DOI:10.24041/ejmr2017.13

BIOSIMILARS IN MEDICINE

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Received on : 06-04-2017
Accpected on : 09-05-2017

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ABSTRACT

Biopharmaceutical drugs or biologicals have become an essential part of modern pharmacotherapy. Biosimilars or similar biologics have been defined as drugs that have shown to have comparable quality, safety and efficacy to the original biopharmaceutical drugs. The past decade has seen a significant increase in interest in these products from the biotechnology industry. Major developments in order to establish a regulatory path for approval of these products have taken place . In order to understand how the different quality attributes of a biosimilar impact its safety and efficacy we need further efforts. India is globally regarded to have great potential for development and commercialization of biosimilars

KEYWORD: Biosimilars, Biopharmaceuticals.

INTRODUCTION

What are biosimilars ?

Biopharmaceutical drugs comprise proteins derived from recombinant DNA technology and hybridoma technique. Examples include biological proteins (cytokines, hormones, and clotting factors), monoclonal antibodies, vaccines, cell and tissue based therapies. Living organisms such as plant and animal cells, bacteria, viruses and yeast are employed for the production of biopharmaceuticals.

Biopharmaceuticals have potential to reach up to 50% share in global pharmaceutical market in the next few years.(1)

The expiry of patent protection of many biopharmaceuticals has initiated the development of a category of alternative versions of innovator biopharmaceuticals known as biosimilars or similar biologics. Because of the structural and manufacturing complexities, these biological products are considered as similar, but not generic equivalents of innovator biopharmaceuticals. The term "biosimilar" is in common use in the European Union, while the term "follow on biologics" is more popular in the American context.(1)

Biosimilars : How are they different ?

Unlike structurally well-defined, low molecular weight chemical drugs, biopharmaceuticals are high molecular weight compounds with complex three-dimensional structure. For example, the molecular weight of aspirin is 180 Da whereas interferon-β is 19,000 Da. The typical biologic drug is 100 to 1000 times larger than small molecule chemical drugs and possesses fragile three-dimensional structure as compared to well-characterized one-dimensional structure of chemical drug. While chemical drugs are easy to reproduce and specify by mass spectroscopy and other techniques, there is a lack of appropriate investigative tools to define the composite structure of large proteins.(2,3)

The first biosimilar medicine, Omnitrope® (biosimilar recombinant human growth hormone [rhGH]; Sandoz, Kundl, Austria), was approved in Europe by the EMA(European Medical Association) in 2006.Since then, 20 biosimilars have been approved in Europe; these medicines are based on hematopoietic growth factors (such as filgrastim and epoetin), insulin, follitropin, and monoclonal antibodies (such as infliximab and etanercept).(4)

DISCUSSION

Efficacy and safety of biosimilars

There has been a concern regarding the efficacy and safety of biosimilars.Different manufacturing processes use different cell lines, protein sources, and extraction and purification techniques, which result in heterogeneity of biopharmaceuticals. Versatile cell lines used to produce the proteins may have an impact on the gross structure of the protein, and may affect glycosylation and other post-translational modifications. Such alterations may significantly impact receptor binding, stability, pharmacokinetics and safety. Immunogenic potential of therapeutic proteins is another unique safety issue which is not observed with chemical generics.(2,3)

A study compared quality parameters (such as identity, purity, content and efficacy) of several biosimilar

brands taken from the Indian market and with those of the innovator drug products.The study was carried out on 16 commercial brands covering three different biopharmaceuticals.A marked lack of comparability between biosimilars and innovator products was seen. Also, a significant difference in the level of purity was observed among various brands of biosimilars of G-CSF and erythropoietin.(5)

The concern regarding immunogenicity is highlighted by the increase in number of cases of pure red cell aplasia associated with a specific formulation of epoetin alfa.(6 ,7) The development of pegylated thrombopoietin (megakarocyte growth and development factor) was stopped in clinical trials because of treatment-associated-thrombocytopenia in 13 of 325 healthy volunteers.(8)

Approval of biosimilars

Various complexities associated with "approval" of a biosimilar include:

i) Evidence of integrity and consistency of the manufacturing process,

ii) Conformance of manufacturing standards to applicable regulations,

iii) Demonstration of product consistency with appropriate innovator product or comparators using assays that should be relevant and most of all standardized, so that several biosimilars of the same biologic can be comparable, including comparative pharmacokinetic and pharmacodynamic data and the extent of clinical data.(9)

EMA (European Medicines Agency) is the international regulatory authority for approval of biosimilars.The recent EMA guidelines on comparability of biosimilars, state that preclinical data may be insufficient to demonstrate immunologic safety of some biosimilars. In these cases, the immunological safety can only be demonstrated in cohorts of patients enrolled in clinical trials and post marketing surveillance.(10,11).

The regulatory bodies responsible for approval of 'similar biologics' in India are the Department of Biotechnology (DBT – under the Ministry of Science and Technology), through its Review Committee on Genetic Manipulation (RCGM), and the Central Drugs Standard Control Organization (CDSCO – under the Ministry of Health and Family Welfare). India's list of approved and marketed 'similar biologics' is constantly changing.

It should be noted that 'similar biologics' approved in India might not have been authorized following as strict a regulatory process as is required for approval of biosimilars in the European Union. The EMA regulatory requirements ensure the same high standards of quality, safety and efficacy for biosimilars as for originator biologicals, and also include a rigorous comparability exercise with the reference product (12).

Similar Biologics approved and marketed in India (4-6, 9-15)

Product name*	Active substance	Therapeutic area**	Approval/ launch date in India#	Company
AbcixiRel	Abciximab	Angina, Cardiac ischemia	23 Apr 2013	Reliance Life Sciences
Actorise	darbepoetin alfa	Anaemia, Cancer, Chronic kidney failure	6 Jan 2014	Cipla/Hetero
Adfrar	Adalimumab	Ankylosing spondylitis, Plaque psoriasis, Psoriatic arthritis, Rheumatoid arthritis, Ulcerative colitis	11 Jan 2016	Torrent Pharmaceuticals
Basalog	insulin glargine	Diabetes	2009	Biocon
Bevacirel	bevacizumab	Colorectal cancer	10 Jun 2016	Reliance Life Sciences (Lupin)
Biovac-B	hepatitis B vaccine	Hepatitis B	2000	Wockhardt

Product name*	Active substance	Therapeutic area**	Approval/ launch date in India#	Company
CanMab	Trastuzumab	Breast cancer	23 Oct 2013	Biocon
Ceriton	epoetin alfa	Anaemia, Cancer, Chronic kidney failure	NR	Ranbaxy
Choriorel	chorionic gonadotrophin hormone r-hCG	Female infertility	22 Jun 2011	Reliance Life Sciences
Cizumab	bevacizumab	Colorectal cancer	27 Jun 2016	Hetero
Cresp	darbepoetin alfa	Anaemia, Cancer, Chronic kidney failure	23 Mar 2010	Dr. Reddy's Laboratories
Darbatitor	darbepoetin alfa	Anaemia, Cancer, Chronic kidney failure	2014	Torrent Pharmaceuticals
Emgrast	Filgrastim	Cancer, Neutropenia	16 Mar 2010	Gennova Biopharmaceuticals (Emcure)
Epofer	epoetin alfa	Anaemia, Cancer, Chronic kidney failure	NR	Emcure
Epofit/ Erykine	epoetin alfa	Anaemia, Cancer, Chronic kidney failure	Aug 2005	Intas Pharmaceuticals
Eporec	erythropoietin	Anaemia, Chronic kidney failure	9 Aug 2011	Bioviz Technologies
Epotin	epoetin alfa	Anaemia, Cancer, Chronic kidney failure	NR	Claris Lifesciences
Erypro	epoetin alfa	Anaemia, Cancer, Chronic kidney failure	NR	Biocon
Etacept	Etanercept	Ankylosing spondylitis, Rheumatoid arthritis, Psoriatic arthritis, Psoriasis, Juvenile Rheumatoid Arthritis	2013 Apr	Cipla
Exemptia	Adalimumab	Rheumatoid Arthritis	25 Sep 2014	Zydus Cadila
Fegrast	Filgrastim	Cancer, Hematopoietic stem cell transplantation, Neutropenia	NR	Claris Lifesciences
Filgrastim	Filgrastim	Neutropenia	22 Oct 2013	Cadila Pharmaceutical
Filgrastim	Filgrastim	Neutropenia	5 Mar 2013	Lupin

Product name*	Active substance	Therapeutic area**	Approval/ launch date in India#	Company
Filgrastim	Filgrastim	Neutropenia	3 Jun 2013	USV
Folisurge	follitropin alfa (follicle stimulating hormone)	Female infertility, Spermatogenesis in men	14 May 2013	Intas Pharmaceuticals
FostiRel	follitropin beta (follicle stimulating hormone)	Female infertility	30 Apr 2010	Reliance Life Sciences
Glaritus	insulin glargine	Diabetes mellitus	Mar 2009	Wockhardt
Grafeel	ilgrastim	Neutropenia, Hematopoietic stem cell transplantation, Cancer	NR	Dr. Reddy's Laboratories
Infimab	nfliximab	Ankylosing spondylitis, Crohn's disease, Psoriasis, Psoriatic arthritis, Rheumatoid arthritis, Ulcerative colitis	15 Sep 2014	Epirus Biopharmaceuticals
Insugen	human insulin	Diabetes mellitus	NR	Biocon
Insulin	Insulin	Diabetes mellitus	9 Aug 2011	Gland Pharma
Intacept	Etanercept	Ankylosing spondylitis, Juvenile idiopathic arthritis Psoriasis, Psoriatic arthritis, Rheumatoid arthritis	Mar 2015	Intas Pharmaceuticals
Intalfa	interferon alfa-2b	Carcinoid tumour, Chronic hepatitis B,Chronic hepatitis C, Hairy cell leukaemia, Chronic myelogenous leukaemia, BCR-ABL positive, Follicular lymphoma, Malignant melanoma, Multiple myeloma	Apr 2007	Intas Pharmaceuticals
Maball	Rituximab	Lymphoma, Non-Hodgkin's Lymphoma	3 Feb 2015 (12)	Hetero Group
MabTas	Rituximab	Lymphoma, Non-Hodgkin's Lymphoma	26 Feb 2013	Intas Pharmaceuticals

Product name*	Active substance	Therapeutic area**	Approval/ launch date in India#	Company
Molgramostim	Recombinant human granulocyte macrophage colony stimulating factor (molgramostim)	Neutropenia	14 May 2013	Zenotech Laboratories
Mirel	reteplase (tissue plasminogen activator)	Myocardial infarction	2009	Reliance Life Sciences
Myokinase	streptokinase	Acute myocardial infarction, Deep venous thrombosis, Acute pulmonary embolism	NR	Biocon
Neukine	Filgrastim	Neutropenia, Hematopoietic stem cell transplantation, Cancer	Jul 2004	Intas Pharmaceuticals
Neupeg	Pegfilgrastim	Cancer, Neutropenia	Aug 2007	Intas Pharmaceuticals
Nufil	Filgrastim	Cancer, Neutropenia	NR	Biocon
Pegex	Pegfilgrastim	Cancer, Neutropenia	29 Jan 2010	Gennova Biopharmaceuticals (Emcure)
Peg-filgrastim	Pegfilgrastim	Cancer, Neutropenia	3 Sep 2013	Lupin
Peg-grafeel	Pegfilgrastim	Cancer, Neutropenia	10 May 2011	Dr Reddy's Laboratories
Peg-interferon alfa 2b	Pegylated recombinant human interferon alfa 2b	Chronic hepatitis B, Chronic hepatitis C	25 Apr 2013	Intas Pharmaceuticals
Platelet derived growth factor	rh-PDGF-BB+β-TCP	Peridontal defect, Gingival recession	28 Apr 2010	Virchow Biotech
Rasburicase	Rasburicase	Malignancy associated hyperuricemia	28 Aug 2012	Virchow Biotech
Razumab	Ranibizumab	Wet macular degeneration, Macular edema, Degenerative myopia, Diabetes complications	19 Jun 2015 (13)	Intas Pharmaceuticals
Reditux	Rituximab	Leukaemia, Lymphoma, Rheumatoid arthritis	30 Apr 2007	Dr. Reddy's Laboratories
Relibeta	interferon beta-1a	Multiple sclerosis	2 May 2011	Reliance Life Sciences

Product name*	Active substance	Therapeutic area**	Approval/ launch date in India#	Company
Reliferon	interferon alfa-2b	BCR-ABL positive, Carcinoid tumour, Chronic hepatitis B, Chronic hepatitis C, Chronic myelogenous leukaemia, Follicular lymphoma, Hairy cell leukaemia, Melanoma Multiple myeloma	2008	Reliance Life Sciences
Religrast	Filgrastim	Neutropenia	2008	Reliance Life Sciences
Relipoietin	epoetin alpha	Anaemia, Autologous blood transfusion, Chronic kidney failure, HIV	2008	Reliance Life Sciences
Repoitin	erythropoietin	Anaemia, Chronic kidney failure	29 Nov 2011	Serum Institute of India
Rituximab	Rituximab	Non-Hodgkin's Lymphoma, Rheumatoid arthritis	12 Feb 2015	Reliance Life Sciences
Rituximab	Rituximab	Non-Hodgkin's Lymphoma	27 Feb 2013	Zenotech Laboratories
Shankinase	streptokinase	Arterial occlusions, Deep vein thrombosis, Pulmonary embolism	Jun 2004	Shantha Biotechnics/Merieux Alliance
Shanferon	interferon alfa-2b	BCR-ABL positive, Carcinoid Tumour, Chronic hepatitis B, Chronic hepatitis C, Chro,nic myelogenous leukaemia, Follicular lymphoma, Hairy cell leukaemia, Melanoma, Multiple	Apr 2002	Shantha Biotechnics/Merieux Alliance
Shanpoietin	erythropoetin	Anaemia, Chronic kidney failure	Jan 2005	Shantha Biotechnics/Merieux Alliance
Terifrac	teriparatide (parathyroid hormone)	Post menopausal women with osteoporosis who are at high risk for fracture	1 Nov 2010	Intas Pharmaceuticals
Teriparatide	teriparatide (parathyroid hormone)	Post menopausal women with osteoporosis who are at high risk for fracture	21 Aug 2012	Cadila Healthcare
Teriparatide	teriparatide (parathyroid Hormone)	Post menopausal women with osteoporosis who are at high risk for fracture	13 Aug 2012	USV
Wepox	epoetin alfa	Anaemia, Cancer, Chronic kidney failure	Mar 2001	Wockhardt
Wosulin	human insulin	Diabetes mellitus	13 Aug 2003	Wockhardt
Zavinex	interferon alfa-2b	Chronic hepatitis B, Chronic hepatitis C	21 Jun 2011	Cadila Healthcare

Product name*	Active substance	Therapeutic area**	Approval/ launch date in India#	Company
Zyrop	erythropoietin	Chronic kidney failure	28 Apr 2010	Cadila Healthcare

*** Where brand-name is not known active substance name is given;**
**** Therapeutic area taken from company information, from originator product information on EMA website or from CDSCO information; NR: not reported; # 'similar biologics' launched in India before the Indian 'similar biologics' guideline came into effect on 15 September 2012, were approved using an ad-hoc abbreviated procedure on a case by-case basis.**
Source: CDSCO (Central Drugs Standard Control Organization)

CONCLUSION

Biosimilars offer a new ray of hope to patients who need these life saving medicines.The regulatory environment for biosimilars continues to evolve globally, in recognition of advances in technology/analytical methods and the availability of new targets for their use.It is high time that in our country too strict regulatory policies are formulated and executed for the overall benefit of our needy and financially weak patients.

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How to cite this article :Siddiqi Z., Biosimilars In Medicine, Era's Journal of Medical Research.2017;4(1):56-62.