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Postmarketing Safety of Biosimilars: Current Status, Challenges, and Opportunities in the Spontaneous Reporting System

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Abstract

Recombinant drug products successfully treat many life-threatening and chronic diseases. The high cost of these drugs makes them inaccessible to the patients particularly in developing countries. Patent expiration of innovator recombinant drug products has led to the development of biosimilars or similar biologics by several manufacturers. Unlike generics, these are not identical to their innovator products because of the differences in the manufacturing process; however, they are similar in quality characteristics, biological activity, safety, and efficacy. The regulatory procedures used for generic drugs cannot be applied for biosimilars as they are large complex structures produced from living cells and can produce potential risk of immune-based adverse reactions. Out of several safety issues related to biosimilars, two main safety concerns are variable potency and immunogenicity, for which a robust long-term pharmacovigilance system is needed. Various guidelines have been issued for the regulatory approval and pharmacovigilance of biosimilars by USFDA, EU, and pharma-emerging countries like China and India. The article includes the pharmacovigilance plan of biosimilars in these countries, discusses the challenges and opportunities in pharmacovigilance through spontaneous reporting systems, and suggests amendments in the existing suspected adverse event reporting form of the Pharmacovigilance Programme of India.

Keywords

biosimilars, spontaneous reporting system, pharmacovigilance, adverse drug reactions, USFDA, EU

Introduction

Recombinant therapeutics (rDNA based drug products and Biosimilars) are recognized as an important class of therapeutics because of their selectivity and specificity toward molecular target on cell surface. In spite of having high molecular weight and complex structures and being manufactured through living systems, these recombinant therapeutics had revolutionized the treatment of chronic diseases like solid tumors or hematologic cancers, immune-mediated disorders, rheumatoid arthritis, psoriasis, psoriatic arthritis, Crohn disease, ankylosing spondylitis, neurologic diseases, etc[1,2-4] in the past 3 decades. Recombinant therapeutics includes protein therapeutics, monoclonal antibodies, and fusion proteins. Expiry of patents/data protection for these innovator recombinant drugs encouraged various manufacturers for developing "similar biologics" or "biosimilars" or "follow-on biologics." As the name implies, these are similar to the innovator product in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise but not identical to the innovator product because of variations that may occur during the manufacturing process.[3]

The objective of this article is to (1) review the current status and challenges in pharmacovigilance of biosimilars and (2) describe opportunities in pharmacovigilance of biosimilars through a spontaneous reporting system (SRS).

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Pharmacovigilance of rDNA-Based Drug Products and Biosimilars: Global Status

Development of biosimilars not only reduces the health care cost but also increases the number of marketing authorizations, thereby increasing the access to these biotherapeutics,[4] which was demonstrated through an analysis in 21 European countries that the average cost of erythropoietin decreased to 35% from 2006 to 2013.[4] An important concern of these similar biologics is their safety. Similar biologics with similar safety profile to that of their reference product is a challenge owing to complexity in structure, complicated manufacturing process, and stability profile.[5,6] Safety of biosimilars varies because of immunogenicity, hypersensitivity reactions, and an increased risk for other adverse effects.[7] Studies have also emphasized the need for an adequate and robust postmarketing pharmacovigilance system for biosimilars.[4,8,9]

Unites States America (USA), European Union (EU), and pharma-emerging countries like India, China, etc have issued various guidelines for regulatory approval and pharmacovigilance of biosimilars.[10-13] The European Medicines Agency (EMA), responsible for pharmacovigilance of drugs approved for marketing in EU, adopted new recommendations for pharmacovigilance of biosimilars with respect to biologic-specific challenges in the year 2016.[11] The EMA has also issued product-specific guidelines for pharmacovigilance of biosimilars such as cohort studies to monitor safety of erythropoietin biosimilars, collection of long term safety data on the use of granulocyte colony–stimulating factor etc.[14] The Unites States Food and Drug Administration (USFDA) provides "biosimilar" or "biosimilar and interchangeable" status to these biosimilars based on "totality of the evidence approach" and the Center for Drug Evaluation and Research (CDER) is responsible for the pharmacovigilance of biosimilars in USA.[10,15] Postmarketing surveillance of drugs including biosimilars were done by both an SRS through the MedWatch and Active Surveillance (AS) methods through a retrospective analysis of medical records.[16] USFDA adopted a new guideline for nomenclature of biosimilars, which will improve the pharmacovigilance of biosimilars, in which USFDA intends to suffix 4 lowercase letters as biologics qualifier to the International Nonproprietary Name (INN) in case of biosimilars,[17,18] for example, Filgrastim-sndz. In 2015 the first biosimilar filgrastim-sndz was approved by USFDA.[10] EMA and USFDA recommend attention on pharmacovigilance due to immunologic reaction and its reflection in a pharmacovigilance plan. Different safety profiles may be observed among the innovator biosimilar(s) postmarketing in the long term as these products evolve through their life cycle.[19] Biosimilars approved by USFDA[10] and EMA[11] since 2007 are shown in Table 1.

Pharma-emerging countries like India and China have also released guidelines for biosimilars in the year 2012 (revised in 2016) and 2015, respectively.[12,13,20] In India, these rDNA-based drugs are approved as "New Drugs," not as biosimilars or similar biologics and more than 50 rDNA-based drugs have been approved for marketing by the Drugs Controller General of India since 1999 (Table 2).[12] Guidelines state that postmarketing pharmacovigilance should be as per the schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945.[12] The pharmacovigilance plan should primarily be able to monitor safety but should also be capable of monitoring efficacy and immunogenicity (long-term and short-term).[12,21] To ensure the safety of drugs in India, the Indian Pharmacopoeia Commission (IPC) functions as the National Coordination Centre (NCC) for the Pharmacovigilance Program of India (PvPI) since April 15, 2011,[22,23] which is also a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services.[23] The pharmacovigilance plan in China emphasizes on monitoring of safety and immunogenicity of biosimilars. China had approved 382 genetically engineered drugs and vaccines, among which only 21 are innovator products while the rest are biosimilars, according to SMEI data.[24] Comparison of pharmacovigilance regulation in USA, EU, India, and China are shown in Table 3.

Challenges in Pharmacovigilance of Biosimilars

Current pharmacovigilance paradigm applied for small-molecule drugs is highly insufficient for monitoring the safety of biosimilars because of the manufacturing differences and complexities among biosimilars and structural difference between similar biologics and their reference products,[11,17,25] structural characteristic of drug, which may initiate long- or short-term immunologic reactions. Immunogenicity to these biosimilars results in the development of anti-drug antibodies (ADAs). These ADAs are neutralizing antibodies (NAs) that neutralize the activity of these therapeutic proteins and cause reduced efficacy. In the worst case, ADAs neutralize the endogenous counterpart also, or non-neutralizing antibodies (NNAs), which in some cases enhance the rate of clearance of drug.[26] It is also important to understand the significant time lag between the administration of biosimilars and appearance of adverse event(s) because of delayed immunogenic reactions, which also creates difficulty in defining causal relation to the particular batch or lot or product. Anaphylaxis and hypersensitivity reactions are the two main safety concerns due to immunological reaction to these drugs.[5,6] Process- and product-related impurities also lead to immunogenicity in many therapeutic proteins. Humanized therapeutic monoclonal antibodies are less immunogenic than non-humanized therapeutic monoclonal antibodies.[5,6,26] Post-translational modifications like glycosylation, oxidation, amidation, etc also cause immunogenicity. Difference in process and process-related impurities among innovator and similar biologics leads to differences in safety profile. Adverse events due to immunologic reactions and different impurities profile warrant the long-term postmarketing pharmacovigilance plan for both similar biologics and their reference products.[26]

Table 1. Biosimilars Approved by USFDA[5] and EMA[5].

	USFDA (ref)			EMEA First in 2006			
Biosimilar	Therapeutic Indication	Year	Manufacturer	Biosimilar	Therapeutic Indication	Year	Manufacturer
Filgrastim biosimilar							
Filgrastim-sndz	Febrile neutropenia, acute myeloid leukemia, congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia	2015	Sandoz Inc	Filgrastim	Neutropenia	2014	Accord Healthcare Ltd
				Filgrastim		2013	Apotex Europe BV
Filgrastim-aafi	In myelosuppressive chemotherapy, acute myeloid leukemia, bone marrow transplantation, autologous peripheral blood progenitor cell collection and, severe chronic neutropenia	2018	Pfizer labs	Filgrastim	Neutropenia, hematopoietic stem cell transplantation, cancer	2008	Ratiopharm GmbH
				Filgrastim		2010	Pfizer Europe MA EEIG
				Filgrastim		2009	Hexal AG
				Filgrastim		2008	Teva GmbH
				Filgrastim		2009	Sandoz GmbH
Pegfilgrastim biosimilar							
Pegfilgrastim-cbqv	Febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs	2018	Coherus BioSciences, Inc	Pegfilgrastim	Neutropenia	2018	Accord Healthcare Limited
Pegfilgrastim-jmdb		2018	Mylan GmPH,				
Adalimumab biosimilar							
Adalimumab-adaz		2018	Sandoz Inc,	Adalimumab	Juvenile rheumatoid arthritis, skin diseases, papulosquamous, hidradenitis suppurativa, psoriasis, Crohn disease, uveitis, rheumatoid arthritis, arthritis, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis	2018	Sandoz GmbH
Adalimumab-adbm	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn disease, ulcerative colitis, plaque psoriasis	2017	Boehringer Ingelheim Pharmaceuticals, Inc				
Adalimumab-atto		2016	Amgen Inc	Adalimumab	Hidradenitis suppurativa, ankylosing spondylitis, psoriasis, juvenile rheumatoid arthritis, uveitis	2018	Sandoz GmbH
				Adalimumab	Hidradenitis suppurativa, psoriasis, Crohn disease, uveitis, rheumatoid arthritis, arthritis, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis	2017	Samsung Bioepis UK Limited (SBUK)
				Adalimumab		2018	Sandoz GmbH
				Adalimumab		2017	Amgen Europe BV
				Adalimumab		2017	Amgen Europe BV
				Adalimumab		2017	Boehringer Ingelheim International GmbH
Infliximab biosimilar							
Infliximab-dyyb	Crohn disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis	2016	Celltrion, Inc	Infliximab	Ankylosing spondylitis, rheumatoid arthritis, Crohn disease, ulcerative colitis, psoriatic arthritis, psoriasis	2016	Samsung Bioepis UK Limited (SBUK)
Infliximab-abda	Crohn disease, pediatric Crohn disease, ulcerative colitis, rheumatoid arthritis in combination with methotrexate, psoriatic arthritis, plaque psoriasis	2017	Samsung Bioepsis Co, Ltd,	Infliximab		2013	Celltrion Healthcare Hungary Kft
Infliximab-qbtx		2017	Pfizer Inc,	Infliximab		2013	Pfizer Europe MA EEIG
				Infliximab		2018	Sandoz GmbH

Table 1. (continued)

	USFDA (ref)			EMEA First in 2006			
Biosimilar	Therapeutic Indication	Year	Manufacturer	Biosimilar	Therapeutic Indication	Year	Manufacturer
Trastuzumab biosimilar							
Trastuzumab-dkst	Breast cancer, metastatic gastric or gastroesophageal junction adenocarcinoma	2017	Mylan GmbH	Trastuzumab	Stomach neoplasms, breast neoplasms	2018	Celltrion Healthcare Hungary Kft
				Trastuzumab		2018	Amgen Europe BV, Breda
				Trastuzumab		2018	Pfizer Europe MA EEIG
				Trastuzumab		2017	Samsung Bioepis UK Limited (SBUK)
Bevacizumab biosimilar							
Bevacizumab-awwb	Metastatic colorectal cancer, nonsquamous non-small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, cervical cancer	2017	Amgen Inc	Bevacizumab	Renal cell carcinoma, peritoneal neoplasms, ovarian neoplasms, breast neoplasms, non–small-cell lung carcinoma, fallopian tube neoplasms	2018	Amgen Europe BV
Rituximab biosimilar				Rituximab	Non-Hodgkin lymphoma, lymphocytic chronic, B-cell leukemia	2017	Celltrion Healthcare Hungary Kft
				Rituximab	Non-Hodgkin lymphoma, rheumatoid arthritis, chronic lymphocytic B-cell leukemia, Wegener granulomatosis, microscopic polyangiitis	2017	Sandoz GmbH
				Rituximab	Non-Hodgkin lymphoma, microscopic polyangiitis, Wegener granulomatosis	2017	Celltrion Healthcare Hungary Kft
				Rituximab	Lymphoma, non-Hodgkin, microscopic polyangiitis, leukemia, B-cell chronic lymphocytic, Wegener granulomatosis	2017	Celltrion Healthcare Hungary Kft
				Rituximab	Non-Hodgkin lymphoma, rheumatoid arthritis, Wegener granulomatosis, B-cell lymphocytic, chronic leukemia, microscopic polyangiitis	2017	Celltrion Healthcare Hungary Kft
				Rituximab	Non-Hodgkin lymphoma, rheumatoid arthritis, Wegener granulomatosis, B-cell lymphocytic, microscopic polyangiitis	2017	Sandoz GmbH
Epoetin alfa biosimilar							
Epoetin alfa-epbx	Treatment of anemia due to chronic kidney disease	2018	Hospira, Inc, a Pfizer company	Epoetin alfa	Anemia, chronic kidney failure	2007	Sandoz GmbH
				Epoetin alfa		2007	Medice Arzneimittel Pütter GmbH Co KG
				Epoetin alfa		2007	Hexal AG

(continued)

Table 1. (continued)

	USFDA (ref)			EMEA First in 2006			
Biosimilar	Therapeutic Indication	Year	Manufacturer	Biosimilar	Therapeutic Indication	Year	Manufacturer
Epoetin zeta biosimilar							
				Epoetin zeta	Anemia, blood transfusion, autologous, chronic kidney failure, cancer	2007	Hospira UK Limited
				Epoetin zeta		2007	Stada Arzneimittel AG
Etanercept biosimilar Etanercept-szzs	Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis in patients aged 2 y or older, psoriatic arthritis, ankylosing spondylitis	2016	Sandoz Inc	Etanercept	Psoriatic arthritis, rheumatoid arthritis, psoriasis, juvenile ankylosing rheumatoid arthritis, spondylitis	2017	Sandoz GmbH
				Etanercept	Psoriatic arthritis, rheumatoid arthritis, psoriasis	2016	Samsung Bioepis UK Ltd
Enoxaparin biosimilar				Enoxaparin sodium	Venous thromboembolism	2016	Techdow Europe AB
				Enoxaparin sodium		2016	Pharmathen SA
Teriparatide biosimilar				Teriparatide	Osteoporosis	2017	STADA Arzneimittel AG
				Teriparatide		2017	Gedeon Richter Plc
Insulin glargine biosimilar				Insulin glargine	Diabetes mellitus	2017	Merck Sharp & Dohme BV
				Insulin glargine		2014	Eli Lilly Nederland BV
				Insulin glargine		2018	Mylan SAS
Insulin lispro biosimilar				Insulin lispro	Diabetes mellitus	2017	Sanofi-Aventis Groupe
Follitropin alfa biosimilar				Follitropin alfa	Anovulation	2014	Gedeon Richter Plc
				Follitropin alfa		2013	Teva Pharma BV
Somatropin biosimilar				Somatropin	Turner syndrome, Prader-Willi syndrome, dwarfism, pituitary	2006	Sandoz GmbH

Table 2. List of rDNA-Based Drugs Approved in India.

Name of Drug	Manufacturer	Date	Indication
Pegfilgrastim	Wockhardt Limited	2/25/2015	Chemotherapy-induced neutropenia
	Reliance Life Limited	5/13/2016	
	Torrent Pharmaceuticals Limited	Not available	
	Dr Reddy Laboratories Limited		
	Roche Scientific Company		
	Sarabhai Chemicals Specialities		
	Zydus Cadila Healthcare Limited		
Filgrastim	Cadila Healthcare Pivate Limited	7/14/2015	Increase neutrophilic count after bone marrow transplantation, neutrophilic granulocytopenia induced by chemotherapy of cancers—malignant lymphoma, embryonic cell tumour, neuroblastoma
	Gennova Biopharmaceuticals Limited	1/06/2004	
	Marksans Pharma Limited	1/12/2005	
	Ranbaxy, Gurgaon	5/22/2005	
	G.C. Chemie	6/23/2010	
	R.K. Medicare	9/09/2010	
	VHB Medi Sciences Limited	3/04/2010	
	Bioviz Technologies Private Limited	6/14/2010	For decreasing severity of chemotherapy-induced neutropenia in cancer patients receiving myelosuppressive chemotherapy
	Claris Life Sciences	5/29/2009	Increase neutrophilic count after bone marrow transplantation, neutrophilic granulocytopenia induced by chemotherapy of cancers—malignant lymphoma, embryonic cell tumour, and neuroblastoma.
	Gufic life Sciences	5/29/2009	
	Chandra Bhagat Pharma Limited	7/21/2009	
	KSR pharmacy	7/10/2009	
	VHB life Sciences	8/04/2009	
	USV Limited	9/02/2009	
	Trigenesis Life Sciences	9/08/2009	
	Roche Scientific	1/01/2003	
	Miracalus Pharma Private Limited	Not available	
	Torrent Pharmaceuticals Limited		
	RPG Life Sciences Limited		
	Biocon Limited		
	Dr Reddy Laboratories Limited		
	Intas Pharmaceuticals Limited		
	Sarabhai Chemicals Specialities		
	Emcure Pharmaceuticals Limited		
Darbepoetin alfa	Reliance Life Sciences Private Limited	6/14/2016	Anemia due to chronic kidney disease, and chemotherapy in patients with cancer
	Dr. Reddy's Labs Limited	Not available	
	Hetero Drugs Limited	1/06/2014	
Insulin Glargine	Lupin Limited	2/13/2015	Type 1 diabetes mellitus or type 2 diabetes mellitus
	Aventis	1/03/2003	
	L.G. Lifesciences	12/20/2011	
	Eli Lilly and Company (India)	Not available	
	Biocon (India) Limited		
	Sanofi Aventis		
	Novo Nordisk India Private Limited		
Aflibercept	Bayer Pharmaceuticals Private Limited	2/25/2015	Treatment of Neovascular (wet) age-related macular degeneration (wet AMD)
Recombinant human insulin	Eli Lily	1/01/2003	Diabetes mellitus
	Pfizer Limited	11/05/2007	
	Scigen Biopharma Private Limited	2/03/2015	
	Gland Pharma Limited	10/08/2015	
	Novo Nordisk India Private Limited	3/17/2015	
	Cadila Pharmaceuticals Limited	Not available	
	Torrent Pharmaceuticals Limited		
	USV Limited		
	Piramal Healthcare		
	Wockhardt Limited		
	Shreya Healthcare Private Limited		

(continued)

Table 2. (continued)

Name of Drug	Manufacturer	Date	Indication
	Biocon (India) Limited		
	Abbott India Limited		
	Sanofi Aventis Limited		
Insulin lispro	Eli Lily	5/20/2009	Diabetes mellitus
Soluble insulin injection i.p.	Novo Nordisk	5/14/2009	Diabetes mellitus
Biphasic isophane insulin injection	Novo Nordisk	5/14/2009	Diabetes mellitus
Isophane insulin injection	Eli Lily	1/04/2004	Diabetes mellitus
	Novo Nordisk	5/14/2009	
	Sanofi Aventis		
Insulin aspart	Novo Nordisk	5/14/2009	Diabetes mellitus
Erythropoietin (r-Hu-EPO)	Roche Products (India) Private Limited	1/01/2003	Anemia due to chronic renal failure
	Emcure Pharmaceuticals	1/01/2003	
	Claris Life Sciences	1/12/2003	
	VHB Life Sciences	9/10/2006	
	Johnson & Johnson Limited	6/11/2008	
	Bioviz Technologies Private Limited	6/14/2010	
	KSR Pharmacy	1/28/2011	
	Lupin limited	8/17/2011	Anemia due to renal inadequacy
	Vita pharma	4/24/2012	
	Wockhardt Limited		
	Zuventus Health Care Limited		
	Biocon Limited		
	Shantha Biotechnics Private Limited		
	Ranbaxy Laboratories Limited		
	Klarvoyant Biogenics Private Limited		Anemia due to renal inadequacy
	Intas Pharmaceuticals Limited	Not available	
	Micro Labs Limited		
	RPG Life Sciences Limited		
	Hindustan Antibiotics Limited		
	La Renon Healthcare Private Limited		
	LG Life Sciences India		
	Panacea Biotec Limited		
	Celon Labs		
	Zydus Cadila Healthcare Ltd		
r-Human erythropoietin concentrated solution	Cadila Healthcare Limited	10/14/2014	
Pegylated erythropoietin	Intas Pharmaceuticals Limited	4/13/2015	Anemia associated with chronic renal failure (CRF) in adults, including patients on dialysis and not on dialysis.
Interferon alfa-2a	Roche Products (India) Pvt. Limited	1/01/2003	Neoplasm of lymphatic and hematopoietic system, Solid Neoplasm, Viral Diseases
	Intas Laboratories Limited		
	Biological Evans Limited		
	Zydus Cadila Healthcare Limited	1/12/2004	
	LG Life Sciences	Not available	
	Fulford (India) Limited		
	Serum Institute of India Limited		
Interferon alfa-2b	Fulford (India) Limited	1/01/2003	
	Shantha Biotechnics Pvt Limited	Not available	
	Kee Pharma Ltd.		
Pegylated interferon alfa-2b	Fulford (India) Limited	1/01/2003	
Pegylated interferon alfa-2a	Emcure Pharmaceuticals Limited	6/28/2012	Treatment of chronic active Hepatitis B and C and co infected with clinically stable HIV.
	Taksal Limited	8/21/2012	
Interferon beta-1a	UCB India Private Limited	1/03/2016	Relapsing multiple sclerosis characterized by at least 2 recurrent attacks of neurologic dysfunction (relapse) over the preceding 3 years period
	Nicholas Piramal Limited	1/28/2008	
	Merck Limited	4/22/2009	Relapsing multiple sclerosis

(continued)

Table 2. (continued)

Name of Drug	Manufacturer	Date	Indication
Pegylated interferon beta-1a	UCB India Private Limited	1/04/2016	
Insulin degludec/Liraglutide	Novo Nordisk India Private Limited	2/08/2010 10/07/2015	Type 2 diabetes mellitus
Rituximab	Hetero Drugs Limited	3/25/2015 3/30/2015	For the treatment of the patients with non-Hodgkin lymphoma and diagnosed chronic lymphocytic leukemia
	Reliance Life Sciences	12/02/2015	Non-Hodgkin lymphoma, rheumatoid arthritis
	Emcure Pharmaceuticals Limited	6/29/2012	
	Taksal Limited	8/21/2012	
	Roche Scientific Limited	1/01/2003	
	Dr Reddy Laboratories Ltd		
Trastuzumab	Roche Scientific	1/01/2003	Breast cancer, metastatic breast cancer, metastatic gastric cancer
	Reliance Life Sciences Private Limited	6/02/2015	
	Cadila Healthcare Private Limited	10/28/2015	Treatment of patients with HER2-positive metastatic breast cancer
	Emcure Pharmaceuticals Limited	6/29/2012	
	Taksal pharma Private Limited		
Adalimumab	Reliance Life Sciences Private Limited	6/26/2015	Rheumatoid arthritis (RA) (in adults) (moderate to severe, active RA, severe, active and progressive RA), juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and axial spondyloarthritis, Crohn disease, ulcerative colitis
	Cadila Healthcare Limited	9/25/2014	Moderate to severe, active rheumatoid arthritis in adult patients
Bevacizumab	Roche Limited		
	Hetero Drugs Limited	5/13/2016	Metastatic colorectal cancer (mCRC).
	Intas Pharmaceuticals Limited	6/23/2016	Unresectable advanced, metastatic, or recurrent non–small cell lung cancer
	Emcure Pharmaceuticals Ltd	8/21/2012	
Secukinumab	Novartis Limited	6/18/2015	Moderate to severe plaque
	Sandoz Limited	8/21/2015	
Infliximab	Reliance Life Sciences	3/21/2014	Rheumatoid arthritis
	M/s Johnson & Johnson Limited	3/12/2013	Crohn disease, rheumatoid arthritis, ankylosing spondylitis, fistulizing Crohn disease, plaque psoriasis, ulcerative colitis, psoriatic arthritis, Crohn disease in patients aged 6-17 y
Canakinumab	Novartis India Pvt Limited	1/05/2011	CAPS in adults, CAPS include familial cold auto-inflammatory syndrome/familial cold urticarial, Muckle-Wells syndrome, neonatal-onset multisystem inflammatory disease/chronic infantile neurologic cutaneous articular syndrome (CINCA)
Tenecteplase bulk	Gennova Pharmaceuticals Limited	4/29/2014	
Etanercept	Intas Pharmaceuticals	9/30/2014	Rheumatoid arthritis, juvenile rheumatoid arthritis, alkalizing spondylitis, psoriatic arthritis, plaque psoriasis, plaque psoriasis in children and adolescents
	Cipla Limited	10/08/2012	Rheumatoid arthritis, juvenile chronic arthritis, psoriatic arthritis, active ankylosing spondylitis refractory to conventional therapy
Turoctocog alfa	Novo Nordisk India Pvt Ltd	8/19/2015	Treatment and prophylaxis of bleeding in patients with hemophilia A (congenital factor)
Albiglutide powder	GlaxoSmithKline Pharmaceuticals Limited	8/12/2015	Type 2 diabetes mellitus
Siltuximab	Johnson & Johnson Limited	6/01/2016	Multicentric Castleman disease, for patients who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative
Natalizumab	UCB India Private Limited	3/22/2016	Relapsing multiple sclerosis (MS)
	Biogen Idec Biotech India Private Limited	5/28/2010	

(continued)

Table 2. (continued)

Name of Drug	Manufacturer	Date	Indication
Ofatumumab	Novartis Healthcare Private Limited	12/04/2016	Chronic lymphatic leukemia
Pembrolizumab	MSD Pharmaceuticals Private Limited	6/16/2016	Metastatic melanoma.
Tocilizumab	Taksal Limited	1/07/2009	Rheumatoid arthritis
r-Hu-Growth Hormone (Somatropin)	Novo Nordisk Limited	1/01/2003	Long-term treatment of children who have growth failure because of inadequate secretion of growth hormone and for the long-term treatment of growth retardation due to Turner syndrome
	German Remedies	1/12/2003	
	Shreya	1/04/2004	
	VHB Life Sciences	1/10/2004	
	Ferring Pharmaceuticals	4/04/2010	
	Scigen Biopharma Private Limited	6/18/2010	
	LG Life Sciences India	12/20/2013	
	Merck Specialities Private Limited	4/22/2009	
Coagulation factor IX	Baxalta Bioscience India Private Limited	3/21/2016	Coagulation factor IX (recombinant) is an antihemophilic factor
Aldurazyme (Laronidase)	Sandor Medicaids Private Limited	5/13/2010	Hurler and Hurler-Scheie forms of mucopolysaccharidosis I (MPS) and Scheie form with moderate to severe symptoms
Belatacept	Bristol Myers Squibb	6/13/2012	Prophylaxis of graft rejection and preservation of renal function in adults receiving a renal transplant
Methoxy polyethylene glycol-EPO beta	Emcure Pharmaceuticals Limited	8/21/2012	Anemia associated with chronic kidney disease
Denosumab	GlaxoSmithKline Pharmaceutical Limited	10/03/2012	Prevention of skeletal-related events in patients with advanced malignancies involving bone
Alglucosidase alfa	Sandor Medicaids Limited	10/19/2012	Pompe disease
Panitumumab	GlaxoSmithKline Pharmaceutical Limited	3/19/2013	Metastatic colorectal carcinoma with nonmutated (wild-type) KRAS
Fabrazyme (Agalsidase beta)	Sandor Medicaids Limited	3/04/2009	Fabry disease
Cerezyme	Sandor Medicaids Limited	6/ 01/2009	Nonneurologic Gaucher disease
Follitropin alfa (r-hu-FSH)	V.H. Bhagat	1/01/2003	Female infertility
	Chemeeh Labs	1/03/2003	
	Life Medicare	1/03/2003	
	Win Medicare	1/01/2003	
	Martin & Harris Limited	1/09/2003	
	Ferring Pharmaceuticals Pvt. Limited	1/05/2005	
	Merck Specialities	4/01/2009	
Follitropin beta	Organon (I) Limited	12/29/08	
Rasburicase	Sanofi Synthelabo Limited	12/22/2009	Acute hyperuricemia
Daclizumab	Roche Scientific Co	1/01/2003	Relapsing forms of multiple sclerosis
Human chorionic gonadotropin hormone	Organon	1/01/2003	Female infertility
	Ferring Pharmaceuticals	1/02/2003	
	Chemeeh Labs	1/03/2003	
	Win Medicare	1/01/2003	
	Life Medicare	1/03/2003	
	Bharat Serum	1/07/2003	
	Chandra Bhagat	1/11/2003	
	Kee Pharma	1/01/2004	
	V.H. Bhagat	1/01/2003	
Human menopausal gonadotropin (hMG)	V.H. Bhagat	1/01/2003	Menopausal
	Win Medicare	1/01/2003	
	Life Medicare	1/03/2003	
	Martin & Harris	1/09/2003	
	Ferring Pharmaceuticals Pvt. Limited	7/01/2009	
	Chandra Bhagat	1/11/2003	
Human recombinant interleukin-2	Ambala	1/04/2004	
Nimotuzumab	Biocon Limited	4/07/2006	squamous cell carcinomas
Ranibizumab	Novartis (I) Limited	11/13/2006	Neovascular (wet) age-related macular degeneration
Omalizumab	Novartis (I) Limited	12/29/2008	Asthma

Table 3. Comparison of Pharmacovigilance regulation in USA, EU, India, and China.

Pharmacovigilance	USA	EU	India	China
Regulatory authority	United States Food and Drugs Administration	European Medicines Agency	Central Drugs Standards Control Organisation (CDSCO)	National Medical Products Administration (NMPA), formerly China Food and Drug Administration (CFDA)
Regulatory pathways	No different pathways and/or data requirements for imported drugs vs locally manufactured drugs		Different pathways and/or data requirements for imported drugs vs locally manufactured drugs	
Supporting institution for pharmacovigilance	Center for Drug Evaluation and Research (CDER)	-	NCC-PvPI	Centre for Drug Evaluation
Biosimilar guideline year of publication	2010	2005	2012	2015
Nomenclature	Biological qualifier scheme	No biological qualifier scheme		
Pharmacovigilance plan	Safety and immunogenicity		Safety, efficacy, and immunogenicity	Safety and immunogenicity
Applicable guidelines	Scientific considerations in demonstrating biosimilarity to a reference product	• Guideline on similar biological medicinal products • Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues • Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues • along with product-specific guidelines	• CDSCO guidance for industry, 2008 • Submission of Clinical Trial Application for Evaluating Safety and Eficacy • Requirement for permission of new drug approval • Postapproval changes in biological products: quality, safety, and efficacy documents • Preparation of quality information for drug submission for new drug approval: biotechnological/ biological products • Guidelines on similar biologics: regulatory requirements for marketing authorization in India 2016.	
Number of biosimilars approved	14	48	No approval as biosimilar but 58 rDNA-based drugs are approved as "New Drugs"	No approval as biosimilar

Abbreviation: NCC-PvPI, National Coordination Centre (NCC) for the Pharmacovigilance Program of India.

Opportunities in Spontaneous Reporting System

Worldwide, in most of the developing and developed countries, the pharmacovigilance system depends on the SRS through which health care professionals, patients, and pharmaceutical manufacturers report adverse drug reaction / adverse event (ADR/AE) to the national database. International drug monitoring of the World Health Organization (WHO) also relies on SRSs, through which national centers submit collected ADRs to the global database.[25] The SRS is a passive surveillance method which is easy to establish and cost-effective; however, it has the disadvantage of poor-quality reports and underreporting,[27] SRS has the advantage of early identification of signals,[25] identifies potential rare AEs not identified during clinical trials and the postmarketing phase. It also detects the AEs associated with changes in quality of the drug throughout its life cycle.[10,26,28]

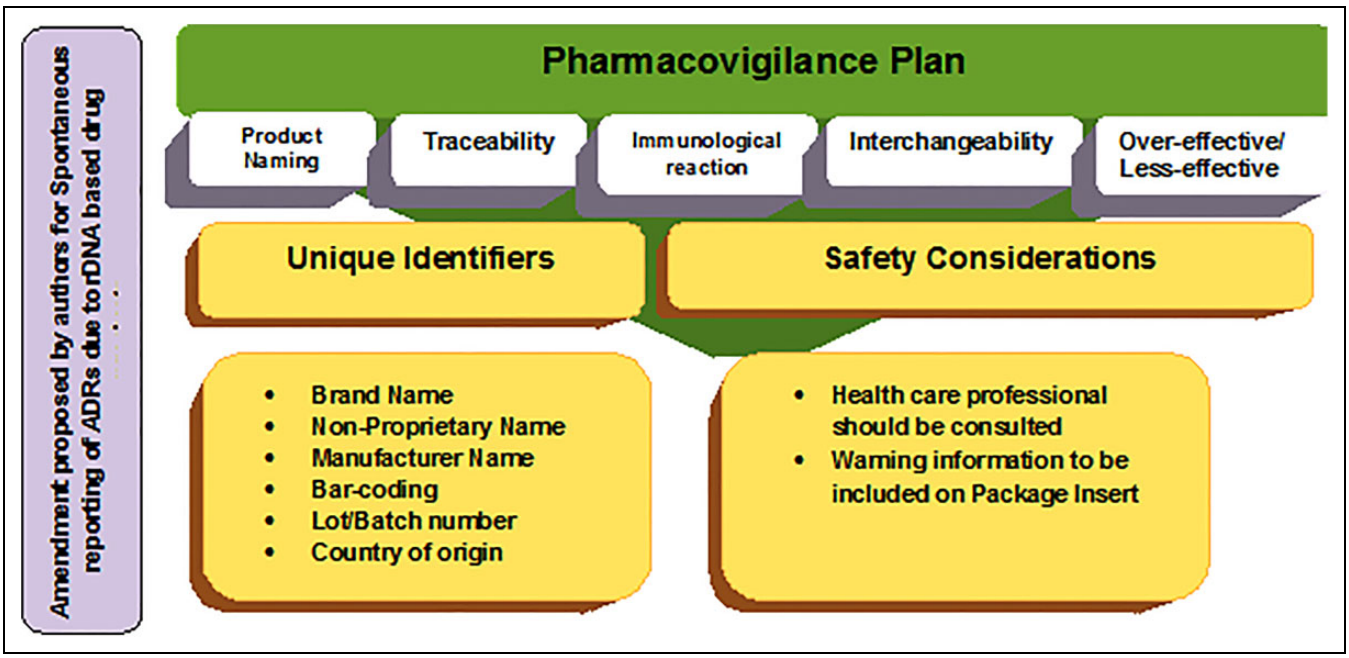

Figure 1. Pharmacovigilance of rDNA-based drugs through the spontaneous reporting system.

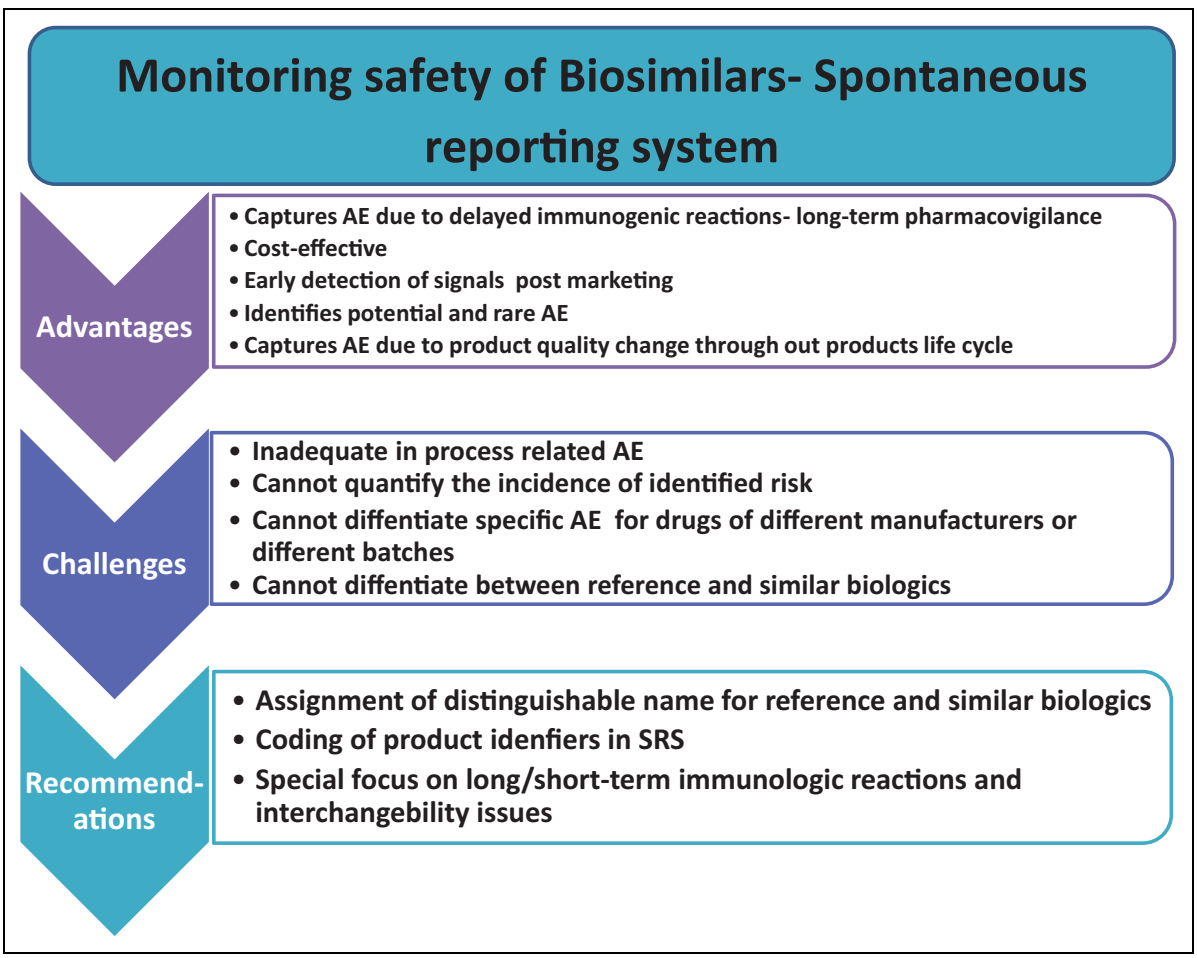

Figure 2. Amendment proposed by authors in SRS for reporting of ADRs due to rDNA-based drugs and biosimilars.

Table 4. Comparison of Information required in a "Suspected Adverse Drug Reaction Reporting Form" for Drugs and Biosimilars.

Information to be Provided in the Form	
For Drugs (Small Molecules)	For Biosimilars (Proposed)
Patient information	Patient information
Suspected adverse reaction	Suspected adverse reaction
Date reaction started (dd/mm/yyyy)	Date reaction started (dd/mm/yyyy)
Date of recovery (dd/mm/yyyy)	Date of recovery (dd/mm/yyyy)
Describe reaction or problem	Describe reaction or problem
Suspected medication(s)	Suspected medication(s)
Name (brand/generic)	Name (brand/generic)
Manufacturer (if known)	Manufacturer (if known)
Batch no. / lot no.	Batch no. / lot no.
Expiry date (if known)	Expiry date (if known)
Dose used	Dose used
Route used	Route used
Frequency (OD, BD, etc)	Frequency (OD, BD, etc)
Therapy dates	Therapy dates
Indication	Indication
Causality assessment	Causality assessment
-	Bar coding
-	Country of origin
-	Immunogenicity reactions—long-term and short-term
-	Interchangeable biosimilar or not
-	More or less effective as compared to innovator
Action taken	Action taken
Reaction reappeared after reintroduction	Reaction reappeared after reintroduction
Concomitant medical product including self-medication and herbal remedies with therapy dates	Concomitant medical product including self-medication and herbal remedies with therapy dates
Relevant tests/ laboratory data with dates	Relevant tests/ laboratory data with dates
Relevant medical/ medication history (eg, Allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc)	Relevant medical/ medication history (eg, Allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc)
Seriousness of the reaction	Seriousness of the reaction
Outcomes	Outcomes
Additional information	Additional information

Abbreviations: BD, twice daily; OD, once daily.

SRS will be beneficial in pharmacovigilance of biosimilars, which are sensitive to manufacturing conditions, subject to changes in product quality throughout its life cycle, and may induce long-term and/or short-term immunogenic reaction. Apart from anaphylaxis and hypersensitivity reactions, immunogenicity of this therapeutics also leads to reduced efficacy, neutralization of endogenous reaction, and changes in pharmacokinetic profile. The current SRS also provides information on altered efficacy.[29]

Challenges and Recommendations to SRS for Biosimilars

SRS is advantageous in capturing adverse events due to delayed immunogenic reactions of biosimilars but is inadequate for identifying manufacturing process- or batch-associated issues and it cannot differentiate product-specific ADRs/AEs of biosimilars by different manufacturers and reference products because of a lack of product-specific information, which is very much important in determining the safety of biosimilar and innovator products. Retrospective analysis of ADRs/AEs in the global database also showed that 100% of the reports only had their INNs, unlike the safety profile of small-molecule recombinant DNA (rDNA)-based therapeutics, which is product and process specific (Figure 1).[30,31]

Biosimilars are biologic in nature and are highly heterogeneous because of their properties such as aggregation, oxidization, deamidation, and presence of various glycoforms, which may affect the safety of these products, and they also have product-specific safety issues. The "Suspected Adverse Drug Reaction reporting form" through which health care professionals submit ADRs to the National Coordination Centre for the Pharmacovigilance Program of India was reviewed in this study. The form is very well suited for small molecules, but for biosimilars there is a need to modify the form for inclusion of the following mandatory information (Figure 2, Table 4):

- *Product naming:* The product's INN name should be supplemented with the information of product identifiers such as the brand name, manufacturer name, bar coding,

country of origin, and batch/lot number of the product, and there should be a provision for capturing this information in SRSs. Inclusion of these product identifiers not only provides product-specific information but also improves the traceability of the product. Apart from product identifiers, the WHO and USFDA recommended a biological qualifier scheme for differentiating biosimilars and innovator products.[11,14,15] These biological qualifiers can also be included in SRSs, which will be highly beneficial in differentiating the safety of biosimilars from different manufacturers and innovators.

- *Immunologic reaction:* Long- or short-term use of these protein therapeutics may provoke mild/severe immunologic reactions; milder reactions are often neglected, which may turn out to be an important risk. All potential immunogenicity reactions during the short and long term need to be assessed critically and reported in the SRS.
- *Interchangeability of biosimilars:* Only USFDA has guidelines for interchangeability of biosimilars, and it approves the product as only "Biosimilar" or "Biosimilars and Interchangeable Product." Pharma-emerging countries like India and China approve these products as "New drugs"[12] and "genetically engineered products,"[13] respectively but not as biosimilars, which may lead to ADR/AE as a result of interchanging of biosimilars from two different manufacturers. Health care professionals (HCPs) should well understand the risk of interchanging these products and ADR/AE related to interchangeability should also be reported in SRSs.
- *Overeffective or less effective:* In a few cases, similar biologics are more effective or less effective than reference products, though equivalency is established for the marketing approval. Reports related to this will also be helpful in improving the safety of biosimilars.

Discussion and Conclusion

Monitoring safety through the appropriate pharmacovigilance system is critical throughout the lifetime of biosimilars and their innovator products because biosimilars are unlike small molecule generics. The article highlights the fact that to monitor the safety of biosimilars through an SRS, there is a need for amendments in the existing spontaneous reporting form, an important and effective tool to collect additional information on the safety of these products, in particular, long-term safety. The following are recommended: (1) amendments to the current SRS form by including additional mandatory columns to report the information on product identifiers, product traceability, immunologic reactions, interchangeability, and over effective / less effective; (2) online SRS should prompt for including product identifiers—the product brand name (if available), nonproprietary name, manufacturer name, and lot number for biologics; (3) in addition, proper education to the health care community on importance, process, and practice of good pharmacovigilance. This may improve the quality of SRS data and increase the number of rare or unexpected ADRs/AEs that are not reported during the premarketing phase. Targeted long-term pharmacovigilance through SRS for biosimilars can also be recommended for early detection of safety signals and difference in safety signals between biosimilars and reference biologics. This will assist manufacturers in bringing out safe, effective, and economic biosimilars, which will revolutionize the treatment of many chronic diseases at an affordable cost.

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