KCE REPORT 199CS

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

BARRIERS AND OPPORTUNITIES FOR THE UPTAKE OF BIOSIMILAR MEDICINES IN BELGIUM - SYNTHESIS

SYNTHESIS

Belgian Health Care Knowledge Centre

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HEALTH SERVICES RESEARCH

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FOREWORD

Why the need for a KCE study on biosimilar medicines? Are they not simply the generics of biological medicines? Copies of hormones, growth factors or other molecules of biological origin that have lost their patent? Well no, things are not that simple. Clarifying this issue was one of the minister's aims when commissioning this study to the KCE.

Firstly, it was a matter of checking whether biosimilars can be regarded as equivalent to generic medicines. Already here, appearances – or perhaps one should say similarities – are misleading. Biological medicines are in fact complex molecules, consisting in particular of chains of dozens if not hundreds of amino acids, possessing intrinsically a degree of variation in their structure. This variability is also characteristic of their "copies". Biosimilars can therefore be slightly different to the original medicine. As a result, promoters of biosimilars probably encounter as many if not more difficulties in gaining acceptance for their equivalence and to gain market shares than was the case for generic medicines.

Secondly, as these products are mainly for hospital use, they face the same obstacles as generics encountered in penetrating this market. It is difficult to generalise, however, as each molecule has its own particularities and specific issues.

Finally, the market for biosimilars and generics is evolving rapidly and possesses great growth potential in the coming years.

Enough reasons for analysing the obstacles that have to date prevented biosimilars from generating the budgetary savings that have been expected. Many people generously shared their knowledge and expertise with our team of researchers and we would like to thank them very warmly for this. Their contribution was essential in clearing up some of the mysteries that seemed to surround this complex and fascinating field.

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Assistant Chief Executive Officer

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Chief Executive Officer

ABSTRACT

Context

Biologicals are produced using “living organism”. They are used for the treatment of chronic and life-threatening diseases such as cancer, multiple sclerosis and rheumatoid arthritis. Treatment with biologicals is usually expensive and represents ever-increasing pharmaceutical expenditures for the National Institute for Health and Disability Insurance (RIZIV – INAMI). The apparition of first biosimilars, i.e. biological “copies”, is seen as an opportunity to improve access to needed treatments at a lower cost for the third-party payer. Biosimilars are currently available in three product classes: Erythropoiesis-stimulating agents (epoetins), granulocyte-colony stimulating factors (filgrastim) and growth hormones (somatropin).

Uptake of biosimilars varies among countries. Compared to other European countries, the clinical use of biosimilars has been particularly low in Belgium and until today have not lead to substantial savings. The patent expiry of several blockbuster biologicals is imminent (especially the tumor necrosis factor alfa inhibitors).

Objectives and methods

This report includes a description of biosimilar uptake, price reduction and related savings for the third-party payer in Europe as well as a closer look at measures influencing biosimilar uptake in France, The Netherlands, Germany and Sweden.

For Belgium, a field screening was done based on semi-structured, face-to-face interviews with stakeholders involved in the use of current and future biosimilars (pharmaceutical companies, specialists, hospital pharmacists and concerned national authorities). Results and opinions were cross verified in a websurvey among specialists and chief hospital pharmacists.

International experience

Biosimilar uptake and price reduction vary among countries as well as among product classes. However, little reliable information on current and potential saving related to biosimilar uptake was available. Policy measures have been implemented in different countries to stimulate biosimilar uptake, but it still too early to assess their overall impact. Moreover, countries with no specific policies for biosimilars (such as

Sweden) have attained a large uptake. Consequently, biosimilar uptake seems to be related to the larger national context regarding pharmaceutical use: acceptability of less expensive alternatives, procurement policies for pharmaceuticals as well as general pricing and reimbursement policies.

Belgian experience

Different barriers that may hamper biosimilar uptake were identified for Belgium.

First, despite 20% to 34% price reduction compared to the list price of the reference product, biosimilars are not necessarily the least expensive alternative for the hospital. Indeed, direct negotiations between purchasers and providers may result in prices for reference products at substantially lower level. In addition to these discounts, clinical research in hospitals and continuing education of hospital pharmacists and physicians are also financed by the producers of reference products.

Second, the lack of knowledge or the distrust of biosimilars among specialists, and to a lesser extent among hospital pharmacists is also a barrier for use of biosimilars. There is a gap between the expectations surrounding current clinical data and the accessibility to or availability of "sufficient" clinical data. Lack of confidence by health care professionals in services provided by biosimilar companies (especially in terms of information) may also limit the use of biosimilars. In addition, lack of clear information on the use of biosimilars, originators and even on second-generation biological products for specific indications may lead the prescriber to stick to the product they are used to.

A broader problem

Low uptake of biosimilars in Belgium reflects the broader problem of pharmaceutical use in hospital settings, linked in particular to the lack of transparency of costs, discounts and other advantages. Although these gains constitute perfectly legal earnings and may well be used in meaningful ways within the hospital, it disturbs competition and may make it nearly impossible for the authorities to set appropriate and long-term cost-containment policies.

SYNTHESIS

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1. INTRODUCTION

To control pharmaceutical expenditures in Belgium, a number of policies for pharmaceuticals in both ambulant and inpatient settings have been implemented. Recent measures undertaken to curb expenditures include among others: higher price reductions for both pharmaceuticals within the reference price system and pharmaceuticals reimbursed for periods over 12 and 15 years and pharmacist substitution by less expensive alternatives for International Non-proprietary Name (INN) prescription and for antibiotic and antifungal prescriptions. It was also decided to claim a part of discounts granted by pharmaceutical companies to hospital pharmacies via a reduction of the hospital prospective budget for pharmaceuticals. It is within this context of need for cost-containment that the Minister of Social Affairs and Public Health introduced during the summer of 2012 measures that offer an incentive to use biosimilars in Belgium.

When appropriate from a medical point of view, biosimilars offer an alternative treatment to an already commercialized biological medicine at a lower cost for the third-party payer (see Box 1). Yet, Belgium has one of the lowest uptake rates in Europe of currently available biosimilars. Lack of current market penetration of commercialised biosimilars is seen by national authorities as a lost opportunity in terms of current savings as well as a barrier for future savings. Indeed, patent expiry of major blockbuster biologicals will create an opportunity for biosimilars in new product classes.

The Minister of Social Affairs and Public Health asked the KCE to identify reasons for the low uptake of biosimilars in Belgium. The scope of this report is limited to the analysis of barriers and policy measures relating to uptake of biosimilars in Belgium and abroad. We include a description of uptake, price reduction and related savings for the third-party payer in Europe as well as a closer look at measures influencing biosimilar uptake in France, The Netherlands, Germany and Sweden. For Belgium, we provide a description of pricing and reimbursement rules encompassing biosimilars as well as a field analysis of reasons leading to their low uptake. Appraisal of the regulatory approval pathway of biosimilars, including the requirements for clinical data, are out of scope. Effectiveness and safety of biosimilars are considered as implicit in this report and are a prerequisite to promote the use of biosimilars.

In analogy with the introduction of generics for chemical medicines, the expiration of patents for the first biologicals opened new hopes for affordable copies and increased competition. Given the different nature of the active substance included in biosimilars and generics, the European Medicine Agency (EMA) developed a separate market authorization (MA) procedure for biosimilars.

The most important part of the evaluation of a biosimilar in the European Union is the comparison of the product with the reference product in order to demonstrate that there is no significant difference between them, i.e. the comparability exercise. The aim of the comparability exercise is to demonstrate that the biosimilar and the reference product have similar profiles in terms of quality, safety and efficacy.

Box 1 – Definitions

Biological medicines (biologicals) contain a biological substance that is produced by or derived from a living organism.[1] The active substances of biologicals are usually larger and more complex than those of chemically derived medicines (non-biological medicine).

"A similar biological medicinal product, also known as "**biosimilar"**, is a product which is similar to a biological medicine that has already been authorised, the so-called "reference medicinal product". The active substance of a biosimilar medicine is a known biological active substance and similar to the one of the reference medicinal product. A similar biological medicinal product and its reference medicinal product are expected to have the same safety and efficacy profile and are generally used to treat the same conditions".[2]

A biosimilar is not a generic. The development process of a biosimilar is usually more complex than for a generic, which usually has a simpler chemical structure and is considered to be identical to the reference medicine.

Biosimilars should not be confused with biogenerics, non-comparable biologics, me-too or second-generation biologicals. Some biologicals marketed in countries such as China and India are often

referred as “biosimilars” without following the rigorous regulatory scrutiny used in Europe.

Me-too biologicals and second-generation biologicals are authorized through the normal full clinical development approval pathway for biologics, while biosimilars have a scaled down procedure. “Me-too biologicals” are approved after a pioneering (“first-generation”) product and are defined as comparable but not necessary clinically superior products. A second-generation biological achieves an improved clinical performance compared to a pioneering pharmaceutical (“first-generation”).[3]

A **therapeutic category** can include a reference-product (pioneering pharmaceutical), biosimilars and non-reference products (me-too biologicals and second-generation products).

2. AVAILABLE BIOSIMILARS IN EUROPE

The first biosimilar was approved in Europe in 2006. Biosimilars are currently available in three product classes: Erythropoiesis-stimulating agents (epoetins), granulocyte-colony stimulating factors (filgrastim) and growth hormones (somatropin) (see Table 1). There are five biosimilars for epoetin on the market which are produced by two different manufacturers. Seven biosimilars for filgrastim have obtained market authorization and are produced by three manufacturers. Two biosimilars for somatropin have obtained market authorization and are manufactured by different companies.

Table 1 – Biosimilars currently approved in the European Union

Product class	Reference product	Biosimilar	INN	MA holder	Manufacturer of active substance	MA date
Somatropin (Human growth factor)	Genotropin	Omnitrope	somatropin	Sandoz	Sandoz	12/4/2006
	Humatrope	Valtropin	somatropin	BioPartners	LG Life Sciences	12/4/2006, withdrawn 12/05/2012[1]
Epoetin (Treatment of anemia, increases red blood cell production)	Eprex	Retacrit	epoetin zeta	Hospira	Norbitec	18/12/2007
	Eprex	Silapo	epoetin zeta	Stada	Norbitec	18/12/2007
	Eprex	Abseamed	epoetin alfa	Medice	Rentschler Biotecnologie	28/08/2007
	Eprex	Binocrit	epoetin alfa	Sandoz	Rentschler Biotecnologie	28/08/2007
	Eprex	Epoetin alfa Hexal	epoetin alfa	Hexal (now Sandoz)	Rentschler Biotecnologie	28/08/2007
Filgrastim (Treatment of neutropenia)	Neupogen	Biograstim	filgrastim	CT Arzneimittel	Sicor Biotech	15/09/2008
	Neupogen	Filgrastim Ratiopharm	filgrastim	Ratiopharm (now Teva Generics)	Sicor Biotech	15/09/2008, withdrawn 20/07/2011[1]
	Neupogen	Ratiograstim	filgrastim	Ratiopharm (now Teva Generics)	Sicor Biotech	15/09/2008
	Neupogen	Tevagrastim	filgrastim	Teva Generics	Sicor Biotech	15/09/2008
	Neupogen	Nivestim	filgrastim	Hospira	Hospira Zagreb	08/06/2010
	Neupogen	Zarzio	filgrastim	Sandoz	Sandoz	06/02/2009
	Neupogen	Filgrastim Hexal	filgrastim	Hexal	Sandoz	06/02/2009

Source: Adapted from Minghetti (2011)[4] using official information from the European Medicine Agency (up to 29 January 2013). [1]Valtropin and Filgrastim Ratiopharm were voluntary withdrawn from the market. INN: International Non-proprietary Name. MA: market authorization. Brand names are written using an uppercase for the first letter of the word.

3. BIOSIMILARS IN THE BELGIAN CONTEXT

A brief overview of the context in which biosimilar competition takes place is presented hereafter. First, prescription in ambulatory care of low-cost alternatives includes generics but also reference products (brand pharmaceuticals) having reduced their price. National authorities decided to define low-cost prescription in this way to ensure savings for patients and the third-party payer. Second, in hospital settings, direct negotiations between purchasers (hospital pharmacists) and providers (pharmaceutical companies) lead in some cases to large discounts on list prices fixed by the authorities. Discounted prices are not disclosed, neither to the authorities nor among hospitals. As discounted prices are not known by all parties, the necessary conditions guaranteeing an open competition are lacking. In addition to discounts on list prices, clinical research in hospitals and continuing education of hospital pharmacists and physicians are also financed by the pharmaceutical sector. Whether this conflict of interest strengthens the loyalty of pharmacists, physicians and hospitals to reference products is an open question. We may hypothesize that biosimilars enter a difficult arena.

Box 2 – Key elements on the pricing and reimbursement system of pharmaceuticals in Belgium

Pricing and reimbursement procedures

The request for reimbursement for medicinal products in inpatient and outpatient settings follows the same pathway in Belgium. The Drug Reimbursement Committee (CTG – CRM) gives the final appraisal of the request for reimbursement for any pharmaceutical. The CTG – CRM appraisal report includes the reimbursement basis, the list price, the reimbursement category (patient share in the cost of care or "cost-sharing") as well as any specific conditions for patient reimbursement.

The reimbursement basis usually corresponds to the list price. Exceptions mainly concern pharmaceuticals included in the reference price system (RPS) and pharmaceuticals for which the reimbursement basis is calculated as a flat rate that may differ from the list price.

The reimbursement basis takes into account the added therapeutic value of the pharmaceutical. Therapeutic value is divided into three main classes.

Class 1 corresponds to pharmaceuticals for which the company claims an added therapeutic value and therefore, can claim a price premium.

Class 2 corresponds to pharmaceuticals which have an analogous therapeutic value with respect to another product (comparator), and their prices cannot exceed that of the comparator. Reimbursement requests for biosimilars have been filed in class 2 (see more details in section 3.2).

Finally, class 3 includes generics and copies. Prices of generics and copies must be reduced by at least by 31% (minimum mandatory reduction) with respect to the ex-factory list price of the reference product.

The reimbursement category reflects the therapeutic importance of the pharmaceutical and determines the patient share in the cost of care. A distinction in patient cost-sharing is made between vital pharmaceuticals for serious and long-term illnesses (category A and Fa), socially and medically useful pharmaceuticals (category B and Fb), and socially and medically less useful pharmaceuticals (category C, Cs and Cx). It should be noted that only for pharmaceuticals included in the category F (Fa and

Fb alike) the reimbursement basis corresponds to a flat rate per treatment. Currently, only epoetins are included in category F (see section 3.3 for details). For each of these categories patient cost-sharing is calculated as a percentage ("coinsurance") of the reimbursement basis limited to a fixed ceiling.

Reference Price System (RPS)

A reference price system limits the reimbursement for pharmaceuticals belonging to clearly defined "clusters" (groups) to the level of the reference price. Within each cluster, if the price of a pharmaceutical exceeds the reference price, the patient pays the difference (named "reference supplement"). In Belgium, a "generic reference price system" exists since 2001. Clusters include pharmaceuticals having the same active substance (reference products and generics independent of dosage and administration routes). The reference supplement is limited by a security margin of a maximum of 10.8 euros. Other countries have set a "therapeutic reference price system" where clusters include therapeutic equivalent pharmaceuticals which may have a different active substance.

Quota of low-cost prescription

Belgium has a policy of quota of low-cost prescription pharmaceuticals in ambulatory care. Before the summer of 2012 (see section 3.3 for the inclusion of biosimilars) "low-cost" prescription included chemical molecules when: (1) reference products (brand pharmaceuticals) for which a generic alternative exists and which reduced the list price so that patients do not have to pay the reference supplement, (2) generics and copies, (3) prescriptions under the International Non-proprietary Name (INN). Prescription quotas vary among different specialities and are monitored by the RIZIV – INAMI.

Reimbursement (invoicing) of pharmaceuticals in hospital settings

Broadly, invoicing of pharmaceuticals from hospitals to the third-party payer takes two forms. For pharmaceuticals integrated in the hospital prospective budget, the hospital retrospectively charges 25% of the reimbursement basis of each delivered pharmaceutical and receives a prospective lump sum allocation per inpatient admission. For pharmaceuticals not included in the hospital prospective budget, the hospital invoicing is based on the reimbursement basis taking into account the reimbursement category. Details on invoicing for biosimilars in hospital settings are provided in section 3.3.

Table 2 – RIZIV – INAMI expenses for selected biologicals (2011)

Group		ATC-5	INN	Euros	Pharmacy setting
Most expensive biologicals (Top 5)					
Monoclonal antibodies (anti-TNF)		L04AB04	Adalimumab	97 673 654	Community
Monoclonal antibodies (anti-TNF)		L04AA12	Infliximab	90 266 686	Hospital
Monoclonal antibodies (anti-HER2)		L01XC03	Trastuzumab	61 337 274	Hospital
Monoclonal antibodies (anti-TNF)		L04AB01	Etanercept	60 585 181	Community
Epoetin		B03XA02	Darbepoetin alfa	53 457 323	Hospital
Therapeutic class* where a biosimilar is available					
Epoetin	(long acting)	B03XA02	Darbepoetin alfa	53 457 323	Hospital
	(short acting)	*B03XA01*	*Erythropoietin*	*25 771 878*	*Hospital*
	(long acting)	B03XA03	Methoxy-polyethylenglycol-epoetin beta	13 883 347	Hospital
Somatropin		*H01AC01*	*Somatropin*	*19 512 592*	*Community*
		H01AC01	*Somatropin*	*108 254*	*Hospital*
Filgrastim	(long acting)	L03AA13	Pegfilgrastim	31 981 299	Hospital
	(long acting)	L03AA13	Pegfilgrastim	27 284	Community
	(short acting)	*L03AA02*	*Filgrastim*	*4 903 752*	*Hospital*
	(short acting)	*L03AA02*	*Filgrastim*	*447 358*	*Community*

*Source: RIZIV – INAMI data provisory for 2011. *Therapeutic classes include biosimilars, reference products and non-reference products (see Box 1 for definitions). In italics: molecules where a biosimilar is available. TNF: tumour necrosis factors. ATC: Anatomical Therapeutic Chemical. HER2: Human epidermal growth factor receptor-2*

3.2. Price and reimbursement for biosimilars in Belgium

Currently, companies producing biosimilars have submitted a marketing authorization application via the centralised procedure at the EMA. After obtaining market authorization, companies can file a reimbursement request to national pricing and reimbursement authorities. Requests for reimbursement for biosimilars follow the same pathway as any other pharmaceutical in Belgium. The current reimbursement framework does neither contain clauses determining the reimbursement basis nor a mandatory price reduction for biosimilars. All reimbursement claims for biosimilars have been filed under class 2 probably because requirements in class 1 or 3 do not encompass them. On the one hand, biosimilars cannot claim a therapeutic advantage over the reference product, therefore the request for reimbursement is not likely to be accepted in class 1. On the other hand, class 3 only includes generics and copies.

Table 3 presents information on pricing, market share and measures for biosimilars in Belgium. All reimbursement requests for biosimilars have included a voluntary price reduction. The price negotiations occur on a per case basis for each new biosimilar, in contrast to generics where a mandatory price reduction is fixed. Negotiations between authorities and biosimilar producers led to a price reduction ranging from 20% to 34% with respect to the price of the reference product. Not all available biosimilars are currently commercialized in Belgium. Until December 2012, six reimbursement request files were filed resulting in five positive decisions (Binocrit, Retacrit, Omnitrope, Zarzio, Tevagrastim) and in one negative decision (Nivestim). In 2011, uptake of biosimilars for epoetin and filgrastim was almost zero (less than 0.1% of total use as expressed in daily defined dosage (DDD)). A biosimilar for somatropin, mostly prescribed in community pharmacies, achieved a market penetration of 4.08% of total reimbursed DDDs. This percentage is lower than reported sales (6% in terms of DDD) available in the IMS data (see figure 1).

3.3. Measures to stimulate biosimilar uptake

In 2012, the Minister took a number of measures to increase the market share of biosimilars in Belgium. The objective was not only to generate savings for RIZIV – INAMI but also to ensure that the Belgian market remains interesting for companies that will offer biosimilars in new product classes. Measures to stimulate use of biosimilars included:

- **Inclusion of biosimilars in the quota for low-cost prescription in ambulatory settings.** Since 1 July 2012, the inclusion of biosimilars enlarges the initial framework of “low-cost” prescription quota. As a general rule, the system previously only included chemical molecules where a generic alternative is available. It should be noted that only the biosimilars themselves are now included in the low-cost prescription quota. A biological for which a biosimilar is available and which reduces its price to the level of the biosimilar is not included in the quota of low-cost prescription.
- **Inclusion of epoetin and somatropin in the hospital prospective budget.** Since 1 July 2012, the hospital prospective budget for pharmaceuticals also includes all epoetins (short- and long-acting) as well as all pharmaceuticals containing somatropin. Before this date, these pharmaceuticals were invoiced by the hospital to the RIZIV – INAMI based on actual consumption. Pharmaceuticals containing filgrastim (reference product and biosimilars) are not included in the hospital prospective budget.
- **Flat rate reimbursement for epoetins (category F).** Since 1 September 2012, all epoetins are also included in category F. The reimbursement basis for these pharmaceuticals (i.e. Aranesp, Binocrit, Eprex, Mircera, Neorecormon, Retacrit) is determined according to a flat rate per treatment. This flat rate was fixed according to the lowest reimbursement basis of the least expensive reference product having a biosimilar (Eprex) and covers prescriptions in inpatient and outpatient settings. A difference between the list price and the flat rate is in charge of hospitals. In general, the payment from the third-party payer to a hospital cannot exceed the reimbursement basis of a pharmaceutical. However, as an exception to this rule, from 1 February 2013, hospitals will receive this flat rate that is higher than the list price for the biosimilars Binocrit and Retacrit (i.e. reimbursement basis exceeds the list price for Binocrit and Retacrit).

Table 3 – Pricing, market share and measures for biosimilars in Belgium

Reference product	Biosimilar reimbursed since	Ministry decision[1]	Market shares in 2011		RIZIV – INAMI reimbursement	Measures for biosimilars		
		Price difference with RP*	DDD per product	% of total market[2]	Euro	Prospective budget	Flat reimbursement	Low-cost quota in ambulatory
Eprex	Binocrit, 01/2010	-30%	62	>0.1%	447	Yes	Yes	n.a.[3]
	Retacrit, 10/2010	-34%	0		0	Yes	Yes	n.a.[3]
Genotropin	Omnitrope, 04/2008	-22%	21 375	4.08%	318 560	Yes	No	Yes
Neupogen	Zarzio,01/2010	-20%	277	>0.1%	18 938	No	No	Yes
	Tevagrastim, 02/2010	-20%	71	>0.1%	5 516	No	No	Yes

Source:.[1] Ministerial Decisions (http://www.inami.fgov.be/drug/fr/drugs/decisions_report/decisions_minister/index.htm). DDD: daily defined dosage. [2] Percentage of market share is calculated as the number of DDD per biosimilar divided by total DDD per product class (including reference products and biosimilars). RP: Reference Product. [3] Does not apply as not sold in community pharmacies. RIZIV – INAMI data.

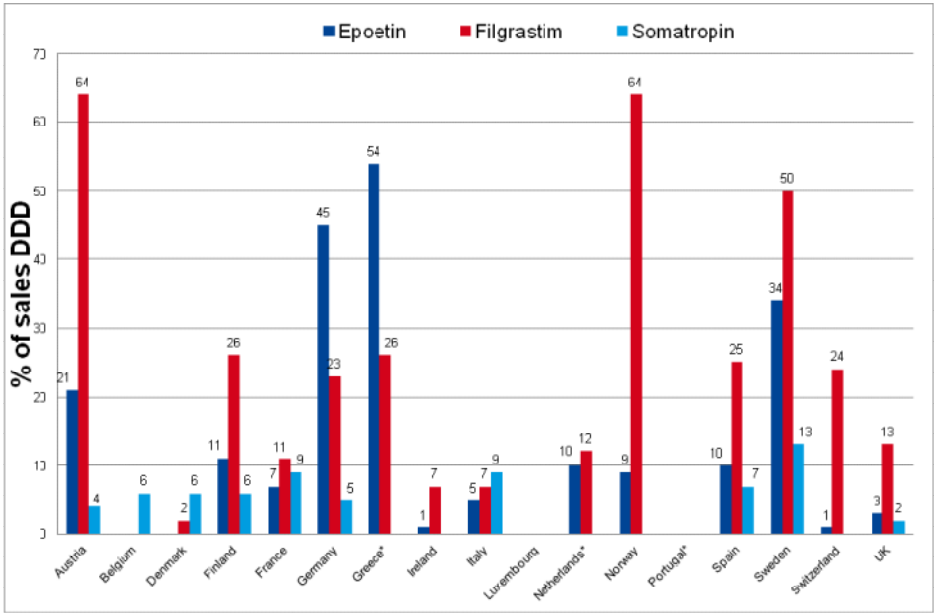
4. BIOSIMILARS IN AN INTERNATIONAL PERSPECTIVE

A structured literature review as well as an international comparison including three neighbouring countries (France, The Netherlands and Germany) and one country with a strong policy concerning generic use (Sweden), were performed to obtain information on current biosimilar uptake, price reduction and related savings for the third-party payer. The literature review and the international comparison were also used to obtain information on factors (barriers and measures) influencing biosimilar use. Information kindly provided by members of the EU project group "Market Access and Uptake of Biosimilars" was also included in this report[a].[5]

4.1. Uptake of biosimilars in Europe

Figure 1 presents IMS Health data on uptake of biosimilars among selected European countries. Market shares for biosimilars are calculated as a percentage of DDD in each product class. Product classes include biosimilars and reference products as well as me-too pharmaceuticals (second-generation products are excluded). Filgrastim biosimilars market shares are highest in Austria, Norway and Sweden. Uptake for epoetin biosimilars was highest in Germany, Greece and Sweden. The uptake of somatropin biosimilar is generally lower than for the other two product classes (filgrastim and epoetin). Highest uptake for somatropin biosimilars was found in Sweden, France and Italy. Belgium is lingering behind, with uptake only in one product class (somatropin).

Figure 1 – Percentage of sales of biosimilars per product class in total market (in DDD)



*Source: IMS data 2nd trimester 2011. *Only retail sector. DDD: Defined daily dose. Second-generation products are not included*

[a] The KCE had access to drafts to the Consensus Information Document: "What you need to know about Biosimilar Medicinal Products" with a Q & A for patients, physicians and payers.

4.2. How much price reduction and savings can be expected from the uptake of biosimilar?

Most evidence seems to point out that competition will lead to smaller reductions on list prices between the reference product and the biosimilar than is the case between generics and their reference products. This may particularly be true in countries such as the UK or Germany where prices may differ by up to 80% between the reference product and the generics. The lower price reduction between the reference product and the biosimilar has been attributed to a higher production cost as well as to the stronger need for marketing strategies for biosimilars than for generics. Moreover, high production costs may also result in fewer companies producing biosimilars and therefore also to less price competition.

Most empirical information concerning price reductions (as well as uptake) is based on IMS data. Reported price reductions of biosimilars with respect to the reference product usually range between 10% and 35%. However, the figures vary from country to country and between the different product classes. Mandatory price reductions have not been set in any country. Among the four countries studied in detail for this report, Sweden showed price reductions for epoetin and filgrastim exceeding the ranges reported elsewhere (up to 40% for epoetins and 50% for filgrastim). Data for Sweden comes from national authorities while for other countries the main data source is the IMS database. We cannot rule out that price reduction estimates are higher for Sweden compared to other countries because they are calculated using a different data source. From the three product classes where biosimilars are currently available, somatropin biosimilars feature the lowest price reduction (around 20%). It is noteworthy that only one biosimilar is available, providing some support to the hypothesis that fewer competitors may lead to lower price discounts.

The available estimates on biosimilar-related savings are based on different modelling strategies and hypotheses, making them difficult to compare. In addition, estimates for Europe mostly come from the pharmaceutical sector itself. Consequently, there is a lack of independent analyses of the current and future savings from the use of biosimilars.

4.3. Factors influencing biosimilar use

4.3.1. Physician prescription habits and loyalty to a reference product

In theory, as for all pharmaceuticals, physician prescription habits and loyalty to a product (incl. brand loyalty) may determine the choice between a biosimilar and the reference product. Biologicals are inherently different from generic copies of small molecule chemical medicines as they are in general larger and more complex. For biologicals, substitution during treatment tends only to be recommended under the supervision of a physician. In contrast, for small molecule chemical medicines having a generic alternative (with the exception of pharmaceuticals with a narrow therapeutic margin), substitution during treatment is accepted without the supervision of a physician. In several countries, generic substitution is left over to the pharmacist (automatic substitution). Therefore, when using a biological, a physician's loyalty to the reference product logically cannot be circumvented by policies such as automatic substitution or INN prescribing. Clearly, biosimilar market penetration will critically depend on their acceptability among physicians. But in order to become acceptable, a biosimilar should acquire the necessary trust among health care professionals and key opinion leaders with regard to their characteristics (effectiveness and safety).

4.3.2. Competition with second-generation products

Competition with second-generation pharmaceuticals (see Box 1 for a definition) may also influence biosimilar use. Second-generation pharmaceuticals may offer therapeutic advantages as compared to the reference product. As a result, potential uptake of biosimilars will be limited whenever second-generation products happen to be more widely used than the reference product (for which the biosimilar is available).

4.3.3. Policy decisions

Globally, the literature provides little or no evaluation of the effectiveness of policies aimed at influencing biosimilar uptake, which might be partly due to their relatively recent appearance. A survey conducted by the European Generic medicines Association (EGA) provides a listing of biosimilar-related policies put in place by national authorities. Details on the exact nature of the measures or on any form of evaluation are not available. According to the survey, policy measures typically include the instalment of quota for biosimilars and prescription target.

Our international comparison provided some additional details on the measures, which may influence biosimilar uptake. Yet, as the available information remains quite limited, we can only provide some hypotheses, to be verified by future research.

Noteworthy, in Sweden, uptake of biosimilars is amongst the highest in Europe, despite the lack of any specific policy to stimulate their uptake. A possible explanation is its history of high generic uptake, causing prescribers and other actors determining the choice of treatment options to be more open to adopt biosimilars.

4.3.3.1. Procurement policies

Gains in market shares for biosimilars may be linked to specific hospital pharmaceutical procurement policies, which usually differ from the ones in the outpatient sector. In hospitals, purchasers may have larger bargaining power and product selection may be negotiated with fewer suppliers. As a consequence, a company producing a reference product may provide large discounts, and biosimilars will need to compete against this discounted price and not against the list price, in order to be the least expensive alternative. As such, biosimilar companies should provide an even larger discount in absolute terms.

Public procurement at the regional or national level (such as in Sweden) could help to get more control on the uptake of biosimilars, a.o. because of the disconnection between the “individual” prescription habits of physicians and the procurement. Hence, the final choice of national or regional authorities will mainly depend on the most competitive offer from the side of the producers (biosimilar and reference product companies alike). Moreover, tenders at a national/regional level limit the number of actors discussing product characteristics (quality, safety and efficacy), discounts and concomitant (information) services and other benefits offered to hospitals and clinicians. When negotiations are conducted at a lower level (per hospital or per physician), biosimilar companies need to have these discussions with each purchasing agent. Unless biosimilar companies can enhance the trust in the effectiveness and safety of their products and are willing to provide the same fringe benefits as the reference product, we can hypothesise that in the current regulatory context, market uptake will remain low. Still, whether tenders at a national/regional level will facilitate competition for companies producing biosimilars remains to be proven.

4.3.3.2. Reimbursement policies for biosimilars

In a number of countries, there are fixed prices or reimbursement levels for specific drug categories. Examples are epoetins in Germany and all biologicals with a biosimilar in the Netherlands, via a reference price system. For filgrastim in Germany, there is a fixed additional reimbursement *(“Zusatzentgelte ZE40”* separate from the amount for pegfilgrastim*)* paid on top of the Diagnosis-Related Group (DRG) and all epoetins in France have a same “responsibility price” (*“tarif forfaitaire de responsabilité”*). These policies are not specific for biosimilars but come in an overall context of pharmaceutical expenditure reduction. Their overall impact will among others depend on the acceptability of the policy among prescribers. As of today, biosimilar uptake in the Netherlands is not particularly high for epoetin or filgrastim and is nil for somatropin. This may, however, be due to the fact that measures are quite recently implemented.

Our international comparison also showed that because biologicals and biosimilars are therapeutically important, patient cost-sharing is usually limited.

4.3.3.3. Specific quota for biosimilars: the German experience

From the four countries studied, only Germany has established quota (for epoetins) to promote biosimilar uptake in the outpatient setting. Its high uptake for epoetin biosimilars may in part be due to this quota, but also to the adoption of biosimilars by the biggest group of dialysis centres in Germany (KfH). Dialysis is provided in ambulatory centres and as such, prices for epoetins correspond to those fixed within the reference price system (RPS). The German policies for epoetins were implemented hand in hand with information campaigns and prescription guidelines. Physicians in the KfH were informed on biosimilar use in specific indications and on their impact on costs (transparency in prices). Therefore, we cannot but credit the combination of measures (instead of a single policy such as quota) with Germany's success with the uptake of epoetin biosimilars.

5. ACTORS, ROLES, AND POSITIONS IN BIOSIMILAR UPTAKE IMPROVING POLICIES IN BELGIUM

The reasons for the very low market penetration of approved biosimilars (in product classes epoetin, filgrastim and somatropin) in Belgium were investigated by means of confidential interviews with physicians, hospital pharmacists and managers, representatives of pharmaceutical companies and national pricing and reimbursement institutions and by means of a web survey (see Box 3). In addition, a stakeholder meeting was organised to present the results and draft recommendations arising from this study. As such, opposing and common positions were finally appraised and described to have a full view of the current situation.

In this study, the actual knowledge about biosimilars was not formally tested, and therefore it was not always possible to determine in how far the barriers mentioned during the interviews could be due to an insufficient or incorrect knowledge (e.g. understanding that requirements for market approval for biosimilars are more stringent than for generics). On the other hand, as we did not perform a scientific appraisal of the biosimilar pathway nor of clinical research questions on effectiveness, safety, and interchangeability of currently available biosimilars, we cannot reject nor subscribe the points of view expressed by the interviewees, even among well-informed ones.

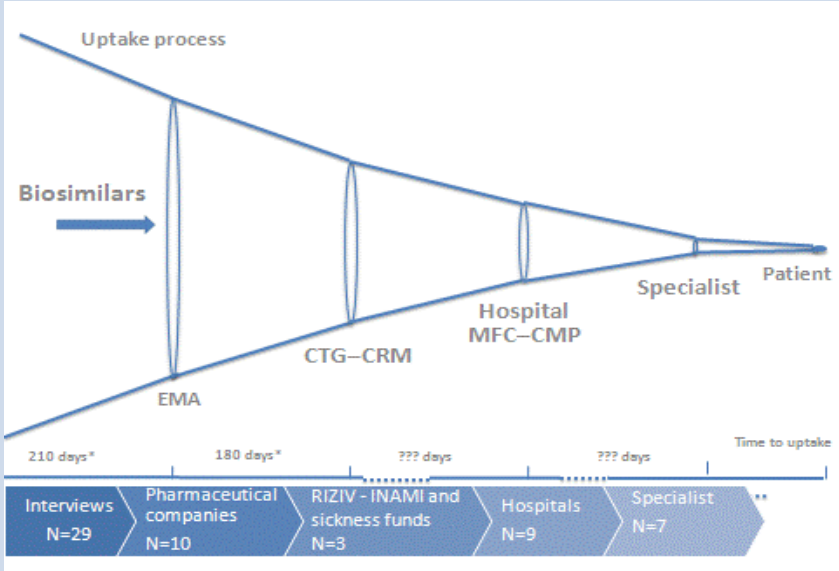
The reported reasons for the quasi absence of biosimilars in Belgium can be classified in two main categories:

1. Clinical barriers related to knowledge of and attitudes towards biosimilars.
2. Lack of financial incentives and services for hospitals, prescribers and patients.

Box 3 – Methods in brief

Face-to-face interviews

The sampling of key players for the face-to-face interviews aimed at including at least one representative of each main interest group involved in market access, dispensing or prescription of a biosimilar. Final sampling corresponds to the figure hereafter:



EMA: European Medicines Agency. CTG – CRM: Drug Reimbursement Committee. MFC – CMP: Pharmaceutical Therapeutic Committee

Web survey

The web survey aimed at quantifying findings from face-to-face interviews among chief hospital pharmacists or specialists with the collaboration of 8 scientific societies or professional associations: Hematological Society (BHS), Belgian Society of Medical Oncology (BSMO), Belgian Royal Society for Rheumatology (KBVR – SRBR), Groupement des néphrologues francophones de Belgique (GNFB), Nederlandstalige Belgische Vereniging voor Nefrologie (NBVN), Belgian Study Group for Pediatric Endocrinology (BSGPE), Vlaamse vereniging van ziekenhuisapothekers (VZA) and Association Francophone des Pharmaciens Hospitaliers de Belgique (AFPHB).

The link to the web survey was sent to 1 126 members of the scientific societies and professional associations and the final response rate was of 11.2% (126 respondents).

5.1. Clinical barriers

5.1.1. Lack of knowledge or confidence in efficacy and safety...

During the interviews, in particular with physicians, concerns either on safety or efficacy of the biosimilars or a combination thereof were mentioned as reason not to prescribe them. Their arguments, explaining the reluctance towards biosimilars, often reflect an insufficient or incorrect knowledge of the “biosimilar pathway”. For instance, less than 1 in 10 of the web survey participants correctly defined a biosimilar. But even interviewees with an expected broad knowledge on the biosimilar pathway still claimed that more evidence is needed with regard to the efficacy and safety of the currently available biosimilars. Even though, from a scientific point of view, some physicians acknowledge that all data requirements set by the EMA are met, the field experience shows that this does not fulfil the expectations of many physicians in Belgium. Clearly, uncertainty about the efficacy and the safety are the most often cited reasons not to prescribe biosimilars for physicians in the survey (59.2%).

5.1.2. … but less so for newly initiated treatments

In general, both physicians and hospital pharmacists mentioned in the interviews that biosimilars could be used for initiating a new treatment (naïve patients) without major safety or efficacy concerns. It should be noted that in the survey a higher percentage of pharmacist (82.2%) than of physicians (57.2%) were of the opinion that biosimilars could be used with no or minor safety and efficacy concerns among naïve patients. On the contrary, switching from the originator to a biosimilar molecule is an area of discussion, in particular among physicians. Only 42.9% of all respondents

reported that a patient could be switched to a biosimilar with no or minor safety and efficacy concerns.

5.1.3. Lack of available data or access to it

An important clinical barrier underlying the lack of trust among physicians is the alleged lack of clinical data supporting safe and effective use in specific indications or situations. Biosimilars prove clinical equivalence versus the reference product in one indication. Companies can – under certain pre-defined conditions – request an extrapolation to additional indications of the reference product without performing additional clinical trials. The extrapolation of data is based on the systematic comparability exercise (on preclinical and clinical level) and on relevant scientific and clinical argumentation. Yet, during the interviews it became clear that extrapolations to other indications were not always considered acceptable by physicians (e.g. use of filgrastim for stem cell mobilization in healthy individuals).

Another point that may in part explain the limited knowledge and trust concerning biosimilars is the lack of appropriate information dissemination channels. First, biosimilar companies acknowledge their reluctance to invest in marketing activities because, due to current market barriers, the expected gains are limited. Hospital pharmacists as well as physicians stated that an easily reachable, competent person who can provide accurate and relevant product information (for example similarities and differences with the reference product and interaction with other pharmaceuticals) is a prerequisite for complex medicines such as biosimilars. Biosimilars are more complex than generics, therefore there is a need for more information (for example on similarities and differences with the reference product and interactions). Likewise, it was mentioned that administration device differences (e.g. different injection pens) may need to be explained more fully. Hospital pharmacists as well as physicians clearly sense that biosimilar/generic companies do not offer enough support and information.

Biosimilar companies, and also some of the pharmacists, found that the information given on public websites (i.e. Federal Agency for Medicines and Health Products[b] (FAMHP)) was ambiguous or insufficient. Only 25 % of pharmacists and 9 % of physicians in the web survey cited FAMHP as source of information on biosimilars.

5.2. Barriers to enter the hospital market

Biosimilars meet specific barriers when trying to enter the hospital market and these barriers may be linked to each other. There are the physician prescription habits; there is the inherent complexity of the setting (with issues of safety, storage); and there is the current financing mechanism of pharmaceuticals. This financing mechanism is specific to the Belgian context. It encompasses direct negotiations between purchasers (hospital pharmacists) and providers (companies) which lead in some cases to large discounts on list prices fixed and reimbursed by the RIZIV – INAMI.

In the face-to-face interviews, respondents mentioned as factors determining the discount level: the size of the pharmaceutical basket purchased from one company, the volume purchased of a given pharmaceutical, and presence of competitors (me-too or second-generation alternatives) and the hospital characteristics (e.g. size of hospital, university hospital). Large discounts were also justified as part of a marketing effort aimed at steering prescription habits of opinion leaders in larger hospitals. Based on the interviews, we could estimate that hospital pharmacies in Belgium obtain on average 10 to 20% of discounts on the pharmaceutical products, including volume discounts. However, discounts can amount to as much as 75% for the reference product of some currently marketed biosimilars, making the biosimilars' lower list price (between -20% and -34%) unattractive from a hospital financing point of view.

[b] In French Agence Fédérale des Médicaments et des Produits de Santé (AFMPS) – in Dutch Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG).

While biosimilars could in principle also compete for market shares by granting large discounts in absolute terms, this is currently not the case. In contrast to the situation in France where the discounts obtained for expensive pharmaceuticals ("Spécialités pharmaceutiques prises en charge en sus des prestations d'hospitalisation – Liste limitative de medicaments onéreux") have to be split 50/50 between the health insurance and the hospital, in Belgium the hospitals fully benefit from the discounts, as the list prices remain the basis for RIZIV – INAMI reimbursement.

Larger hospitals argue that the prospective budget does not fully cover medication costs for severe pathologies and that these discounts compensate for this loss. Moreover, interviewees also argued that "benefits" at the level of the pharmacy were reinvested either to cover allegedly underfinanced expenditures within the pharmacy itself (e.g. continuing education of hospital pharmacists) or used to finance other services within the hospital.

In addition to the discounts, hospitals may receive funding for personnel (pharmacists, study nurses in oncology), for material or for educational services such as unrestricted educational grants for chairs, conference organization or attendance. The sponsoring pharmaceutical company will consider the total package of discounts and services to a hospital, while hospital management may not be aware of some of the direct services to the prescribing physicians. Although not all marketing approaches or services have (measurable) added values, some tools (e.g. off-label use programs, education of patients on disease and device use leading to higher compliance) which can be product-specific, are perceived by the interviewees as relevant for the physician/pharmacist and patients.

5.3. Impact of the recent policy measures

As the measures introduced by the Minister (detailed in section 3.2) date from less than one year before publication of this study, it might be too early to judge on their effective impact. The analysis performed in this report merely reflects the current views gathered during the face-to-face interviews on these policies, which should be evaluated more formally in the future.

During the interviews, the respondents were clearly of the opinion that these measures may fail to increase market shares for biosimilars in Belgium (see section 3.3 for a description of the measures).

- **Flat reimbursement (category F) and inclusion in the prospective budget of epoetins and higher reimbursement for biosimilars**

Introducing epoetins in the prospective budget and in category F may at first sight seem appropriate as a means to increase biosimilar uptake and obtain short-term cost savings for the third-party payer. However, in the way the measure is currently implemented, savings appear to arise from reducing the reimbursement basis of on-patent epoetins only, and not from an increase in biosimilar uptake. The higher reimbursement for biosimilars (not based on the list price but on the flat rate for category F) may fail to increase their uptake since physicians prefer the product they have experience with, in particular when both pharmaceuticals are equally expensive. In addition, because biosimilars and the reference product Eprex are reimbursed to the hospital at the same level, an increase in biosimilars manifestly cannot lead to savings for the third-party payer. Moreover, discounts received at the hospital pharmacy for the reference product may outpace gains from the increased reimbursement for biosimilars.

Category Fa seems a step closer to a "therapeutic reference price system" in which all products in a therapeutic class get the same level of reimbursement. However, several interviewees mentioned that a common reimbursement level for a whole therapeutic category is not acceptable without clear rules on how prices are fixed and without considering its impact on medical practice (and patient health). A therapeutic reference system could be envisaged if there are appropriate guidelines on the use of different pharmaceuticals in a class (as was done in Germany for epoetins) and issues surrounding interchangeability should be openly communicated to health care professionals and patients alike. This information must be provided by an independent body.

- **Introduction of somatropins in the prospective budget and inclusion in prescription quotas in ambulatory settings**

Introducing somatropin in the hospital prospective budget is likely to have only a limited impact on biosimilar uptake as these pharmaceuticals are mostly delivered in community pharmacies. Limited savings could arise from the enforcement of minimum biosimilar quota in ambulatory care for somatropin. However, for chronic illnesses, physicians will be reluctant to switch patients to new products, given the differences in dosage and the need to also swap to another injection device. In addition, including only biosimilars and not the reference product (if ever this would lower its price) in the low-cost prescription quota takes away the trigger of price competition for the reference product, and, consequently, an opportunity for savings for the third-party payer.

5.4. Impact of other forthcoming or potential measures

- **Public tender for pharmaceuticals in hospitals**

Other measures might also have an impact on biosimilar uptake. The forthcoming obligation to purchase by means of public tenders may lead to more transparency in prices. With public tenders the current indirect hospital financing through discount" becomes less straightforward. Yet it is not easy to forecast whether biosimilars and reference products will enter the same tender. This will depend on the tender selection criteria and on companies' ability to provide a competitive offer.

- **Quota for low-cost alternatives/biosimilars in hospital settings**

During the interviews, we also confronted the respondents with the hypothesis of setting prescription quota for the least expensive alternative for the third-party payer at the level of the hospital. It was felt that quota only for biosimilars would be discriminatory, not trigger competition per se and could even reinforce the passive marketing strategy of companies producing biosimilars. Moreover, if quota would be set for biosimilars only, reference product companies would have no incentive to reduce their prices. To effectively stimulate competition, quota may need to be defined in the same way as in ambulatory setting: low-cost prescription includes both biosimilars and reference products having reduced their price.

A quota system also needs to be accompanied by monitoring and appropriate financial incentives (or penalties). Still, with the current financing of pharmaceuticals in hospitals, it might well be that these financial incentives (or penalties) are outpaced by the gains from discounts on the reference products. In addition, such quota may add complexity to hospital financing and bar the normal selection of pharmaceuticals in public tendering procedures (e.g. should the quota be part of the tender?).

A key success factor in the implementation of quota would be to actively involve all partners in the design and fine tuning of the policy. Unless the prescribing physician has adequate guarantees on the safety and effectiveness of biosimilars and substitution, no single measure is likely to succeed. Therefore, a clear position and a communication plan explaining the rationale is needed. Involvement of stakeholders (pharmacist and specialist) preceding such measures would engage the community, could create ambassadors for the cause and increase adoption. In addition, reluctance among professionals could be addressed by increasing knowledge, spreading information or demanding extra information/trials from manufacturers or physicians when necessary, and generate any missing clinical data where needed.

6. CONCLUSION AND DISCUSSION

When studying the reasons for the poor uptake of biosimilars in the Belgian health care system and, more particularly, in the Belgian hospitals, it became clear that biosimilars are just an emblematic instance of a much broader problem afflicting a transparent hospital drug policy since decades. Indeed, in our system, direct negotiations between purchasers (hospitals) and providers (pharmaceutical companies) may result in prices for reference products at substantially lower level than the list prices of biosimilars. From the point of view of the third-party payer, biosimilars provide the least expensive alternative in terms of list prices. But despite 20% to 34% price reduction compared to the reference product, biosimilars are not necessarily the least expensive alternative from the point of view of the hospital.

As was the case ten years ago for generics, health care professional preference to stay with reference products may also be an important barrier to market penetration of biosimilars. Yet, biosimilars differ from generics in more than one respect, as their nature is more complex making substitution even less straightforward for a clinician. The services (including information services) and other advantages provided by reference product companies may reinforce current physician prescription habits.

In addition, hospitals assert that their financing depends partly on price discounts, which is more than likely also influencing the hospital pharmacist purchasing habits.

In view of this context, the recent policies to stimulate biosimilar uptake (category F, inclusion of biosimilars in low-cost prescription in ambulatory care, inclusion of epoetin and somatropin in the hospital prospective budget and increased reimbursement for biosimilars for the hospital) may fail to promote biosimilars in Belgium. This seems to confirm theoretical views that setting the incentives for the biosimilar and the reference product at the same level might not be enough to change physician prescription habits. The literature states that biosimilar companies may need to be active and set marketing strategies to make health care professionals aware of biosimilars and their advantages. This study confirms that, in the case of Belgium, health care professionals have had insufficient exposure to information on biosimilars, whether from biosimilar companies themselves or from other sources. All factors combined, it is not surprising that the market for biosimilars in Belgium has been limited up to today.

6.1. Information and clinical barriers

As the concept is relatively new, many actors may not have sufficient knowledge on “biosimilarity”. Information improving this knowledge needs to be openly and clearly provided to different target groups. The fact is that some specialists in Belgium are not satisfied with the current availability of clinical data proving the effectiveness and safety of biosimilars. More specifically, criticisms concerning the extrapolation of indications are a point that needs to be taken into account. Guidelines by EMA for such extrapolation are missing at the start of the development of a biosimilar medicine.

Although we found a wide consensus that additional data are needed, it was less clear who should provide them, and who should pay for it. Biosimilar companies argue that this would increase the price of biosimilars and make the biosimilar model unsustainable. While studies on safety and efficacy of biosimilars may actually exist, there is a lack of appropriate information dissemination. During the interviews, a majority of physicians and hospital pharmacists declared not having had a direct contact with or information from the companies producing biosimilars. This was further confirmed by biosimilar companies who acknowledged that the level of marketing activities was linked to expected gains. And although physicians as well as hospital pharmacists did not put in question the producers manufacturing capacity and quality aspects of the biosimilar, they report a lack of services and information provided by biosimilar companies (e.g. information about interactions).

6.2. Financing of pharmaceuticals in hospitals: a Pandora box for policy makers

During the interviews, all stakeholders agreed on one point: current financing of “expensive pharmaceuticals” in hospitals interferes with an open and transparent competition. According to pharmaceutical executives, the extent of discounts and other incentives to hospitals is larger in Belgium than abroad. Based on the information from the interviews, we estimate that this phenomenon accounts for 2 to 5% of the

overall hospital income, but this remains totally untransparant. Although none of the involved parties defend the system, discounts are generally regarded as an acquired right by the hospitals, who claim to depend on these discounts for their financing. As a consequence, they state that taking away this budget from the hospitals will need to be compensated, otherwise – they argue – most hospitals will suffer a substantial loss. Still according to the hospitals, government funding for the continuing education of hospital physicians and pharmacists will be insufficient if the additional resources from the discounts would be taken away. Clearly, competition on discounts rather than on list prices is one of the reasons explaining the limited penetration of biosimilars in Belgium.

Less clear is how to allow biosimilars to gain market shares. In the short term, policies aiming at increasing biosimilar uptake may help in "circumventing" the above-cited financial barriers. Not unexpectedly, the companies currently producing biosimilars are in demand of more policy measures to counter existing barriers to enter the market. Other actors, on the contrary, fear that such policies would bias the market, leading to unfair competition in favour of biosimilar producers.

Meanwhile, the policies introduced by the Minister during the summer of 2012 are far from being accepted by all involved parties. Moreover, current "biosimilar-related savings" for the third-party payer are not coming from an increase in their market share but only from the lower reimbursement of second-generation, on-patent products. The forthcoming mandatory public tendering in hospital pharmacy purchasing may reduce the untransparent discount-related competition for some pharmaceuticals. However, transparency on prices also needs to be obtained in situations where tenders will not be applied (e.g. below a certain threshold amount). By all means, policy measures which do not address the current discount-related barriers in the long term, will only build a weak bridge over a problem that lies down in deep waters.

But measures tackling the financial barriers will not be enough either to open the way for biosimilars, unless they also address the lack of appropriate information (dissemination of current data or collection of new data), and the concerns with respect to the loss of research funds or other services. Both official bodies and the scientific medical associations need to make very clear, possibly on a product-to-product basis, on the appropriateness of the extrapolation of indications or on product interchangeability. In addition, any decision should be followed by communicating and explaining these decisions in a clear and unbiased way to health care professionals.

6.3. Limitations and research agenda

The scope of the study was limited to the analysis of barriers as well as to policy measures determining biosimilar uptake in Belgium. We did not critically appraise the EMA regulatory pathway for biosimilars nor provide evidence on clinical research questions on effectiveness, safety, or interchangeability of biosimilars. More specifically, the barriers to a wider acceptance of biosimilars that were mentioned by physicians, i.e. the lack of information on the biosimilar pathway as well as doubts on safety and efficacy have not been further analysed, let alone validated. Moreover, we did not analyze either whether enough information or data on issues such as extrapolation of indications or safety during switching is available to clinicians. Health technology assessments (HTA) analyzing the safety, effectiveness and cost-effectiveness of specific biosimilars could improve their acceptability.

The study pointed out that discounts and other advantages interfere with open competition in hospital settings. The qualitative research methods used in this report did not aim at quantifying the phenomenon but at trying to have a grounded description on this reality. Future research is needed to fully evaluate the amount of discounts and the degree to which they interfere with competition. The overall impact of these financial advantages on hospital financing also needs to be assessed. In addition, an evaluation of how tenders could lead to more transparency in prices should be considered in an open discussion with all involved partners.

6.4. A look into the future

Expiry of market exclusivity of major biological blockbusters will likely be a main driver for future biosimilar industry. As was expressed during the interviews, biosimilars are already being developed by many leading "traditional" originator companies. Originator companies will probably produce biosimilars in new product classes (for instance mAb) and may have different marketing strategies towards health professionals than current biosimilar manufacturers. Whether these companies will use the same strategies for their innovator products and for biosimilars remains an

open question. Yet, we cannot but hypothesize that the existing trust in these companies may change the current perception of biosimilars and even the current biosimilar business model. Information is a key issue and in the future more and easier access to clinical data may open new markets for biosimilars.

Expectations on future savings related to forthcoming biosimilars are also a key driver for interest and concern by national authorities on their current market penetration. Belgian authorities are no exception to this rule. Lack of market penetration of the currently available biosimilars is seen as a lost opportunity, maybe less in terms of current savings than as a barrier for potential future savings.

REFERENCES

1. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ 28 november 2001 L 311
2. European Medicines Agency (EMA) Questions and answers: Similar-biological-product applications [2012 [cited 2013/01/15]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000529.jsp&mid=WC0b01ac0580533e0b
3. Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Narayanan G, et al. Biosimilars-why terminology matters. Nature Biotechnology. 2011;29(8):690-3.
4. Minghetti P, Rocco P, Del Vecchio L, Locatelli F. Biosimilars and regulatory authorities. Nephron. 2011;117(1):c1-7.
5. Project Group on Market Access and Uptake of Biosimilars. What you need to know about Biosimilar Medicinal Products. A consensus information document. Brussels: 2013. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/tor_biosimilars_en.pdf

RECOMMENDATIONS[c]

To the Federal Agency for Medicines and Health Products, FAMHP to the Belgian information center for pharmaceutical therapies (BCFI – CBIP), to Farmaka "non-profit organization", to the Network of Pharmaceutical therapeutic committees (MFC – CMP), to the National Council for Quality Promotion, to the health care industry:

- **Efforts should be made to increase information dissemination to health care professionals on biosimilars and the biosimilarity concept: the comparability exercise, safety and efficacy track record and pharmacovigilance requirements.**

To the Scientific Associations of health care professionals, to the National Council for Quality Promotion and to the College of Medical Doctors:

- **Besides dissemination of information on the biosimilarity concept, use of biosimilars for naïve patients and substitution during treatment needs to be explicitly addressed.**
- **Measures to stimulate use of biosimilars should not prevent the continued development and promotion of good clinical practice guidelines, as the potential savings based on well-targeted biopharmaceutical use (reference product, biosimilars and second-generation products) could even outpace savings from higher biosimilar use.**

To the Minister of Social Affairs and Public Health:

- **It should be envisaged to set measures to increase use in hospital settings of the least expensive alternatives (including biosimilars) for the third-party payer:**
  - **In the short-term, a quota system for hospitals could be set after discussion with all involved partners. Requirements for this system should converge to those defined for the current system of "low-cost pharmaceuticals". Minimum requirements for implementation of quotas are:**
    - **applicable to naïve patients**
    - **defined per hospital**
    - **accompanied by guidelines for appropriate use of pharmaceuticals**
    - **enforced by appropriate financial incentives or penalties**
  - **In the short-term, pharmaceutical companies, hospitals and clinicians should be enforced to make public the discounts, advantages and services granted by the health**

[c] The KCE is the only responsible for the recommendations given to the public authorities.

care industry.

- **In the medium-term, alternative modes of financing for pharmaceuticals in hospital settings should be studied in order to reform the reimbursement of pharmaceuticals in particular for those excluded from the hospital prospective budget.**
  - **The reimbursement from the RIZIV – INAMI should reflect prices paid and other advantages received by hospitals.**
  - **Savings from these policy measures should be in part reinvested to fund continued education of physicians/clinical pharmacists and to fund clinical research in hospitals.**

To the European Medicines Agency (EMA) and to the health care industry:

- **The KCE supports the EMA position with respect to clinical-trial transparency. The proactive EMA policy of full disclosure of clinical trials should be pursued, and should ensure an easy access to the clinical-trial results.**

To universities:

- **Information on biosimilars and the biosimilarity concept and on economical prescribing should be included in health care professional curriculum.**