]. Because of its unique INN, epoetin zeta is more readily distinguished from other epoetin products. Unique INNs for biopharmaceuticals may help to facilitate accurate prescribing and dispensing of biopharmaceuticals, as well as pharmacovigilance[22].

The Committee for Medicinal Products for Human Use (CHMP) also issued positive opinions for four biosimilar filgrastim products for the treatment of neutropenia in February of 2008: Ratiograstim and Filgrastim ratiopharm (Ratiopharm GmbH), Biograstim (CT Arzneimittel GmbH) and Tevagrastim (Teva Generics GmbH). These biosimilar versions of filgrastim were shown to be similar to the reference product Neupogen. These products are awaiting final marketing approval by the EMEA and so the non-clinical and clinical data presented in the EPARs have not yet been made available to the public. It is important to recognize that the EMEA provides a rigorous and balanced approach to the approval process. Regulators are attempting to meet the demands of the healthcare market while ensuring the quality and safety of biopharmaceutical products. The approval of these biosimilar products does not substantiate interchangeability with reference products[23]. Furthermore, the EMEA has not approved all biosimilar applications. Alpheon, a biosimilar version of Roferon-A (interferon alfa-2a), was recently rejected by the EMEA. The manufacturer of Alpheon had submitted non-clinical data (protein structure, composition and purity) on the biosimilar and conducted a randomized controlled trial in 455 patients with hepatitis C to demonstrate comparable efficacy and safety between the biosimilar and reference product. The reasons for the rejection by the EMEA included quality and clinical differences between Alpheon and the reference product, inadequate data on the stability of the active substance, inadequate validation of the process for the finished process and insufficient validation of immunogenicity testing [24].

2.0 Regulatory considerations in US

A race between the USA and Europe in biosimilars can be defined in several ways: the first launch of a biosimilar; the first cross-border use of a biosimilar in the USA; the first legal provision for an abbreviated regulatory pathway applied in a consistent and continued manner; and the race for interchangeability or substitution of biosimilars for reimbursement, a race that is just beginning. The USA has won three of the five races, first-launch, first cross-border use and greatest value of biosimilars according to 2004 sales, but Europe is ahead in the most important race that is the application of a consistent and continued regulatory pathway. This paper provides the race results and looks at this race for biosimilars regulatory pathways. Once the

regulatory pathway is applied by governments in a consistent and continued manner and many biosimilars are launched, the race begins for interchangeability that affects physician prescribing and generic substitution. Biosimilar interchangeability and subsequent biopharmaceutical affordability is the ultimate prize for the real winners of the race [4]. The Omnitrope case has garnered significant industry and policymaker attention because of the use of the 505(b) (2) process to approve a follow-on, recombinant protein drug. Sandoz, the applicant, submitted its 505(b) (2) NDA application for Omnitrope on July 30, 2003. The FDA indicated that it could not reach a final decision on the Omnitrope application because of uncertainty regarding the scientific and legal issues related to follow-on biologics. Because of this delay Sandoz filed suit against the FDA in September 2005, claiming that the FDA was statutorily mandated to rule on its application within 180 days of submission under the terms of the *Prescription Drug User Fee Act.* The Federal District Court agreed, and on April 10, 2006, ordered the FDA to make an assessment and hold a hearing on the Omnitrope application. The FDA approved the Omnitrope application under section 505(b) (2) on May 30, 2006. Even though protein products are more complex than small molecules, FDA has applied its expertise and experience to approve certain follow-on protein products in applications described in section 505(b) (2) of the Food, Drug and Cosmetic Act (FD&C Act). Some examples of products approved in this manner are: Hylenex (hyaluronidase recombinant human), Hydase (hyaluronidase), Fortical (calcitonin salmon recombinant) Nasal Spray, Amphadase (hyaluronidase), GlucaGen (glucagon recombinant for injection), and Omnitrope (somatropin [rDNA origin]) [25].

2.1 Approval for follow-on biologics in US

Three major pathways exist by which a generic version of a previously approved drug ("branded product") can secure FDA marketing approval, namely:

A. New Drug Application (NDA) or Biologics Licensing Application (BLA)
B. Abbreviated New Drug Application (ANDA)
C. Food, Drug and Cosmetic Act (FFDCA) § 505(b) (2) Application

A. NDA or BLA

The new drug application route (FFDCA § 505(b) (1)) is available for FDA approval of all molecular entities, regardless of whether the FDA has previously considered the safety and efficacy of that molecule. However, filing an NDA or BLA undercuts the purposes of a generic drug. These new applications require detailed investigations of safety and efficacy, including

clinical studies outlined above. Thus, large monetary investments would be required that have to be recouped. The resulting product would not result in lower priced drugs, and the time required to complete the trials would delay the introduction of generics as soon as the patent expires. Therefore, NDAs have rarely been used for approval of generic drugs. Consequently, it is extremely unlikely that a full NDA or BLA would be filed for a follow-on generic, though these remain as options, especially if other routes are not available.

B. ANDA Application

The Hatch-Waxman act has provided the ANDA approach for the marketing of a generic drug. In order to utilize the ANDA process, the generic manufacturer must demonstrate that its product is pharmaceutically equivalent to the branded product, i.e., it has the same amount of the same active compound(s) administered in the same dosage form. Thus, the generic product has to be equivalent to the branded product in *in vitro* and *in vivo* tests. The *in vitro* tests measure the rate of release of the active compound(s) in solution, while the *in vivo* tests measure the bioavailability of the product, i.e., the rate and extent of absorption of the active compound(s) into the blood stream of the subjects in pharmacokinetic studies.

The generic product is approved if the differences between the branded product and the generic product are within acceptable limits with respect to the levels of impurities and release rates of the active compound(s). If the *in vitro* and *in vivo* data for the generic and the branded drug are similar, then the pre-clinical and clinical data of the branded product is extrapolated to assess the generic product. The two products will be treated as therapeutically equivalent and the generic product may be used interchangeably with the branded product.

The ANDA process could be utilized for biologics that were originally approved under FFDCA. Biotechnology companies maintain that the ANDA process cannot be applied to biologics because "the process is the product". They argue that biologic products are harder to define chemically, and their characteristics may be dependent on the way they were expressed, purified, and manufactured, therefore, even minor modifications, such as changes in culture media or growth conditions, will have a major impact on the end product. However, recent experience suggests that the process is not the product and ANDA is an appropriate route for the marketing approval of a significant number of follow-on biologics for several reasons.

First, the FDA issued, and the biotechnology industry advocated, the 2003 Comparability

Protocols Guidance. The Guidance allows manufacturers to make manufacturing changes without performing additional clinical studies to demonstrate safety and efficacy. The Guidance provides details for submitted comparability protocols for biologic products to demonstrate safety and efficacy, to establish comparability between a product made before a manufacturing change and a product made after a manufacturing change. The same guidelines could be used by a generic company to show that their biological product is similar to the branded product.

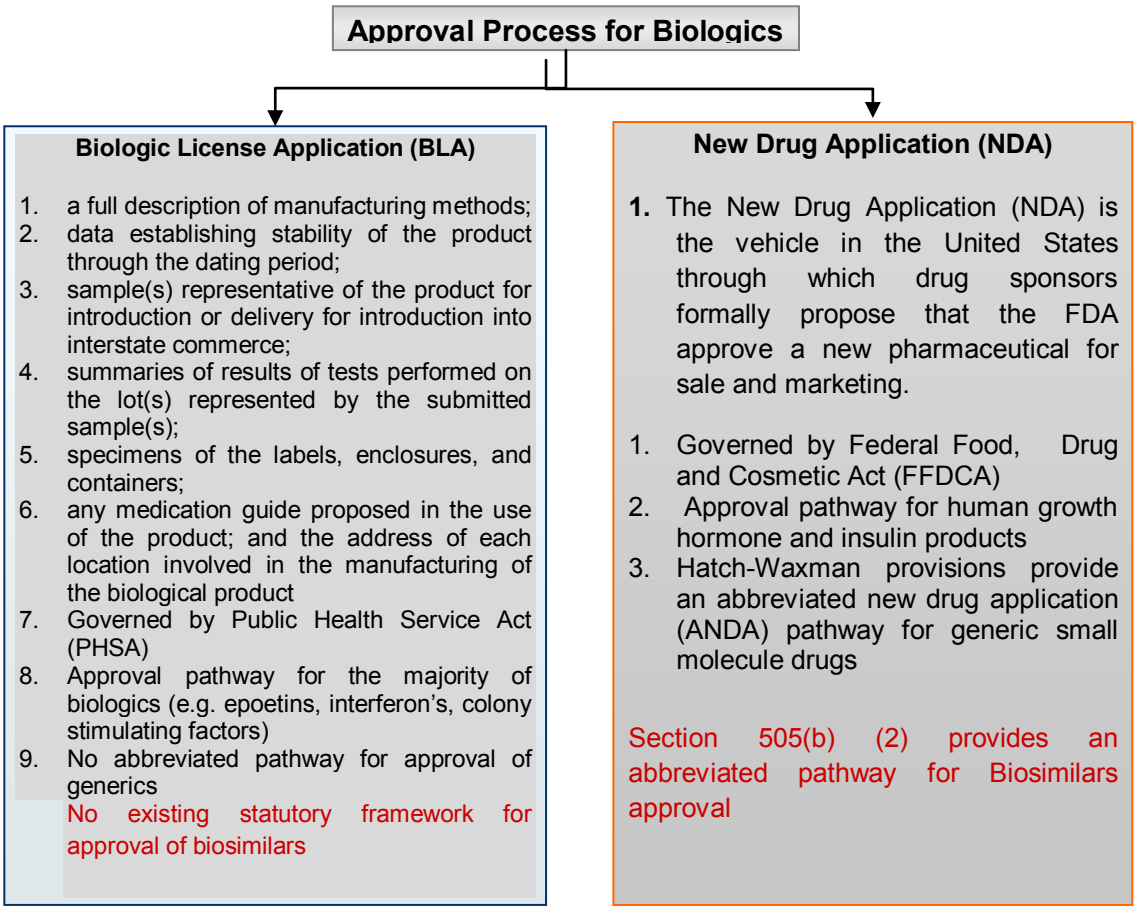

Fig.1. The two distinct regulatory pathways for biologics is associated with a different set of barriers for approval of biosimilars

Second, only a very small number of biologics cannot be characterized at present, and analytical chemistry is progressing rapidly. The definition of biologic drugs includes biological macromolecules, polysaccharides, polynucleotides (DNA, RNA), and polypeptides (proteins). Nucleic acids and proteins, like small molecules, can be extensively characterized

because their exact nucleotide or amino acid sequence can be determined. Nucleic acid-based technologies include gene therapy, antisense oligonucleotides, DNAzymes, ribozymes, and siRNA (RNAi). Because the precise chemical structure of the active substances of nucleic acid-based technologies can be characterized, process is not the product for them.

A number of therapeutic peptides contain eight to ten amino acids and are analogs of endogenous hormones including oxytocin, arginine vasopressin(a human hormone that is released when the body is low on water) (ADH) somatostatin (ADH) somatostatin, gonadotropin releasing hormone, and luteinizing releasing hormone. Because of their small size, these peptides can be synthesized chemically, and virtually all of them are approved via NDAs. The peptides of intermediate complexity contain 20-50 amino acids, and include insulin, glucagon, teriparatide, nesiritide, enfuvirtide, refludan, and sermorelin.

These peptides contain between 20 to 70 amino acids. They are mimics of endogenous proteins, and are also generally not glycosylated; therefore, immunogenicity concerns are lower. Recombinant protein-based therapeutics include interleukins, deoxyribonuclease, replacement enzymes for metabolic disease, growth factors like granulocyte-colony stimulating factor, platelet derived growth factor, and the like. Some of these undergo post-translation modifications that could be difficult to characterize and replicate. Further, there are immunogenicity concerns since they are novel proteins. However, these are a small part of "biologics" and thus, the exceptions should not make the rule.

Therefore, in some cases, ANDA is functionally not applicable to biologics. Further, ANDA is legally not applicable to biologics approved under the BLA. Thus, ANDA has limited utility for the approval of follow-on biologics. However, since the process is not the product for the majority of biologics, appropriate legislation need to be passed to implement ANDA for biologics.

C. SECTION 505(b) (2) application:-

The Hatch-Waxman Act implemented ANDA and § 505(b) (2) are complementary routes to approval of a generic drug. ANDA is functionally and legally not applicable to nearly all biologics and proteins, thus, § 505(b) (2) might be the only pathway by which the FDA could conceivably review applications for approval of follow-on biologics.

Section 505(b)(2) is essentially a hybrid of NDA and ANDA that theoretically allows for expedited review of a follow-on biologic, and applies to drugs that can not be brought under ANDA. A § 505(b)(2) application requires the submission of

"full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use" pursuant to § 505(b). The major difference between NDA and § 505(b) (2) is that NDA applicant has conducted the appropriate studies and trials, while a § 505(b) (2) applicant relies on investigations conducted by someone else-including the original sponsor of an NDA-approved drug. However the § 505(b) (2) applicant must substantiate the "relevance and applicability" of previous findings to the current application and could be required to supply clinical data describing any deviations in safety and efficacy of the new drug from the listed drug. Finally, §505(b) (2) is arguably available to all small molecules, protein-based therapeutics and biologics, given both its broad references to drugs and deletion of the ANDA's concept of "sameness". An issue with using § 505(b) (2) is that FDA would have to compare the clinical, chemistry, manufacturing and controls (CMC), commercial data and information provided in the NDA or the BLA with the data provided by the generic company to approve the follow-on biologic. Traditionally, FDA has considered this information to be trade secrets. Secondly, U.S. law provides 5 years of data exclusivity (10 years in the EU) from the day of registration of the drug. It is not clear whether the innovator's data could be legally used to approve generic products. In fact, treating the submitted data as trade secret, and the use of data-exclusivity are becoming the dominant Intellectual Property (IP) protection for branded biologic products.

The data included in the registration file of a pharmaceutical product, and disclosed to the FDA, is used to approve the drug for market use. The U.S. regulations providing for 5 years of data exclusivity does not provide any exceptions, such as the use of the data to approve a generic. Therefore, the data provided in the NDA or the BLA cannot be used to approve follow-on biologics during the 5 years.

The FDA has traditionally considered the data provided in the NDA or the BLA to be trade secrets, and safeguards the information through non-disclosure. One aim of nondisclosure is to ensure that rival companies, including generic companies, do not gain access to the registration file of the original product. The biotechnology companies have advanced a second aim of non-disclosure, namely to prevent the FDA from relying on the registration file of an innovator's original product in order to compare it to the chemical and toxic levels of a potential generic substitute. They argue that practically there is no difference between the use of the data to approve a generic and the disclosure of the data.

The position of the biotechnology companies may not be correct. First, several statutory provisions

evidence the Agency's authority to rely on information in addition to the data submitted in the generic application when determining safety and efficacy. Congress granted FDA the authority to carry out the Agency's mission, including the authority to promulgate regulations governing the approval of drug and biologic products. Second, no statute appears to explicitly state that the information is protected as trade secret and cannot be internally used by the FDA. Third, applying trade secrets law would extend the protection provided by the data exclusivity regulations, thereby raising anti-trust issues.

Even if the submitted information was a trade secret, the Supreme Court has expressly held that the *Trade Secrets Act* "cannot be construed as any sort of assurance against internal agency use of submitted data during consideration of the application of a subsequent applicant for registration" [Ruckelshuus v. Monsanto Co., 467 U.S. 986, 1009 (1984)]. In that case, the Court held that the EPA (Environmental Protection Agency) did not violate the Trade Secrets Act when it considered the data of one applicant in connection with the application of another. Applying the Court's ruling, the FDA can internally rely on previously submitted safety and efficacy data in the consideration of generic biologics. Thus, § 505(b) (2) appears to be the only pathway by which the FDA could conceivably review applications for follow-on biologics [26].

3.0 Regulatory consideration in INDIA

Off-patent biotech drugs are an emerging business opportunity worldwide. Europe and the US are estimated to have a market size of above $16 billion by 2012 for biosimilars. Indian companies also have initiated to take part for biosimilars market. Several Indian companies including Dr Reddy's Laboratories, Wockhardt, Intas Biopharmaceuticals and Biocon are working on several biosimilar drugs.

Apart from biosimilars, Reliance Life is working on stem cell therapies for Parkinson's disease, spinal cord injuries, diabetic ulcers, and leukoderma, as well as cardiology drugs. These are expected to reach the market in next three to four years. The company is researching on predictive diagnostics, which are medical tools to predict onset of diseases. Researchers at Reliance Life Science are also working on novel therapeutics for treatment of cancer, infectious diseases, inflammatory disorders, ocular disorders and neurodegenerative disorders, based on most advanced drug research platforms such as small interference RNA (siRNA) and monoclonal antibodies Reliance Life Sciences, which launched three biosimilars, or reverse-engineered

versions of biotech drugs last year, which may launch four more such drugs in near future.

Clinical studies are on for these drugs, which belong to the oncology and cardiology segment. "We are working on biosimilar products which most other competitors are not following," said KV Subramaniam, president, Reliance Life Science. The company launched ReliFeron (interferon alpha), ReliPoietin (erythropoietin) and ReliGrast (granulocyte colony stimulating factor) recently. At present, final stage limited Phase III human clinical trials are on in Europe for GCSF (Granulocyte Colony Stimulating Factor), used to stimulate production of white blood cells and used as an adjunct treatment with chemotherapy for cancer patients. A second GCSF product is also under development and is expected to reach markets by 2010. Both these products were added by Reliance Life Sciences through the acquisition of the UK-based drug discovery company, GeneMedix, in 2007[27].

The path required for approval of a biotech product in India is as follows:

(1) The Department of Biotechnology approves protocols up to animal toxicity studies;

(2) The Drug Controller General of India approves clinical trials and final product for marketing; and

(3) The Food and Drug Control Administration, a state governing body, approves the manufacturing license based on a GMP audit, similar to the BLA concept in U.S. All these approvals can be completed within a year In addition, equivalence has to be shown in clinical trial subjects in randomized double-blind studies with placebo, licensed products, and new products. Approval for biosimilar products requires only Phase III clinical trials for 100 patients, and the cost for this is approximately $100,000 per 100 patients [28].

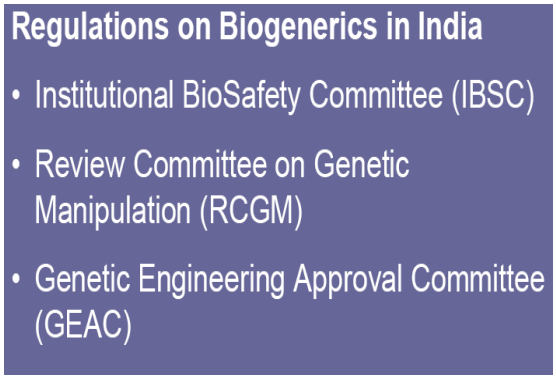

Fig.2 Regulation of biosimilars in India

3.1 Regulatory filing strategy

In India, there are no separate provisions for approval of biogeneric products in Drugs and Cosmetic Act, 1940 and Rules there under, 1945. Each biotech product is considers as a New Drug as per rule 122-E of Drugs and Cosmetic Act, 1940 and Rules, 1945 there under. The application should be made to the Department of Biotechnology (DBT) for *Review committee on*

Genetic Manipulation (RCGM) approval. For conducting clinical trials, necessary approvals/ permission has to be obtained from Drug Controller General of India. Marketing authorisation permission is granted by DCG (I) after reviewing the document submitted by the applicant to ensure safety, efficacy and quality of the product. All other guidelines issued by regulatory agency for approval of biogenerics would also apply [29].

Conclusion

The generic manufacturer may not have access to the original cell line and the "process" of the innovator. Since no cells are exactly similar, therefore, essentially the generic version of biopharmaceuticals can never be the exact copy of the innovator's product. This basic point has puzzled the regulatory agencies in the world, who hesitated in approving the generic versions of biopharmaceuticals. This work summarizes the regulatory approval history of follow-on biologics, emphasizing much more is needed to clearly evolve the regulatory mechanisms for marketing of biosimilars or follow-on biologics.

REFERENCE:

1. Global biotechnology product registration: E.U., U.S., and Japan. Parexel international, p. 450. http://www.mindbranch.com/about/publisher_info.jsp?pubcode=198
2. W. Condon and N Williamson, Australia: the Omnitrope experience…. Is it stop or go for follow on biologics in australia? http://www.mondaq.com/article.asp?/articleid=39638
3. Buehler GJ, Conner D. The FDA Process for Approving Generic Drugs. FDA Office of Generic Drugs. http://www.connectlive.com/events/genericdrugs/2006
4. B. A. Liang, Regulating Follow-On Biologics, *Harvard Journal on Legislation* 2007; 44 http://papers.ssrn.com/sol3/cf_dev/AbsByAuth.cfm?per_id=17095
5. European Medicines Agency. Omnitrope: EPAR summary for the public 2007. http://www.emea.europa.eu/humandocs/PDFs/EPAR/Omnitrope/060706en1.pdf
6. European Medicines Agency. Valtropin: EPAR summary for the public 2006. http://www.emea.europa.eu/humandocs/PDFs/EPAR/valtropin/H-602-en1.pdf
7. European Medicines Agency. Retacrit: EPAR summary for the public 2008. http://www.emea.europa.eu/humandocs/PDFs/EPAR/retacrit/H-872-en1.pdf
8. European Medicines Agency. Silapo: EPAR summary for the public 2007. http://www.emea.europa.eu/humandocs/PDFs/EPAR/silapo/H-760-en1.pdf
9. European Medicines Agency. Epoetin alfa HEXAL: EPARsummary for the public 2007. http://www.emea.europa.eu/humandocs/PDFs/EPAR/epoetinalfahexal/H-726-en1.pdf
10. European Medicines Agency. Binocrit: EPAR summary for the public2007. http://www.emea.europa.eu/humandocs/PDFs/EPAR/binocrit/H-725-en1.pdf
11. European Medicines Agency. Abseamed: EPAR summary for the public 2007. http://www.emea.europa.eu/humandocs/PDFs/EPAR/abseamed/H-727-en1.pdf
12. European Medicines Agency. Omnitrope: scientific discussion 2006.

http://www.emea.europa.eu/humandocs/PDFs/EPAR/Omnitrope/060706en6.pdf
13. European Medicines Agency. Valtropin: scientific discussion 2006. http://www.emea.europa.eu/humandocs/PDFs/EPAR/valtropin/H-602-en6.pdf
14. European Medicines Agency. Epoetin alfa HEXAL: scientific discussion 2007. http://www.emea.europa.eu/humandocs/PDFs/EPAR/epoetinalfahexal/H-726-en6.pdf
15. European Medicines Agency. Binocrit: scientific discussion2007. http://www.emea.europa.eu/humandocs/PDFs/EPAR/binocrit/H-725-en6.pdf
16. European Medicines Agency. Abseamed: scientific discussion 2007. http://www.emea.europa.eu/humandocs/PDFs/EPAR/abseamed/H-727-en6.pdf
17. European Medicines Agency. Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant erythropoietin's 2006. http://www.emea.europa.eu/pdfs/human/biosimilar/9452605en.pdf
18. European Medicines Agency. Silapo: scientific discussion 2007. http://www.emea.europa.eu/humandocs/PDFs/EPAR/silapo/H-760-en6.pdf
19. European Medicines Agency. Retacrit: scientific discussion2007. http://www.emea.europa.eu/humandocs/PDFs/EPAR/retacrit/H-872-en6.pdf
20. Silapo SmPC, STADA Arzneimittel. http://www.emea.europa.eu/humandocs/PDFs/EPAR/silapo/H-760-PI-en.pdf
21. RetacritR SmPC, HOSPIRA Enterprises. http://www.emea.europa.eu/humandocs/PDFs/EPAR/retacrit/H-872-en6.pdf
22. MellstedtH,Niederwieser D, Ludwig H. The challenge of biosimilars.Ann Oncol 2008; 19: 411–41
23. Smith N. EMEA 'will not guarantee' that biosimilars are interchangeable with originator. APM Health Europe 2006. http://health.apmnews.com/story.php?mots=BIOSIMILAR&searchScope=1&searchType=0&depsPage=2&numero=L3250
24. European Medicines Agency. Questions and answers on recommendation for refusal of marketing application for Alpheon 2006. http://www.emea.europa.eu/pdfs/human/opinion/19089606en.pdf
25. L Richard, "Is Europe ahead of the USA in biosimilars?" *Journal of generic medicine* 2006; 3(3):201-208.
26. Alison Langley, "Engineered Drugs Open New Issue of Regulation as Patents Expire" *New york Times,* 2003; August 9
27. www.pharmainfo.net/ drreddys-news/03/29/2009/ reliance-arm-launch-4-biotech- biosimilars-next-year
28. Nalini Motwani. "Biosimilars Jumpstart Biotech in India" *Clinical research & diagnostics Channel Feature Articles,* April15, 2007*;* 27(8)
29. http://www.cdsco.nic.in