



Regulation of biosimilars in India: A review

Anu Sharma^{1*}, Nisha Sharma², Komal Vashistha³

¹⁻³ Biologist, National Institute of Biologicals (Ministry of Health and Family Welfare, Government of India) Noida, Uttar Pradesh, India

Abstract

Monoclonal Antibodies are one of the most evolving and targeted drugs which are being used to treat many diseases like cancers, autoimmune diseases, arthritis, Psoriasis etc. Generics or Innovator molecule of Monoclonal Antibodies are very expensive and some are on their verge of expiry, therefore Evolution of Biosimilars is an urgent need of the hour. Biosimilars are affordable and they are very similar to the innovator molecule when it comes to their structure and function. After the successful Manufacturing of Biosimilar its Approval for the Market is of a great concern. Therefore European Medicinal Agency (EMA) has provided with certain Guidelines for the smooth flowing of Biosimilars in the market. Regulation of Biosimilars in India is concerned by many competent authorities which are interlinked with each other. The above mentioned points have been discussed in this review paper.

Keywords: monoclonal antibody, Biosimilar, Innovator, ADCC, CDC, CTD Module

1. Introduction

Monoclonal Antibodies (mAbZ) are the antibodies which are produced by the identical immune cells that are clones of unique parent cells. They have Monovalent affinity which binds to the same epitope. Monoclonal antibodies represent the structure of a typical IgG with two light polypeptides chains and two heavy polypeptides chains with their respective variable and constant regions. Monoclonal Antibodies (mAbs) now as days are constantly being encountered in the field of Biomedical Research and Medicine. They have evolved as a novel way of personalised therapy and innovative therapeutic agents for various diseases [1]. They are Immunoglobulin (IgG) which are produced by the clones of B- Lymphocytes and are homogenous in nature and have same binding capacity [2]. They come under Hummoral Immunity. mAbs are a major effector component of immune system because of their high specificity, efficacy and safety. mAbs are used to target a specific antigen. Monoclonal antibodies exhibit its activity through ADCC (Antibody dependent cell cytotoxicity), CDC (Complement dependent cytotoxicity), neutralization, agglutination and precipitation which enhances Phagocytosis and inflammation to neutralize the antigen. They work either by receptor blockage or ligand blockage or by depletion or induction of signalling. The first licensed mAb was Orthoclone OKT3 (muromonab- CD3) which was approved in 1986 for the treatment in Kidney transplant [3]. In Hybridoma technology monoclonal antibodies were produced as a result of hybrids which were made by the antibodies extracted from the mouse (mouse were first injected with a specific antigens against which antibodies were produced and then those antibodies were extracted) and the immortalised myeloma which lack the hypoxanthine –guanine phosphoribosyltransferase (HGPRT) gene making them sensitive to HAT (Hypoxanthin aminopterin thymidine) medium [4]. The fusion of these two cells was made by electroporation or by using ethylene glycol. The recombinant DNA technology involves the combination of genetic material from two or more sources [5]. In 1990 John

Mc Cafferty and colleagues have isolated the desired gene of interest or DNA fragment and injected into the bacteriophage virus via a vector and antibody genes were created by Scientists to display on phages and methods were developed for isolation of individual antibodies from the large phage- displayed libraries. This method has become known as Antibody phage display [6]. Monoclonal antibodies have major role in Therapy. They are used for treating cancers, autoimmune diseases, infectious diseases, cardiovascular diseases, diseases related to gastrointestinal inflammation like chron's disease, disease related to rheumatology and transplantation [7]. Drugs like Rituximab, Trastuzumab, Bevacizumab play crucial role in the treatment of leukemia, Breast cancer and umbilical cord cancer respectively. Autoimmune Diseases like Rheumatoid Arthritis, Psoriatic Arthritis can be treated by Infliximab and Etanercept respectively. Chron's disease can also be treated by Infliximab. Palivizumab is used in order to cure respiratory infections. Abciximab prevents platelets crosslinking and aggregation in terms of cardiology. OKT3 is murine antibody which is particularly used in Renal Transplantation [8]. Therapeutic mAbs that can modify tumour cell signalling cascade or tumour-stroma interaction such as trastuzumab (anti-human epidermal growth factor receptor 2 (HER2) mAb, rituximab (anti-CD20 mAb) and bevacizumab (anti-vascular endothelial growth factor (VEGF) mAb) are top-selling anti-cancer drugs. More recently, a class of mAb-based immunotherapy named immune-checkpoint inhibitors, such as ipilimumab and tremelimumab (Abs that target cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), pembrolizumab and nivolumab (mAbs that target programmed cell death protein 1 (PD-1), MPDL-3280A (an mAb target programmed death-ligand 1 (PD-L1) which represent a breakthrough in the cancer treatment was approved by FDA [9]. 50% of the mAbs related R&D Projects are involved in cancer treatment projects, 20% are involved in the immunological indications and 11% are involved in anti-infective programs.

Biosimilar

According to WHO Biosimilar is a Biotherapeutic product that is similar in terms of Quality, Safety and Efficacy to an already licensed Biotherapeutic Product [10]. Biosimilars are the blessed drugs for the humans as they act as affordable copies of the expensive original generic drugs providing quality life to the people. Biosimilar is a biotechnological product which shows high similarity with the biological product which has been already approved by some medicinal agency. Biosimilars of monoclonal antibodies are created on a fast pace in order to meet the same efficacy and safety endpoints as the original mAbs. Biosimilars are expanding due to their huge demand and growing affordability in market. Moreover they are improved by existing manufacturing technology and they are cheaper because there is no investment from Phase I to II clinical

trials [11]. The European Medical Agency have demonstrated the process of production of Biosimilars. The process starts with the characterisation in respect of their structure and function followed by the non-clinical testing to check their biological activities. Factors like similarity in binding to the target antigen, binding to the representative isoform of the Fc gamma receptors and complement, Fab associated functions (neutralization of the soluble ligand, receptor activation or blockade), Fc associated functions (Antibody dependent cell dependent cytotoxicity, complement activation, complement dependent cytotoxicity) are taken into consideration.. Pharmacodynamics, pharmacokinetics and immunogenicity studies were also being performed for the Biosimilars.

Production of biosimilars

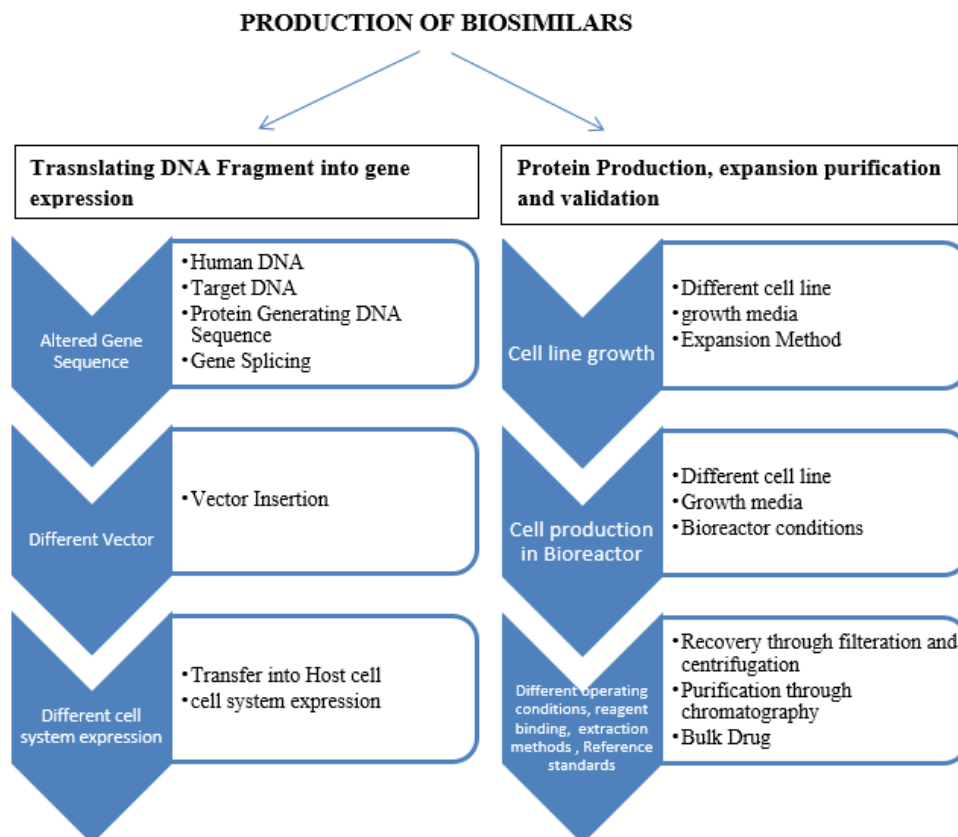


Fig 1: Production of Biosimilars

Regulation of Biosimilars

Biosimilars are complex and heterogeneous in nature when they are compared to their conventional generic versions of the respective biosimilar. Therefore their Proper Regulation is must. Apart from regulation in chemistry and manufacturing, regulation is analysed in analytics control, bio similarity, preclinical, immunogenicity and limited clinical studies also. Regulation includes three processes Development, Authorization and Manufacturing. Regulatory Framework in India is controlled by Competent Regulatory Bodies with the assistance of some competent authorities. CDSCO (Ministry of Health and family welfare) and DBT (Department of Biotechnology under Ministry of Science and Technology) are the uppermost Regulatory Bodies in India. Review Committee on Genetic Manipulation

(RCGM), Genetic Engineering Appraisal Committee (GEAC) are also involved in Biosimilar approval [12]. Drug and Cosmetic Act 1945 and following Guidelines are followed during Regulation of Biosimilar:

1. Guidelines for similar Biologics: Regulatory requirement Marketing Authorization in India
2. Recombinant DNA Safety Guidelines
3. CDSCO Guidelines for industry
4. Guidelines and handbook for Institutional Biosafety Committee.
5. 5.Guidance Documents for Regulatory Approval of stem cells and cell based products
6. guidelines for generating Preclinical and clinical data for Rdna vaccines Diagnostic and Biological Products
7. Guidelines on good distribution practises for biological

8. Pharmacovigilance Requirements for Biological products

Products.



Fig 2: Approval pathway for Biosimilars in India [13]

European Medicinal Agency (EMU)

EMU act as a Forerunner when it comes to Regulation of Biosimilars. It provides one of the robust guidelines for the biosimilar regulation. It was the first to introduce the guidelines on the regulation of biosimilars in 2006 [Biosimilars in the EU Prepared jointly by the European Medicines Agency and the European Commission]. The Market Authorization (MA) of the biosimilars is solely dependent on the approval of EMU Guidelines. Initially it started with the regulation of traditional products like Granulocytes Stimulating Factors, erythropoietin, somatotropin, and follitropin but now complex molecules like Infliximab and other Monoclonal Antibodies and fusion proteins are also being introduced because they are more involved in the treatment of cancers, arthritis and psoriasis [14]. The market authorization form should be accompanied with dossier of CTD (Common Technical Document).

requirements. The MA of Biosimilars includes two main processes Centralised procedure and National Authorization Procedure. The submission strategy for a given product depends on the nature, target indication, history plans and the marketing plans. The centralized procedure leads to the approval in all the 27 EU member states. The letter of intent also initiates the assignment of the Rapporteur and Co. Rapporteur, which are the two appointed members of the committee for Human Medicinal Products (CHMP) representing two EU member states. When using MRP and DCP the applicant must select which and how many EU member states in which to seek approval. In the case of an MRP the applicant must initially receive national approval in one EU member state. This will be the so called reference member state (RMS) for the MRP. Then the applicant seeks approval for the product in other EU member states, the so called (concerned member states) (CMC) in a second step. In the DCP, the applicant will approach all chosen member states at the same time. In practise the applicant is not its condition. In the Centralised procedure when a company applies for MA at EMA data is evaluated at EMA’s Scientific Committee on Human medicines and on safety. (CHMP & PRAC) then it passes to Experts on Biological medicines and then passes through the experts on biosimilars. On a Broader aspect the EMA guidelines evaluate the concerned biosimilar on the basis of three comparative studies. (i) Comparative Quality studies (ii) Comparative non-clinical studies (iii) Comparative Clinical Studies. (Regulatory pathways in the European Union by Manuela Kohler)

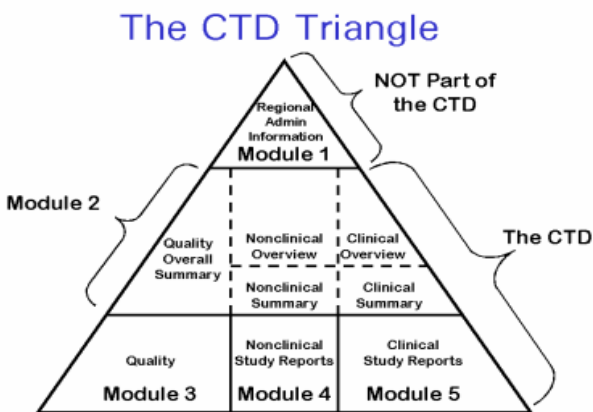


Fig 3: CTD Module

Dossier for the similar biological product contains modules like normal requirements and the comparability

US FDA (Food and Drug Administration): In 2009 US FDA came up with their own guidelines with the help of guidelines of EMA. Approval for Biological product is made through Public Health Service Act and for small molecules drugs through Federal Food, Drug & Cosmetics Act. Biologics Price Competition & innovation Act was signed as a part of the Patient Protection & Affordable Care Act

which created a new licensure Pathway for Biosimilars. Applications were submitted under section 351k of Health Sector Public Service Act.

Central Drug Standard Control Organisation (CDSCO) (India)

India is also called as a Pharmacy of the World. Apex Regulatory Body in India are CDSCO, the office of Drug Controller General of India, Review Committee on Genetic Manipulation and Genetic Engineering Approval Committee

Future Prospects

Monoclonal Antibodies in future can be modified in order to increase its therapeutic value. From more Murine and chimeric mAbs, more Fully Humanized mAbs are to be developed in future. To improve its efficacy mAbs can be developed in more conjugated antibodies with coupling effector molecules. Efforts can be made to minimise non human sequences of therapeutic mAbs. The therapeutic effect of mAbs can be improved by upgrading the binding affinity of an antigen. This can be achieved through phage display libraries to isolate antibodies with strong affinities for the antigen^[14].

Conclusion

Regulatory approval of a biosimilar requires comprehensive knowledge of both the process and the molecule. Process development with the end goal in mind will help to achieve a robust manufacturing process. Efficiencies in manufacturing, cell line testing and characterization, and protein comparability analytics are among the highest priorities for successful biosimilar drug approvals. For that reason, it is best to collaborate with a partner and leverage many years of experience supporting drug manufacturers with complex biologics production, purification and analysis and biosimilar comparability. Unifying and Harmonizing the Approval Pathway Globally will abolish the need for bridging studies which could make Biosimilar development cost effective and with same standards of safety and Efficacy.

References

- Justin Liu KH. The history of monoclonal antibody development e Progress, Remaining challenges and future innovations. *Journal of Annals of medicine and surgery*. 2014; 3(4):113-116.
- Powell RJ. Clinically useful monoclonal antibodies in treatment. *E Drewe*. 2002; 55(2):81-85.
- Xiaomei Geng, Xiangjun Kong, Hao Hu, Jiayu Chen, Fengqing Yang, Hongyu Liang. Research and development of therapeutic mAbs: An analysis based on pipeline projects. 2015; 11(12):2769-2776.
- Justin Liu KH. The history of monoclonal antibody development e Progress, Remaining challenges and future innovation *Journal of Annals of medicine and surgery*. 2015; 11(12):2769-2776.
- Justin Liu KH. The history of monoclonal antibody development e Progress, Remaining challenges and future innovation *Journal of Annals of medicine and surgery*. 2015; 11(12):2769-2776.
- Justin Liu KH. The history of monoclonal antibody development e Progress, Remaining challenges and future innovation *Journal of Annals of medicine and surgery*. 2015; 11(12):2769-2776.
- Powell RJ. Clinically useful monoclonal antibodies in treatment *E Drewe*, *journal of clinically pathology*. 2002; 55(2):81-85.
- Powell Clinically RJ. Useful monoclonal antibodies in treatment *E Drewe*, *journal of clinically pathology*. 2002; 55(2):81-85.
- Immuno-Oncology: Emerging Targets and Combination Therapies Henry T. Marshall* and Mustafa B. A. Djamgoz, Marshall HT, Djamgoz MBA. *Immuno-Oncology: Emerging Targets and Combination Therapies*. *Front Oncol*. 2018; 8:315. Published 2018 Aug 23. doi:10.3389/fonc.2018.00315
- Pooja Paul, Harvinder Popoli, Ankit Saxena, Anamika Jaiswal, Sudha Sah. Current scenario of biosimilar. *The pharma Innovation journal*. 2018; 7(7):188-103.
- Pooja Paul, Harvinder Popoli, Ankit Saxena, Anamika Jaiswal, Sudha Sah. Current scenario of biosimilar. *The pharma Innovation journal*. 2018; 7(7):188-103
- Pooja Paul, Harvinder Popoli, Ankit Saxena, Anamika Jaiswal, Sudha Sah. Current scenario of biosimilar. *The pharma Innovation journal*. 2018; 17(7):188-103
- Pooja Paul, Harvinder Popoli, Ankit Saxena, Anamika Jaiswal, Sudha Sah. Current scenario of biosimilar. *The pharma Innovation journal*, 7(7):188-103.
- Aliyu Mahmuda¹, Faruku Bande³, Khalid Jameel Kadhim Al-Zihiry⁴, Noor Abdulhaleem⁵, Roslaine Abd Majid¹, Rukman Awang Hamat¹, Wan Omar Abdullah⁶ and Zasmy Unyah¹ Monoclonal antibodies: A review of therapeutic applications and future prospects