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CURRENT REGULATORY AND MARKET ENVIRONMENT FOR BIOSIMILARS IN SERBIA

TRENUTNO ZAKONODAJNO IN TRŽNO OKOLJE NA PODROČJU PODOBNIH BIOLOŠKIH ZDRAVIL V SRBIJI

Gordana Pejović[1], Jovan Filipović[1]

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Abstract

Background: *Biosimilars are currently a reality of the pharmaceutical market in the European Union. This paper describes the current regulatory policy for approving biosimilars both in the European Union and in Serbia, which is not a Member State. Also, a comprehensive analysis on biosimilars consumption data on the Serbian market has been performed.*

Methods: *The European Medicines Agency has established a series of biosimilar scientific guidelines that comprises a regulatory policy for biosimilars in the European Union. This has enabled different biosimilar products to be marketed, making the European Union biosimilar market the most developed one globally. In the paper, this regulatory environment has been analysed, emphasising all relevant biosimilar guidelines as well as marketed biosimilar medicines. Also, an analysis is performed on Serbian regulatory requirements for approving and marketing biosimilars, analysing the Serbian regulatory authority's consumption data as well as data available from the National Health Insurance Institution.*

Results: *In the paper, the comprehensive analysis of the current European Union as well as Serbian regulatory environment has been presented, with a special emphasis on the Serbian market potential for biosimilar medicines. Detailed consumption data has been analysed for the period 2007-2011.*

Conclusion: *Serbia has good potential for biosimilar products, which is supported by national health insurance policy and the general trend of cutting the reimbursement costs for prescription medicines. Five year consumption data for biosimilars in Serbia shows that the Serbian biosimilars market is very small in terms of market share values, especially comparing to other large European biosimilar markets.*

Key words: biosimilar, medicine regulatory authority, consumption, Serbia, marketing authorisation

Izvirni znanstveni članek
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Izvleček

Uvod: *Podobna biološka zdravila so trenutno realnost farmacevtskega trga v Evropski uniji. Članek opisuje trenutno zakonodajno politiko pridobitve registracij podobnih bioloških zdravil v državah Evropske unije in v Srbiji, ki ni članica EU. Izvedena je bila tudi podrobna analiza porabe podobnih bioloških zdravil na srbskem trgu.*

Metode: *Evropska agencija za zdravila je uvedla vrsto znanstvenih smernic za registracijo bioloških zdravil, ki veljajo za zakonodajo na tem področju v Evropski uniji. To je omogočilo registracijo številnih podobnih bioloških zdravil in farmacevtski trg v državah Evropske unije velja za enega izmed najrazvitejših na svetovni ravni. V članku je opisano zakonodajno okolje s poudarkom na vseh pomembnih regulatornih smernicah in tudi analiza registriranih podobnih bioloških zdravil. Prav tako je narejena analiza predpisanih regulatornih zahtev za pridobitev registracij in trženje podobnih bioloških zdravil v Srbiji; izvedena je bila tudi analiza porabe registriranih zdravil v Srbiji prek podatkov srbske agencije za zdravila in zavoda za zdravstveno zavarovanje.*

Rezultati: *V članku je predstavljena celovita analiza trenutnega zakonodajnega okolja v državah Evropske unije in v Srbiji s poudarkom na tržnem potencialu podobnih bioloških zdravil v Srbiji. Prav tako je podana podrobna analiza porabe bioloških zdravil za obdobje 2007–2011.*

[1]University of Belgrade, Faculty of Organisational Sciences, Jove Ilića 154, 11000 Belgrade, Serbia
Correspondence to: e-mail: gordana.pejovic@gmail.com

Zaključek: *Srbija ima dober potencial za podobna biološka zdravila, ki so podprta z nacionalno zdravstveno politiko zavarovanja in s splošnim trendom zmanjševanja povračil stroškov za zdravila na recept. Petletni podatki o porabi podobnih bioloških zdravil v Srbiji kažejo, da je srbski trg zelo majhen v njihovi porabi, še posebej v primerjavi z drugimi večjimi evropskimi trgih podobnih bioloških zdravil.*

Ključne besede: podobno biološko zdravilo, agencije za zdravila, poraba zdravil, Srbija, registracija zdravil

1 INTRODUCTION

The biopharmaceutical industry has expanded dramatically over the last 30 years since the first successes of recombinant DNA technology. Biotechnology derived medicinal products, which comprise cytokines, hormones, clotting factors, monoclonal antibodies and vaccines, are presently the best characterised biologicals with considerable production and clinical experience and have revolutionised the treatment of some of the most difficult-to-treat diseases. Considering that during the period 1995-2007, the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approved 174 biologic products, at present over 450 are under development (1). While in 2000 they represented 11% of the market, it is expected they will reach 44% in 2012 (2).

Nowadays, the patent and regulatory data protection periods for the first and second waves of biopharmaceuticals based on recombinant proteins have started to expire, opening the way for other manufacturers to place follow-on products on the market. This has occurred for many years for conventional medicines containing small-molecule active substances. In the latter case, regulations for generic products allow for abbreviated approval based on proof of therapeutic equivalence demonstrated by analytical as well as usually by bioequivalence studies (3). Generics' manufacturers do not have to bear the cost of medicine discovery, do not need to prove the safety and efficacy of their medicines through costly clinical trials and are not subject to significant project attrition during development. Consequently, generic medicines can be offered at a significantly lower price than the innovator's medicine (4).

Meanwhile, it has been recognised by all stakeholders – politicians, regulators, the innovative and generics pharmaceutical industry, payers, physicians, pharmacists and patients that there are fundamental differences between conventional small-molecule based medicines and biopharmaceuticals. This has led to the adoption of distinct legal and regulatory frameworks for follow-on products to biopharmaceuticals ("biosimilars") in various parts of the world.

Fundamental differences between small-molecule based (chemical) medicines and biopharmaceuticals are especially evident in the manufacturing process. Recombinant DNA technology enabled the manipulation of genes and cells to produce structurally complex medicines that would have been impossible to manufacture through chemical synthesis or to purify from natural sources. These medicines are produced through highly controlled manufacturing processes including bacteria, yeast, plant or mammalian cells acting as the "manufacturing facility". The development and manufacturing of recombinant protein products include:

- cloning the coding DNA sequence into a suitable DNA vector;
- transfecting this vector into a host cell;
- screening for the cell that forms the product in the desired quality and required quantity;
- subcloning and developing this cell further concerning expression yield, growth properties, etc. into a master and working cell bank respectively from which all subsequent production runs are performed;
- growing the recombinant cell in large bioreactor vessels (up to, and even exceeding, 10,000 L scale) depending on the supply needs;
- purifying the target protein using a multi-step downstreaming process; and finally
- bringing it into a formulation and device suitable for transport, storage and application to the patients.

The whole process has to be run under strictly controlled, validated conditions in closed systems to ensure consistency and avoid any contamination and in accordance with Good Manufacturing Practice (GMP) requirements. A second manufacturer aiming to replicate a protein product independently has to run through an analogous procedure as above but will not be able to reproduce it in an identical way. Transfection of the host cell represents a unique event that cannot be identically replicated, resulting in a manufacturing cell line with different properties (3). Therefore, for biopharmaceuticals it is often said that "the process is the product", emphasising that the result

of the replicated manufacturing process would be a manufacturing cell line with different properties.
On the other hand, small-molecule based medicines are typically manufactured through chemical synthesis, which means that this is made by combining specific chemical ingredients in an ordered process. Chemical medicines generally have well-defined chemical structures and a finished medicine can usually be analysed to determine all its various components. By contrast, it is very difficult, and sometimes impossible, to characterise a complex biologic medicine using testing methods available in a laboratory and some of the components of a finished biologic may be unknown. It has been recognised by the regulatory authorities that differences in the manufacturing process of biopharmaceuticals necessarily will lead to differences in the product attributes that cannot be fully assessed by analytical characterisation. Therefore, not only physicochemical-biological testing, but also the manufacturing process ("process equals product" paradigm), was made part of the determination of the product quality, emphasising the importance of process control, process validation and product testing. As a consequence, therapeutic proteins derived from independent manufacturing processes can never be identical but can at least be "similar", i.e. possessing the same clinical safety and efficacy profile in spite of not being "the same" molecule.
Like in other European countries, in the past decade biosimilars have entered the Serbian market. This paper gives an overview of the regulatory framework for biosimilars in the European Union as well as a general consideration of regulatory requirements for authorising biosimilars in Serbia. Also, the paper presents analysis of biotechnology medicines consumption data on the Serbian market for the past five years both for authorised innovative biotechnology medicines and biosimilars. Additionally, comparison of market share value for Serbian and some selected European biosimilars markets has been presented.

2 METHODS

The literature review was undertaken by the authors in PubMed, MEDLINE and EMBASE for the retrieval of documents pertaining to pharmaceutical legislation for biotechnology medicines, analysis of regulatory processes in the European Union, manufacturing of biologics and reimbursement policies and analysis of relevant market data using key words. These were "biosimilar", "pharmaceutical legislation, biosimilars", "reimbursement, biosimilars", "biosimilar market share". The focus was on relevant articles on biosimilars published before January 2013. For regulatory documents pertaining to the processes of the approval of biosimilars, biologics and generics, a search for legislative decisions, briefing summaries, concept papers, guidance, reports and evaluations of approved and rejected applications for biosimilars published by the World Health Organisation, European Medicines Agency (EMA), Medicines and Medical Devices Agency of Serbia and National Health Insurance Institution of Serbia was conducted. Whenever possible, data from the primary literature were reviewed. Where no data were available in the primary literature, regulatory and other publications (available in the public domain) were cited.
Following the comprehensive literature review, biosimilars regulatory guidelines were summarised in Table 1 and described in section 3. Also, data on biosimilars authorised in Serbia as well as biosimilars consumption data available from the Serbian medicines regulatory authority and National Health Insurance Institution were analysed and compared to data from other European Union markets.

3 EUROPEAN UNION REGULATORY FRAMEWORK FOR BIOSIMILARS

In the EU, technologically advanced medicinal products, such as those developed by means of a biotechnological process (e.g. recombinant DNA technology), can be placed on the market only after a marketing authorisation has been issued by the Community in accordance with the provisions of Regulation (EC) No. 726/2004 (5) (centralised procedure). The difference between conventional generics and biosimilar products has been acknowledged in Article 10 (4) of EU directive 2001/83/EC as amended by directive 2004/27/EC (6). Based on this legislation, the European Union became the first region globally to introduce a particular regulatory framework for biosimilars developed by EMA's Committee for Medicinal Products for Human Use (CHMP). It consists of an overarching guideline as well as more general guidelines concerning the product quality and other clinical and non-clinical issues. Product-specific guidelines are also available, and the EMA is in the process of developing additional product-specific guidelines and is planning to update these guidelines as new information comes to light (Table 1).

Table 1. *European Medicines Agency guidelines for biosimilars (7).*
Tabela 1. *Smernice za podobna biološka zdravila izdana s strani Evropske agencije za zdravila (7).*

Guideline reference number/ Referenčna številka smernic	Guideline title/ Naslov smernic	Effective date/ Datum začetka veljavnosti	Remarks/ Opombe
Overarching guideline/ Nadrejene smernice			
CHMP/437/04 Rev.1	Similar biological medicinal product (concept paper)/ Podobna biološka zdravila (koncept)		Released for consultation May 2013/ predložene v posvetovanje maja 2013 Deadline for comments 31 October 2013/ rok za pripombe 31. oktober 2013
CHMP/437/04	Similar biological medicinal products (adopted guideline)/ Podobna biološka zdravila) (sprejete smernice)	October/ oktober 2005	
Quality issues guidelines/ Smernice o kakovosti			
EMA/CHMP/ BWP/247713/2012	Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues/ Podobna biološka zdravila, ki kot zdravilno učinkovino vsebujejo biotehnološko pridobljene beljakovine: vprašanja kakovosti (concept paper)/ (koncept)		Released for consultation May 2012 predložene v posvetovanje maja 2012 / Deadline for comments 30 November 2012/ rok za pripombe 30. november 2012
EMEA/CHMP/ BWP/49348/2005	Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues/ Podobna biološka zdravila, ki kot zdravilno učinkovino vsebujejo biotehnološko pridobljene beljakovine: vprašanja kakovosti (adopted guideline)/ (sprejete smernice)	June/ junij 2006	
CPMP/ICH/5721/03	Comparability of medicinal products containing biotechnology-derived proteins as active substance - Quality issues/ Primerljivost zdravil, ki kot zdravilno učinkovino vsebujejo biotehnološko pridobljene beljakovine – vprašanja kakovosti (adopted guideline)/ (sprejete smernice)	December 2003	Superseded by / nadomeščene s CPMP/ICH/5721/03
Non-clinical and clinical issues guidelines/ Smernice o nekliničnih in kliničnih vprašanjih			
EMA/CHMP/ BMWP/572828/2011	Revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues / Sprememba Pregled smernic o podobnih bioloških zdravilih, ki kot zdravilno učinkovino vsebujejo biotehnološko pridobljene beljakovine: neklinična in klinična vprašanja (concept paper)/ (koncept)		Released for consultation October 2011/ predložene v posvetovanje oktobra 2011 Deadline for comments 31 December 2011/ rok za pripombe 31. december 2011
EMA/CHMP/ BMWP/86289/2010	Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use/ Ocena imunogenosti monoklonskih protiteles, namenjenih za klinično uporabo in vivo (adopted guideline)/ (sprejete smernice)	December 2012	

EMEA/CHMP/ BMWP/14327/2006	Immunogenicity assessment of biotechnology-derived therapeutic proteins/ Ocena imunogenosti biotehnološko pridobljenih terapevtskih beljakovin (adopted guideline)/ (sprejete smernice)	April 2008	
EMEA/CHMP/ BMWP/101695/2006	Comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical issues (adopted guideline)/ Primerljivost biotehnološko pridobljenih zdravil po spremembi v proizvodnem procesu – neklinična in klinična vprašanja (sprejete smernice)	November 2007	
EMEA/CHMP/ BMWP/42832/2005	Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues/ Podobna biološka zdravila, ki kot zdravilno učinkovino vsebujejo biotehnološko pridobljene beljakovine: neklinična in klinična vprašanja (adopted guideline)/ (sprejete smernice)	June/junij 2006	
EMEA/CPMP/3097/02	Comparability of medicinal products containing biotechnology-derived proteins as drug substance: non-clinical and clinical issues/ Primerljivost zdravil, ki kot zdravilno učinkovino vsebujejo biotehnološko pridobljene beljakovine: neklinična in klinična vprašanja (adopted guideline)/ (sprejete smernice)	June 2004	Superseded by/ nadomeščene s CHMP/BMWP/101695/06
Product-specific guidelines/ Smernice, ki se nanašajo na posamezna zdravila			
CHMP/ BMWP/671292/2010	Similar biological medicinal products containing recombinant follicle stimulation hormone/ Podobna biološka zdravila, ki vsebujejo rekombinantni folikle spodbujajoč hormon (adopted guideline)/ (sprejete smernice)	1 September 2013	
CHMP/ BMWP/652000/20100	Similar biological medicinal products containing interferon beta/ Podobna biološka zdravila, ki vsebujejo interferon beta (adopted guideline)/ (sprejete smernice)	1 September 2013	
EMA/CHMP/ BMWP/403543/2010	Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues/ Podobna biološka zdravila, ki vsebujejo monoklonska protitelesa: neklinična in klinična vprašanja (adopted guideline)/ (sprejete smernice)	1 December 2012	
EMEA/CHMP/ BMWP/301636/08	Similar biological medicinal products containing recombinant erythropoietins/ Podobna biološka zdravila, ki vsebujejo rekombinantne eritropoetine (adopted guideline)/ (sprejete smernice)	30 September 2010	

EMEA/ CHMP/945626/2005	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 erythropoietins/Dodatek k smernicam o podobnih bioloških zdravilih, ki kot zdravilno učinkovino vsebujejo biotehnološko pridobljene beljakovine: neklinična in klinična vprašanja – Navodila za podobna zdravila, ki vsebujejo rekombinantne eritropoetine (adopted guideline)/ (sprejete smernice)	July/julij 2006	Superseded by/ nadomeščene z EMEA/CHMP/BMWP/301636/08
EMEA/CHMP/ BMWP/118264/2007 Rev. 1	Non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins/ Nekliničen in kliničen razvoj podobnih bioloških zdravil, ki vsebujejo heparine z nizko molekulsko maso (concept paper) / (koncept)		Released for consultation January 2013/ predložene v posvetovanje januarja 2013 Deadline for comments 31 July 2013/ rok za pripombe 31. julij 2013
EMEA/CHMP/ BMWP/118264/2007	Similar biological medicinal products containing low-molecular-weight heparins/ Podobna biološka zdravila, ki vsebujejo heparine z nizko molekulsko maso (adopted guideline) / (sprejete smernice)	October / oktober 2009	
EMEA/CHMP/ BMWP/102046/2006	Non-clinical and clinical development of similar medicinal products containing recombinant interferon alpha/ Nekliničen in kliničen razvoj podobnih zdravil, ki vsebujejo rekombinantni interferon alfa (adopted guideline)/ (sprejete smernice)	April 2009	
EMEA/CHMP/ BMWP/31329/2005	Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Guidance on biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor/Dodatek k smernicam o podobnih bioloških zdravilih, ki kot zdravilno učinkovino vsebujejo biotehnološko pridobljene beljakovine: neklinična in klinična vprašanja – Navodila za biološko podobna zdravila, ki vsebujejo rekombinantni dejavnik, ki spodbuja nastajanje kolonij granulocitov (adopted guideline)/ (sprejete smernice)	June/junij 2006	
EMEA/CHMP/ BMWP/94528/2005	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 somatropin/Dodatek k smernicam o podobnih bioloških zdravilih, ki kot zdravilno učinkovino vsebujejo biotehnološko pridobljene beljakovine: neklinična in klinična vprašanja – Navodila za podobna zdravila, ki vsebujejo somatropin (adopted guideline)/ (sprejete smernice)	June/junij 2006	

EMEA/CHMP/ BMWP/32775/2005	Revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues/ Sprememba Pregled smernic o nekliničnem in kliničnem razvoju podobnih bioloških zdravil, ki vsebujejo rekombinantni humani inzulin in analoge inzulina (concept paper) / (koncept)		Released for consultation December 2012/ predložene v posvetovanje decembra 2012 Deadline for comments 30 June 2013/ rok za pripombe 30. junij 2013
EMEA/CHMP/ BMWP/32775/2005	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 human insulin/Dodatek k smernicam o podobnih bioloških zdravilih, ki kot zdravilno učinkovino vsebujejo biotehnološko pridobljene beljakovine: neklinična in klinična vprašanja – Navodila za podobna zdravila, ki vsebujejo rekombinantni humani inzulin (adopted guideline)/ (sprejete smernice)	June 2006	

In the case of biosimilar medicinal products, because the active substance is similar but not identical to those in the reference product, the requirements for marketing authorisation are based on the demonstration of the similar nature of the two biological products through comparability studies, named the 'comparability exercise'. The comparability exercise is needed to generate evidence substantiating the similar nature in terms of quality, safety and efficacy of the new similar biological medicinal product and the chosen reference medicinal product authorised in the EU (8).

The results of the comparative studies done at the quality level may allow a reduction in the non-clinical and clinical data requirements compared to a full dossier. The clinical studies should be designed to demonstrate equivalence rather than non-inferiority, i.e. "better" outcome is not an option because it indicates lack of similarity. Efficacy and safety have to be justified or demonstrated separately for each claimed indication.

The selected reference product will need to be the same throughout the comparability programme. Such comparability studies involve a thorough process starting by the comparison in terms of product quality and manufacturing process consistency, as the safety and efficacy profile of the product is closely linked to its manufacturing method. Currently, due to the state of the art in science, it is almost impossible to prove that two biologic medicines have the same qualitative and quantitative composition. In order to prove that there are no relevant differences between both medicines, in most, if not all cases, comparison to the reference product has to be performed at a non-clinical level. In all cases, there should be pharmacokinetic/pharmacodynamic comparison of a biosimilar and reference product, and in some cases clinical therapeutic equivalence trials are requested to show similar efficacy and safety, at least in one clinical situation (9).

The European system for biosimilar approval devotes special attention to concerns over potential immunogenicity of a biosimilar and to post-marketing testing and surveillance to detect any potential safety issues. Unfortunately, the immunogenicity of biosimilars often cannot be fully predicted using preclinical studies, and clinical immunogenicity studies are thus required before approval. Therefore, safety data will be needed before marketing authorisation and will also be required post marketing.

It is also worth mentioning that the granting of approval does not mean that the biosimilar product can be automatically substituted for the reference product and vice versa. This decision should only be taken after obtaining the opinion of a qualified health professional. Several countries, such as France, Spain, Italy, the Netherlands, the UK and Sweden, have established legislative measures to prohibit the automatic substitution of these products (10).

Announced revision of biosimilar guidelines will probably solve some of the most critical issues during biosimilars' marketing authorisation, which were especially raised by the pharmaceutical industry. On

the basis of the experience gained since the release of the initial guideline, the revision intends to:

- provide clarification with regards to terminology for biosimilars;
- give better clarity on the principles of biosimilarity, including on safety and efficacy aspects;
- clarify requirements regarding the posology, route of administration and formulation of biosimilars.

The revision will also cover global development aspects, including the choice of the reference product when conducting non-clinical and clinical studies. With the aim of facilitating the global development of biosimilars and to avoid unnecessary repetition of clinical trials, the revised guideline explains that it may be possible for an applicant to compare its biosimilar in certain clinical studies and *in vivo* non-clinical studies with a comparator authorised outside of the European Economic Area (EEA). This comparator will need to be authorised by a regulatory authority with similar scientific and regulatory standards to those of the EMA. It will then be the applicant's responsibility to establish that the comparator is representative of the reference product authorised in the EEA. Therefore, it is expected that the revised biosimilar guideline will speed up the authorisation process in the future and the clinical trials costs will be significantly reduced, which will introduce some biosimilar medicines, authorised on other markets, to European Union patients.

4 BIOSIMILARS ON EUROPEAN UNION MARKET

So far, the EMA has granted 14 marketing authorisations for biosimilar products in the EU, including biosimilars to recombinant human growth hormone, granulocyte-colony stimulating factor and erythropoietin (Table 2), i.e. somatropin, filgrastim and epoetin respectively, as their recombinant versions. Approved biosimilars have been compared with reference products in terms of composition and primary structure, higher order structure conformation, post translational modifications, polarity, charge, isoforms, size, detection of aggregates, binding and biological activity (11). Clear regulatory guidelines (Table 1) and tight control are essential in order to guarantee efficacy and safety to patients.

Table 2. *Biosimilar products currently present in the EU market.*
Tabela 2. *Podobna biološka zdravila na trgu EU.*

INN	Name/Ime	Company/ Proizvajalec	Reference product/ Podoben izdelek	CHMP opinion/ mnenje	EU approval/ sprejem
Somatropin	Omnitrope	Sandoz	Genetropin (Pfizer)	January 2006	April 2006
Somatropin	Valtropin (withdrawn)	BioPartners	Humatrope (Lilly)	February 2006	April 2006
Epoetin alfa	Binocrit	Sandoz	Eprex/Erypro (JnJ/ Amgen)	June 2007	August 2007
Epoetin alfa	Epoetin alfa Hexal	Sandoz (Hexal)	Eprex/Erypro (JnJ/ Amgen)	June 2007	August 2007
Epoetin alfa	Abseamed	Medice	Eprex/Erypro (JnJ/ Amgen)	June 2007	August 2007
Epoetin zeta	Retacrit	Hospira	Eprex/Erypro (JnJ/ Amgen)	October 2007	December 2007
Epoetin zeta	Silapro	Stada	Eprex/Erypro (JnJ/ Amgen)	October 2007	December 2007
Filgrastim	TevaGrastim	Teva	Neupogen (Amgen)	February 2008	September 2008
Filgrastim	Filgrastim Ratiopharm (withdrawn)	Ratiopharm	Neupogen (Amgen)	February 2008	September 2008
Filgrastim	Biograstim	CT Arzneimittel	Neupogen (Amgen)	February 2008	September 2008
Filgrastim	Filgrastim Hexal	Hexal	Neupogen (Amgen)	October 2008	February 2009
Filgrastim	Zarzio	Sandoz	Neupogen (Amgen)	October 2008	February 2009
Filgrastim	Nivestim	Hospira	Neupogen (Amgen)	March 2010	June 2010

As occurred with the introduction of equivalent medicines (generic), the approval of biosimilars could be cost saving for health care providers. It has been suggested that an initial wave of biosimilars could generate cost savings equivalent to over 2 billion USD for European health care providers (12). At launch, medicines approved in the EU (Table 2) were offered with about 15-35% lower price vs. the list prices of the innovator products (depending on the product, country and package size). An example was the price reduction of erythropoietin in Germany, where a biosimilar entered the market with a significantly lower price than the reference medicine, and the price of the reference medicine was reduced accordingly, with an overall 33% price reduction of the initial price of the medicine (13). The rising pressure of cost-containment in all major markets is driving the uptake of generics and also creates a demand for biosimilars. However, the cost and duration of development for biosimilars are much greater than for small-molecule generics and present a significant barrier to entry and a resistor of biosimilars market growth (14).

The EU presents the most advanced market for biosimilars, accounting for 80% of global spending on these molecules. However, despite a strong legislative foundation, to date only a few manufacturers have launched biosimilars in the region. These include a mixture of existing generics houses, the generics arms of major companies and new ventures, most notably Sandoz/Novartis, Stada, Hospira, Medice and Ratiopharma (Teva). Biosimilars are established in three therapy areas in Europe: epoetins for treating anaemia caused by renal dialysis, filgrastim for lowered white blood cell counts after chemotherapy and somatropin. The penetration of biosimilars varies by country, reflecting local pricing and reimbursement policies, stakeholder influence and attitudes towards their adoption and use. Across markets, filgrastims have generally achieved the highest penetration by value and somatropin the lowest (25% and 4% class uptake respectively). The lower penetration of somatropin has been largely driven by the greater element of patient choice and discrimination over devices and convenience. Original brand Genotropin, for example, is available in a form that does not require refrigeration, whereas this is a prerequisite for the biosimilar version. Cautious prescribing has also played a role, with physicians hesitant to use biosimilar somatropin given the time it takes to show an effect; with filgrastims, the impact of treatment is more readily apparent, enabling physicians to change course in a faster timeframe if required. In the case of epoetins, uptake is more driven by payer than patient concerns, given the lack of any discernible difference in the patient experience as a result of switching to a biosimilar. Uptake also varies across countries when therapy areas are considered according to type, being significantly lower in differentiated markets where the stakeholder landscape is extremely complex, the value proposition is high and the market is driven by price (e.g. somatropin), versus commodity markets where access is mostly controlled by payers and the product has limited intrinsic value (e.g. filgrastims and epoetins) (15).

5 BIOSIMILARS ON SERBIAN MARKET – REGULATORY AND MARKET ASPECTS

Placing a medicinal product on the Serbian market requires a marketing authorisation, granted on the basis of an application. Since Serbia is still not an EU Member State, European legislation is transposed one by one, which means that a marketing authorisation in the EU does not automatically mean the recognition of the approval with Serbia's competent authority. Rather, the authorisation procedure is carried out by criteria as harmonised as possible with those in EU. When Serbia becomes a full EU Member State, then the principle of European legislation that extends to the new Member State will start to be applied in full. The Serbian medicines regulatory authority - Medicines and Medical Devices Agency of Serbia – is therefore performing a *national procedure* of medicines authorisation, ensuring that authorised medicine is meeting the criteria of quality, safety and efficacy. An additional measure in ensuring better access to medicines on the Serbian market is the introduction of the *fast track marketing authorisation procedure,* which represents a necessary harmonisation step in Serbian legislation, ensuring that medicines authorised by centralised procedure by EMA could be available to patients in Serbia in a shorter period of time, i.e. 150 days. This also reflects the growing capacity of Serbia's competent authority to assess these types of applications and to prepare for future participation in other European procedures (mutual recognition procedure and decentralised procedure) (16).

In line with intensive negotiations with the European Union as well as preparation for the future World Trade Organisation (WTO) membership, Serbian pharmaceutical legislation has been fully harmonised with the current EU directives. The major principle is to establish the same evaluation criteria for medicine

applications submitted in Serbia as for those in EU regulatory authorities in order to achieve the same quality, efficacy and safety of medicines marketed in Serbia. Having this principle in mind, the Serbian regulatory authority is assessing applications for biosimilar medicines on the grounds established in the relevant EMA guidelines (Table 1), which means that there are no additional or less requirements for marketing authorisation of biosimilars in Serbia. Comparability exercise data are required based on the comparison to reference biotechnology products marketed in the EU on the basis of full dossier. The deadline for issuing marketing authorisation for biosimilar medicine is 210 days on the basis of a complete medicine application.

Having in mind all national measures taken in order to harmonise with the EU legislation and to transpose all the requirements set in EU pharmaceutical directives, the Serbian pharmaceutical market has been growing steadily. While the market is small in terms of absolute numbers, relative per capita spending on medicines is expected to improve over the long term. As Serbia continues its economic convergence with developed Europe, medicine consumption is also expected to rise. However, financial inefficiencies within the health insurance system mean that the National Health Insurance Institution is unable to always meet its obligations on time, leaving patients to pay for formerly reimbursed medicines or hospitals having to cover the difference. Pharmaceuticals expenditure is rising from RSD75.70bn (US$1.03bn) in 2011 to RSD81.44bn (US$0.92bn) in 2012 (+7.6% in local currency terms and -11.0% in US dollar terms, which was due to an unfavourable inflation rate of 13 percent in 2012) (17).

The public fund for healthcare in Serbia mainly originates from salary contributions to the compulsory health structures, and private or complementary voluntary health insurance is not well developed and not well integrated with existing public schemes. The Serbian compulsory health insurance fund includes a positive medicine list (PML) as a benefit of the scheme and listing is typically crucial for achieving a significant share in the Serbian market.

There are multiple PMLs in Serbian healthcare system (List A, A_1, B, C and D) with varying reimbursement levels. In order to avoid the risk of exceeding predefined budget, physicians are encouraged to adjust their prescribing accordingly.

Despite continued underfinancing of healthcare in Serbia and the intensification of cost-containment measures by authorities, a number of new, expensive medicines have been included in the PMLs in recent years. It is important to recognise that behind these observations lie some of Serbia's first experiences with patient access, financial and even risk-sharing agreements. Manufacturers' first attempts to partner with payers in Serbian market were exclusively financial in nature and included agreements such as straightforward hidden discounts, classic price-volume contracts or portfolio agreements, where the positive listing of a new drug is conditional on a price decrease for an already marketed product. For example, in order to enable inclusion on the Serbian PML, manufacturers of three oncology drugs (INN: bevacizumab, cetuximab and rituximab) agreed to offer rebates of 25% in 2008 and 11% in 2009 on the reimbursed price (18).

By the end of 2012, several innovative biotechnological medicines were authorised by the Serbian medicines regulatory authority, mainly various forms of epoetin, somatropin and filgrastim. The first market authorisations were issued in 2006 for epoetin beta and darbepoetin alfa, after which filgrastim and somatropin were authorised in 2007 and 2008 respectively. On the other hand, only one biosimilar product has been authorised for the Serbian market, namely epoetin zeta by local pharmaceutical manufacturer Hemofarm AD.

After its authorisation, careful consumption data for epoetin, somatropin and filgrastim medicinal products have been collected by the Serbian medicines regulatory authority; these are presented in Annual medicine consumption reports (19-23). The data were summarised as presented in Table 3, which presents consumption data both for innovative biotechnological medicines and biosimilars that are marketed in Serbia. Also, Table 3 indicates the brand names of registered products in Serbia.

Table 3. *Epoetins, somatropin and filgrastim consumption data on the Serbian market for the period 2007-2011.*

Tabela 3. *Podatki o porabi epoetinov, somatropina in filgrastima na srbskem trgu za obdobje 2007-2011.*

CONSUMPTION DATA OF INNOVATIVE BIOTECHNOLOGICAL MEDICINES/ PODATKI O UPORABI INOVATIVNIH BIOTEHNOLOŠKIH ZDRAVIL											
ATC Code	INN/ Dosage form, strength and package/ marketed product/ INN/farmacevtska oblika, jakost zdravila in pakiranje/zdravilo z dovoljenjem za promet	Amount/packages sold/ Število prodanih pakiranj					Total price (in 000 RSD)/ Skupna cena (v 000 RSD)				
		2007	2008	2009	2010	2011	2007	2008	2009	2010	2011
B03XA01	Epoetin alfa Inj. 6x2000 i.j./0.5ml/EPREX®, Cilag	no MA	no MA	9100	6320	4227	/	/	90.548	67.326	42.767
	Epoetin alfa Inj. 6x2000 i.j./ml/ EPREX®, Cilag	15300	22130	0	0	0	155.539	224.973	0	0	0
	Epoetin beta Inj. 6x2000 i.j./0.3ml/ RECORMON®, Roche Diagnostic GmbH	0	28357	23420	16867	23323	0	272.383	211.986	163.449	213.589
	Darbepoetin alfa Inj. 1x10mcg/0.4ml/ ARANESP®, Amgen Europe B.V.	8972	0	110	14762	30988	16.224	0	8.324	27.798	54.867
	Darbepoetin alfa Inj. 1x20mcg/0.5ml/ ARANESP®, Amgen Europe B.V.	11122	0	0	26292	32219	40.226	0	0	98.713	112.115
	Darbepoetin alfa Inj. 1x30mcg/0.3ml/ ARANESP®, Amgen Europe B.V.	7808	0	0	11310	24338	42.359	0	0	63.520	126.591
	Darbepoetin alfa Inj. 1x60mcg/0.3ml/ ARANESP®, Amgen Europe B.V.	no MA	no MA	no MA	1353	1611	/	/	/	15.155	17.215
H01AC01*	Somatropin Inj. 5x5.3 mg/ml/*	1130	1436	2198	1157	2112	72.126	91.657	150.179	84633	132.683
	Somatropin Inj. carp.1x1.5ml/10mg (pen) /*	1909	1118	795	912	1773	51.748	30.306	25.006	30.712	56.764

	Somatropin Inj. carp.1x1.5ml/15mg (pen) /*	2783	6015	6951	7850	9105	116.037	250.796	336.307	406.617	360.968
L03AA02	Filgrastim Inj. 1x0.5ml/48 M i.j./NEUPOGEN®, F.Hoffman-La Roche LTD	11947	14492	13559	15590	14994	140.750	155.504	168.829	207.824	161.426
	Filgrastim Inj. 1x0.5ml/30 M i.j. /NEUPOGEN®, F.Hoffman-La Roche LTD	883	1626	1898	2176	1468	8.268	10.738	14.545	17853	10.104
B03XA01	Epoetin zeta Inj. 6x2000 i.j./0.6ml/ EQRALYS, Hemofarm AD	no MA	0	5320	3389	2874	/	0	57.329	39.098	24.616

Legend: no MA – medicine had no Marketing Authorisation (MA),
*- Somatropins with marketing authorization in Serbia (innovative medicines): GENOTROPIN®-Pfizer, HUMATROPE®-Lilly France S.A.S, NORDITROPIN® NORDILET-Novo Nordisc, NORDITROPIN® SIMPLEXX®-Novo Nordisc.
Legenda: brez DP – zdravilo nima dovoljenja za promet (DP)
*– Somatropini z dovoljenjem za promet v Srbiji (inovativna zdravila): GENOTROPIN®-Pfizer, HUMATROPE®-Lilly France S.A.S, NORDITROPIN® NORDILET-Novo Nordisc, NORDITROPIN® SIMPLEXX®-Novo Nordisc.

Based on consumption data presented in Table 3, it can be concluded that although Serbia's medicine market is open to biosimilar medicines, with a favourable regulatory environment that is in accordance with EU pharmaceutical legislation, only innovative biotechnology medicines are marketed. Also, there is one approved biosimilar product, but consumption data indicate that physicians are generally in favour of innovative medicines. General consumption data, available from the National Health Insurance Institution database, indicate that the relative market share of biotechnology medicines has a value of less than 1% throughout the analysed period 2007-2011. This value is calculated for innovative biotechnology medicines, whereas market value of the approved biosimilar in Serbia is of no significance. However, when analysing the market share of biotechnology medicines by ATC code groups in which they are classified (Table 3: B – drugs for blood and blood forming organs, H – systemic hormonal preparations, excluding sex hormones and insulins, L – antineoplastic and immunomodulating agents) for the same period, the following data were obtained (24):

- market share of approved epoetins in Serbia is approximately 6% comparing to other marketed medicine products from ATC group B;
- somatropin shows constant market share growth from 27.36% to 34.53% of all marketed products from ATC group H, from 2007 to 2011 respectively;
- as for filgrastim, the market share value is very low (approximately 2% throughout the analysed period) comparing to other marketed medicines of the same ATC group.

The small size of the biosimilar market in Serbia is additionally emphasised when compared with other large markets in Europe such as in Germany and France. In these markets, biosimilars have already achieved strong market share positions in terms of units sold. Currently, Germany and France account for half of the biosimilars market by value in the region with a 34% and 17% share respectively across Europe. Germany is the largest pharmaceutical market in Europe, with a history of high consumption of small molecule generics thus supporting a strong presence of the generic medicines industry; physicians and their patients accept and have confidence in generic/biosimilar medicines due to well-known company branding of generic/ biosimilar medicines. The systems of reference pricing and incentives for physicians to prescribe generics are well-established in Germany. Furthermore, there is a relatively high reimbursement price for marketed medicines in Germany, which motivates generics pharmaceutical companies to provide more resources and information to increase physician awareness of

competing therapeutic options of biosimilars; with regard to the high uptake of biosimilar epoetins, the implementation of quotas has played an effective role. France, for example, applies the same discounts on biosimilars as on generics, thus making the biomsimilars' price more or less equal to the brand-name's price (25).

As for the reimbursement policy in Serbia, the National Health Insurance Institution is trying to cut the costs for prescription medicines as much as possible, giving favour to generic medicines for every indication possible. Having in mind the clinical significance of approved innovative biotechnological products as well as the fact that only one biosimilar is approved in Serbia, all approved innovative biotechnological and biosimilar medicines in Serbia were placed on the last Positive Medicine List, which is approved and available from 25.12.2012. Various forms of epoetins are on List C, which is the list for medicines with special regime and with full reimbursement by National Health Insurance Institution; medicines with somatropin and filgrastim as INNs are on List A and List B respectively, for prescribed medicines for which patients pay only a symbolic participation price (50 RSD, equivalent to 0.5 EUR) (24).

6 CONCLUSION

Biosimilars have the potential of lowering prices and thus reducing the cost of treatments, improving access and reducing expenditures. Payers and reimbursing authorities have some tools to promote the uptake of biosimilars (e.g. to support the availability of information to doctors and patients on the effectiveness and safety of biosimilars, to provide incentives to doctors to prescribe biosimilars when this is an effective and safe option), although the scope for biosimilars penetration is relatively more limited than for conventional generics for technical reasons, e.g. the restricted substitutability and interchangeability of biosimilars and reference products. The future role of biosimilars in the biotech market looks, in principle, promising since the number of biological products reaching patent expiry in the coming years and the growing cost pressure will certainly create a sound basis for a promising development of biosimilars. They will certainly not produce reductions in the price of biological medicines when exclusivity periods expire in the same relative amounts that conventional generics do. Health authorities assume that biosimilars have the potential of lowering prices and thus reducing the pressures on pharmaceutical expenditure, as happens with generics in the small molecule medicines markets. The limited existing evidence suggests, however, that the relative rates of market share uptake and impact on prices are much lower for biological medicines than for small-molecule medicines. Although it has been constantly growing since 2007, by 2010 biosimilars had only a 15% market share of the aggregate products market. Relative high risk in research and development with high investment is accountable for lower price reductions, but given the high annual costs for originator biologicals, any price reduction will bring considerable savings.

In general, biosimilar medicines have enjoyed limited success in the EU to date. The market accessibility of biosimilars is inhibited by many factors: (1) the difficulties and expenses involved in manufacturing biosimilars; (2) the high cost of fulfilling regulatory requirements to obtain marketing authorisation; (3) the limited number of companies that are able to manufacture and commercialise biosimilars; (4) the brand loyalty of physicians and patients to reference biopharmaceutical medicine; (5) the prohibition against substituting a biosimilar for a reference biopharmaceutical medicine; (6) the life cycle management strategies of companies that are marketing reference biopharmaceutical medicines (e.g. developing second-generation reference biopharmaceutical medicines) (26).

Uptake of biosimilars in Europe is slowly increasing according to a new report published by the European Commission's Enterprise and Industry Directorate-General (27). Biosimilars still account for a relatively small segment of the EU pharmaceutical market, but they do have strong annual growth despite the fact that automatic substitution by pharmacists is not permitted in most countries. For the 12-month period from July 2010 to June 2011, biosimilars represented 19 million of a total market estimate of 175 million defined daily doses – approximately 11% by total patient volume. Although in Germany pharmacists may substitute a biosimilar, currently no country has explicitly authorised the substitution of biologicals from different manufacturers, and a number of EU Member States have gone as far as banning this practice.

The uptake of biosimilars also differed between different countries, with differences across European Member States being attributed to differences in national healthcare systems, structures and processes. Some issues that were seen to have an impact on biosimilars' uptake were:

- physicians' perception of biosimilars,
- patients' acceptance of biosimilars,
- local pricing and reimbursement regulations,
- procurement policies and terms.

Therefore, it is a general opinion that in order to increase the use of biosimilars in Europe it is essential that physicians and patients have a thorough understanding of biological medicines, including biosimilar medicines. This would then increase their confidence in using both biological and biosimilar therapies (27).

The Serbian national medicines authority and National Health Insurance Institute will try to strike an acceptable balance between the objectives of protecting patients' health and providing the industry with appropriate incentives for innovation on the one hand and the objectives of reducing treatment costs and ensuring sufficient incentives for the generics/biosimilars industry on the other. The biosimilars market in Serbia is small, struggling not only with physicians' and patients' low confidence in these types of medicines but also with a serious economic crisis that is reflected in the National Health Insurance Institute's inability to cover all costs. Therefore, it is justifiable to expect that the Serbian biosimilars market would not be able to keep up with the constant growth as in other EU Member States, since an additional burden on biosimilars manufacturers is repetition of authorisation procedures in Serbia as a non-EU Member State, even if the product has already been authorised in the EU.

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