

Biosimilars in Rheumatology: an Indian Scenario

Abstract

With the introduction of biologics, there has been significant improvement in response in rheumatologic disorders like rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. As most of these biologics have approached patent expiry, follow on versions called biosimilars have been introduced. Though only two of them have been approved by the EMA and one by the FDA, quite a few have been introduced in India. The process of approval of bio similars requires strict regulations to demonstrate efficacy, purity and safety. Preclinical, clinical (pharmacokinetic, pharmacodynamics, efficacy and safety) studies are to be done before their approval. Currently, five biosimilars used in rheumatology are approved in India. This review discusses the process of development of a biosimilar, regulatory guidelines in their approval process in India and the current status of biosimilars in rheumatology in India.

Keywords: Biosimilars; Biologics; India; Rheumatology; TNF- α inhibitors

Mini Review

Volume 5 Issue 3 - 2016

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Received: May 17, 2016 | **Published:** July 29, 2016

Abbreviations: TNF: Tumor Necrosis Factor; USA: United States of America; FDA: Food and Drug Administration; WHO: World Health Organisation

Introduction

The introduction of biologics has revolutionised therapy in rheumatology with significantly improved patient outcomes. Biologics are products derived by genetic engineering methods using vectors and can range from hormones to monoclonal antibodies and soluble receptors. They are large proteins with unique tertiary and quaternary structures that are inherently difficult to replicate. Some of these 'reference' or 'originator' products have approached patent expiration (Table1); encouraging development of 'follow on' versions, known as 'biosimilars' [1].

In 2012, worldwide sales of the top three selling TNF α inhibitors (infliximab, etanercept, adalimumab) approached US\$ 20 billion, accounting to 2/3rd of the total annual sales for rheumatic disorders that year. [2] Further in countries like India, there is restricted access to biologics due to financial constraints encouraging development of efficacious and lower cost bio similars. This review provides the current information on bio similars in rheumatology with special focus on their status in India.

Definitions

WHO defines bio Similar as 'a bio therapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference bio therapeutic product.' Similarity has been

defined as 'the absence of a relevant difference in the parameter of interest' [3]. Other terms synonymous with bio Similars are follow-on biologic (USA); subsequent entry biologic (Canada); similar bio therapeutic product (WHO).

Not all follow on versions of biologics are bio Similars as they have not passed the stringent regulatory processes for approval of bio Similars. These follow on biologics without demonstrated comparability to the biooriginator are called 'intended copies' or 'me-too biological' or 'non-innovator biological' [3].

Generics Versus Bio Similars

In contrast to generics which are manufactured synthetically, biologics are made in biologic systems and the active moiety is then extracted and purified. They are larger and more complex than generics and are sensitive to even minor changes during the manufacturing process, for example, increased post translational glycosylation increases the immunogenicity of a biologic. The key differences between generics and biologics are highlighted in Table 2 [4].

Development of A Bio Similar Product

The process of a development of a bio similar and the variations during the development process are highlighted in Figure 1 [5].

Regulatory Guidelines in Bio Similar Approval Process in India

US FDA (Food and drug administration) and EMA (European Medical Agency) have developed guidelines in 2012 for approval of bio similar products [6,7]. On similar lines; India announced

the release of draft regulatory guidelines for ‘similar biologics’ at the BIO industry conference in Boston, USA, on 19 June 2012. Finalized guidelines were implemented on 15 September 2012 [8].

For bio similars approval in India, the drug must go through series of studies that include quality testing, pre-clinical and clinical trials demonstrating tolerance, pharmacokinetics, and pharmacodynamics similar to the reference biopharmaceutical product.

According to this guideline - ‘Similar biologic can only be developed against an authorized reference biologic that has been approved using a complete data package in India. In case the reference biologic is not authorized in India, it should have been licensed and marketed for at least 4 years with significant safety and efficacy data in USA or EU. In case of no medicine or only palliative therapy is available or in national healthcare emergency, this period of 4 years may be reduced or waived of’. The full guideline is available at [8].

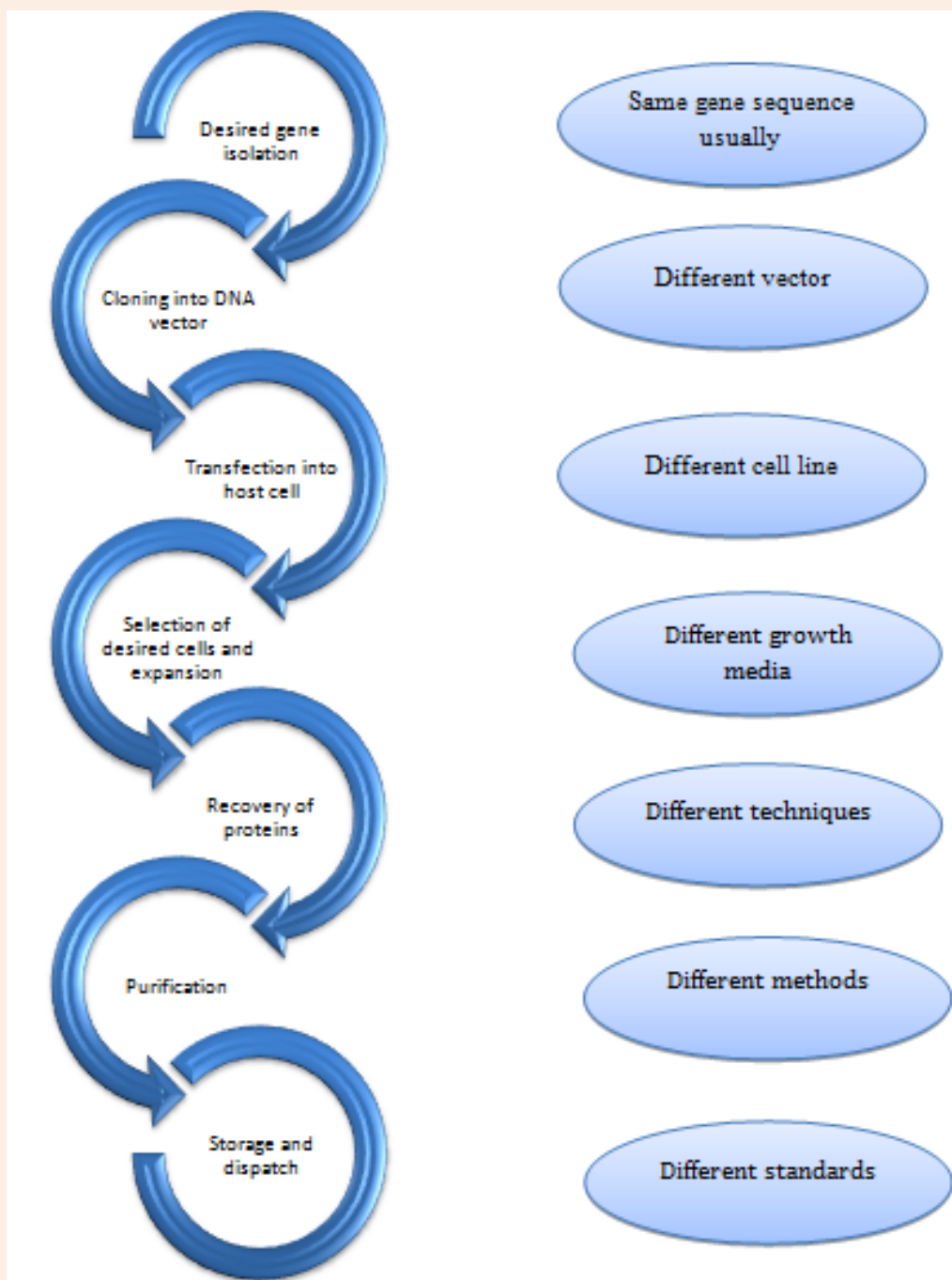


Figure 1: Process of development of a biosimilar and sources of variation between different manufacturers of the same biologic.

Table 1: Patent expiration of commonly used biologics in rheumatology.

Biologic	USA	European Union
Abatacept	Oct 2019	Dec 2017
Adalimumab	Dec 2016	Apr 2018
Certolizumab pegol	Feb 2024	-
Etanercept	Nov 2028	Nov 2015
Golimumab	Feb 2024	-
Infliximab	Sep 2018	Feb 2015
Rituximab	Sep 2016	Nov 2013
Tocilizumab	Dec 2015	July 2010

Table 2: Key differences between generics and biosimilars.

Characteristic	Generic	Biosimilar
Product related	Low molecular weight, uniform, stable, non-antigenic and non-immunogenic	High molecular weight, complex, temperature and shear rate sensitive, antigenic and immunogenic
Manufacturing process	Synthesized chemically, easily reproducible and less contaminated	Produced in biologic systems, difficult to reproduce and higher chance of contamination
Regulation	Demonstration of similar structure and pharmacokinetics sufficient Automatic substitution allowed	PK, PD, efficacy and safety trials needed Automatic substitution requires further studies

Current Status of Bio Similar in Rheumatology in India

India has, by far, demonstrated the greatest acceptance of

'similar biologics'. Hepatitis B vaccine is the first bio Similar approved in India in 2000. More than 25 bio Similar are currently approved and marketed in India. Bio Similar in rheumatology that have been approved to date are listed in Table 3 [9].

Table 3: Biosimilars in Rheumatology approved and marketed in India.

S.no	Biosimilar	Active moiety	Originator	Approved indication	Launch date in India	Company
1	Etacept	Etanercept	Enbrel	As, RA, PsA, Ps, JIA	Apr 2013	Cipla
2	Intacept	Etanercept	Enbrel	As, RA, PsA, Ps, JIA	Mar 2015	Intas pharmaceuticals
3	Infimab	Infliximab	Remicade	AS, IBD, RA PsA, Ps	Sep 2014	Epirus pharmaceuticals
4	Exemptia	Adalimumab	Humira	AS, IBD, RA, PsA, Ps	Dec 2014	Zydus
5	Reditux RA	Rituximab	Mabthera	Leukemia, lymphoma, RA	Apr 2007	Dr. Reddy's laboratories

AS: Ankylosing Spondylitis; RA: Rheumatoid Arthritis; PsA: Psoriatic Arthritis; Ps: Psoriasis; IBD: Inflammatory Bowel Disease

Other Notable Issues with Bio Similar

Certain issues regarding the approved bio similar are still under consideration. One of them is the long term immunogenicity and its effect on efficacy for which post marketing surveillance is ongoing.

Extrapolation of clinical indications is allowed on a case by case basis. Where the mechanism of action is not fully understood, separate clinical trials would be necessary. For example, rituximab

is used both in rheumatology and oncologic indications. A bio similar approved for oncologic indication cannot be extrapolated to a rheumatologic indication.

Automatic substitution of a bio similar would mean that a pharmacist can dispense the bio similar for a reference product prescription. And as of date guidelines for 'interchange ability' of biologics is not available and would definitely mean more rigorous pathway of approval.

Conclusion

With the improved knowledge of rheumatic diseases and early diagnosis, use of biologics and their follow on versions bio similars will increase in the future. Use of bio similars would be cost effective despite their stringent regulations. Physicians and rheumatologists must definitely be aware regarding bio similars and the intricacies in their development and approval process and vigilance is mandated during their use.

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