KCE REPORT 199

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

KCE REPORT 199
HEALTH SERVICES RESEARCH

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

ISABELLE LEPAGE-NEFKENS, SOPHIE GERKENS, IMGARD VINCK, JULIEN PIÉRART, FRANK HULSTAERT, MARÍA ISABEL FARFAN-PORTET

2013 www.kce.fgov.be

COLOPHON

Title:	Barriers and opportunities for the uptake of biosimilar medicines in Belgium
Authors:	Isabelle Lepage-Nefkens, Sophie Gerkens, Imgard Vinck, Julien Piérart, Frank Hulstaert, María-Isabel Farfan-Portet
Reviewers:	Carine Van de Voorde, Germaine Hanquet, Christian Léonard, Raf Mertens
External experts:	Bruno Flamion (Université de Namur), Serge Van Praet (CHU Saint-Pierre), Luc Hutsebaut (LCM)
Acknowledgements:	Claudia Barth (Kuratorium für Dialyse und Nierentransplantation), Gustaf Befrits (Tandvårds- och läkemedelsförmånsverket (TLV)), Irene Kraemer (Johannes Gutenberg–Universität Mainz), Arnold Vulto (Erasmus Medical Centre, Rotterdam), Roland Windt (Universität Bremen), To the scientific associations that sent the link to the web survey: Dominique Wouters (Association Francophone des Pharmaciens Hospitaliers de Belgique (AFPHB)), Luc De Clercq (Belgian Royal Society for Rheumatology (KBVR – SRBR)), Jacques De Grève (Belgian Society of Medical Oncology (BSMO)), Sylvie Tenoutasse (Belgian Study Group for Pediatric Endocrinology (BSGPE)), Jean-Michel Pochet (Groupement des néphrologues francophones de Belgique - GNFB), Yves Beguin (Hematological Society - BHS), Bart De Moor (Nederlandstalige Belgische Vereniging voor Nefrologie (NBVN)), Thomas De Rijdt (Vlaamse vereniging van ziekenhuisapothekers (VZA)), and to all persons who participated in the face-to face interviews and in the websurvey.
External validators:	Francis Colardyn (UZ Gent), Jaime Espin (EASP- Spain), Steven Simoens (KU Leuven)
Stakeholders:	Jean Bury (Santhea), Rudy De Cock (Pfizer), Karen De Smet (FAGG – AFMPS), Patrick Durez (SRBR), Eric Gheuens (NBVN), Julie Gusman (Merck), Anne Hendrickx (Cabinet du Ministre Laurette Onkelinx), Marleen Hoebus (Amgen), Michel Jadoul (GNFB), Philipe Jorens (RUZB), Myriam Nechelput (Roche), Leo Neels (Pharma.be), Dominique Petit (Sandoz), François Sumkay (ANMC), Sylvie Tenoutasse (BSGPE), Joris Van Assche (Febelgen), Robert Vander Stichele (BCFI), Chris Van Hul (OZ), Luc Van Oevelen (Janssen), Dirk Verschueren (Hospira),
Other reported interests:	Membership of a stakeholder group on which the results of this report could have an impact: Joris Van Assche (Febelgen vzw, representative of biosimilars in the Belgian market. Members: Sandoz, Teva en Hospira), Owner of subscribed capital, options, shares or other financial instruments: Eric Gheuens (NBVN) (owner of action from J&J – Janssen Pharmaceutica), Luc Van Oevelen (employee by Janssen), Rudy De Cock (employee by Pfizer) Fees or other compensation for writing a publication or participating in its development: Rudy De Cock (employee by Pfizer) A grant, fees or funds for a member of staff or another form of compensation for the execution of research: Joris Van Assche (Febelgen vzw, representative of biosimilars in the Belgian market. Members: Sandoz, Teva en

	Hospira), Rudy De Cock (employee by Pfizer), Michel Jadoul (GNFB – research funds from different pharmaceutical firms: Amgen, Janssen) Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Joris Van Assche (Febelgen vzw, representative of biosimilars in the Belgian market. Members: Sandoz, Teva en Hospira), Luc Van Oevelen (Janssen), Rudy De Cock (employee by Pfizer), Julie Gusman (Merck – company of originator pharmaceuticals), Michel Jadoul (GNFB – consultant), Myriam Nechelput (employee by Roche), Marleen Hoebus (employee by Amgen – company of originator biopharmaceuticals) Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Eric Gheuens (NBVN – participation in medical conferences: Janssen, Roche), Patrick Durez (SRBR – speaker fee: BMS, Roche, Abbott, MSD, UCB, Pfizer), Michel Jadoul (GNFB) Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Joris Van Assche (Febelgen vzw, representative of biosimilars in the Belgian market. Members: Sandoz, Teva en Hospira) Any other direct or indirect relationship with a producer, distributor or healthcare institution that could be interpreted as a conflict of interests: Leo Neels (Pharma.be, association of pharmaceutical originator companies), Rudy De Cock (employee by Pfizer), Julie Gusman (Merck – company of originator pharmaceuticals), Myriam Nechelput (employee by Roche), Marleen Hoebus (employee by Amgen – company of originator biopharmaceuticals), Serge Van Praet (CHU Saint-Pierre – negotiation of pharmaceuticals in a hospital)
Layout:	Ine Verhulst, Sophie Vaes
Disclaimer:	**The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** **Finally, this report has been approved by common assent by the Executive Board.** **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**
Publication date:	28 March 2013

Domain: Health Services Research (HSR)

MeSH: Biosimilar Pharmaceuticals; Reimbursement Mechanisms; Cost Savings; Economics, Hospital

NLM Classification: QV241

Language: English

Format: Adobe® PDF™ (A4)

Legal depot: D/2013/10.273/13

How to refer to this document? Lepage-Nefkens I, Gerkens S, Vinck I, Piérart J, Hulstaert F, Farfán-Portet M-I Barriers and opportunities for the uptake of biosimilar medicines in Belgium. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). 2013. KCE Reports 199. D/2013/10.273/13.

This document is available on the website of the Belgian Health Care Knowledge Centre.

TABLE OF CONTENTS

1. INTRODUCTION 18
1.1. BACKGROUND 18
1.2. RESEARCH QUESTIONS AND SCOPE OF THE STUDY 18
1.3. STRUCTURE OF THE REPORT 19
2. DEFINITIONS 19
2.1. BIOLOGICAL MEDICINES 19
2.1.1. Definition 19
2.1.2. Biologicals versus small molecule chemical pharmaceuticals 19
2.1.3. Me-too biologicals and biobetters 20
2.2. BIOSIMILARS 21
2.2.1. Definition 21
2.2.2. Current available biosimilars 22
3. REGULATORY FRAMEWORK FOR THE EUROPEAN UNION 25
3.1. MARKET AUTHORIZATION OF BIOLOGICALS 25
3.1.1. Pharmacovigilance and the risk management plan 25
3.1.2. Comparability exercise for changes in manufacturing procedures 26
3.2. MARKET AUTHORIZATION OF BIOSIMILARS 27
3.2.1. Legal biosimilar approval pathway 27
3.2.2. The biosimilar paradigm and the comparability exercise for biosimilars 28
3.2.3. From bench to approval 28
3.2.4. Guidelines for comparability exercise 29
3.2.5. Product class-specific guidelines 30
3.2.6. Pharmacovigilance requirements are the same for all biologicals 31
3.2.7. Extrapolation to other indications and route of administration 32
3.2.8. Interchangeability and substitution 34
3.3. EMA GUIDELINES AND FDA DRAFT GUIDELINES: MAIN DIFFERENCES 36
4. BIOSIMILARS IN THE BELGIAN CONTEXT 38

4.1. REIMBURSEMENT PATHWAY 38
4.2. FUNCTIONING AND REIMBURSEMENT OF PHARMACEUTICALS DISPENSED BY THE HOSPITAL PHARMACY 39
4.3. CHANGES IN PROCUREMENT POLICIES IN HOSPITAL SETTINGS: FROM DIRECT NEGOTIATIONS TOWARDS PUBLIC TENDERING 40
4.3.1. Procurement of pharmaceuticals, the hospital pharmaceutical formulary and the pharmaceutical and therapeutic committee 40
4.3.2. Public procurement of pharmaceuticals 41
4.3.3. Possible impact of the public procurement for pharmaceuticals 42
4.4. PHARMACEUTICAL EXPENDITURES AND COST-CONTAINMENT POLICIES IN BELGIUM 43
4.4.1. Recent evolution of pharmaceutical expenditures for the third-party payer 43
4.4.2. Recent policies aiming at reducing pharmaceutical expenditures 46
4.5. BIOSIMILAR PRICING AND REIMBURSEMENT PROCEDURE 48
4.6. BIOSIMILAR UPTAKE AND EXPENDITURES 49
4.7. MEASURES FOR BIOSIMILARS 52
4.7.1. Policy measures to stimulate biosimilar uptake 52
4.7.2. Intercheangeability and substitution 54
5. IMPACT OF BIOSIMILARS ON THE HEALTH CARE SYSTEM 54
5.1. METHODS 54
5.2. CHARACTERISTICS OF BIOSIMILARS MARKET 55
5.2.1. Theoretical models for biosimilar competition 55
5.2.2. Procurement policies 56
5.2.3. Production cost and marketing strategies 56
5.2.4. Competition and second generation pharmaceuticals 56
5.3. AVAILABLE EMPIRICAL DATA ON PRICE REDUCTIONS, UPTAKE AND SAVINGS 57
5.3.1. Reported price reductions 57
5.3.2. Uptake in DDDs per molecule 57
5.3.3. Savings for the third-party payer 58
5.4. AVAILABLE INFORMATION ON MEASURES AIMING AT INCREASING UPTAKE OF BIOSIMILARS 58

6. INTERNATIONAL COMPARISON OF POLICIES STIMULATING BIOSIMILAR UPTAKE 60
6.1. INTRODUCTION AND METHOD 60
6.2. RESULTS AND DISCUSSION 60
6.2.1. Marketed biosimilars 60
6.2.2. Price differences between countries 62
6.2.3. Physician incentives and constraints 62
6.2.4. Pharmacist incentives and constraints 65
6.2.5. Patient incentives and the reference price system 67
6.2.6. Hospital incentives and constraints 68
6.3. CASE STUDY: POLICIES FOR EPOETIN BIOSIMILAR IN GERMANY 70
7. USE OF BIOSIMILARS, ADVANTAGES AND BARRIERS: A STAKEHOLDER PERSPECTIVE ... 73
7.1. METHODS 73
7.1.1. Face-to-face interviews 73
7.1.2. Web survey 75
7.2. BARRIERS FOR BIOSIMILAR UPTAKE 76
7.2.1. Knowledge and perceptions 77
7.2.2. Attitude 79
7.2.3. Environmental factors 82
7.3. SWOT ANALYSIS FOR MAIN POLICY INTERVENTIONS 84
7.3.1. Recently introduced measures 84
7.3.2. Planned measures 87
7.3.3. Measures to be considered 89
7.4. STAKEHOLDERS MEETING: OPPOSING AND COMMON POSITIONS 91
7.4.1. Is there a need for policy interventions for biosimilars? Free market versus intervention for biosimilars 91
7.4.2. Financing of pharmaceuticals in hospital settings 91
7.4.3. Questions on data and information on biosimilars (and other biologicals) 91
7.4.4. Limits of the KCE study 92
8. SUMMARY, CONCLUSION AND DISCUSSION 92
8.1. BACKGROUND 92

8.2. FACTORS DETERMINING BIOSIMILAR UPTAKE: A LITERATURE REVIEW 93
8.3. EVIDENCE ON UPTAKE AND POLICY FOR BIOSIMILARS IN EUROPE 94
8.4. RESULTS FROM THE INTERNATIONAL COMPARISON: GERMANY, FRANCE, THE NETHERLANDS AND SWEDEN 94
8.5. ACTORS, ROLES, AND POSITIONS IN THE IMPLEMENTATION OF FEDERAL POLICIES AIMED AT IMPROVING BIOSIMILAR UPTAKE IN BELGIUM 95
8.5.1. Clinical barriers 96
8.5.2. Lack of financial incentives and other services for the hospital and physicians 97
8.5.3. Policy analysis based on interviews: why recent biosimilar policies do not increase their uptake 98
8.6. LIMITATIONS AND RESEARCH AGENDA 100
APPENDIX 1. ADDITIONAL INFORMATION FROM A REGULATORY PERSPECTIVE 101
APPENDIX 2. REIMBURSEMENT OF PHARMACEUTICALS 103
APPENDIX 2.1. REMUNERATION OF WHOLESALERS AND PHARMACISTS 103
APPENDIX 2.2. REIMBURSEMENT BASIS AND COST-SHARING FOR PHARMACEUTICALS DELIVERED IN COMMUNITY PHARMACIES 104
APPENDIX 2.3. REIMBURSEMENT BASIS AND COST-SHARING FOR PHARMACEUTICALS DISPENSED BY THE HOSPITAL PHARMACY 105
APPENDIX 3. PUBLIC PROCUREMENT 108
APPENDIX 3.1. DIFFERENT PROCEDURES FOR PUBLIC PROCUREMENT 108
APPENDIX 3.2. SELECTION CRITERIA AND AWARD CRITERIA 109
APPENDIX 3.3. PUBLICATION IN BELGIUM OR IN EUROPE 110
APPENDIX 4. INFORMATION ON THE STRUCTUED LITERATURE REVIEW 112
APPENDIX 5. INTERNATIONAL COMPARISON 114
APPENDIX 5.1. REFERENCES PER COUNTRY 114
APPENDIX 6. FACE-TO-FACE INTERVIEWS 116
APPENDIX 6.1. INFORMATION ON METHODOLOGY USED FOR THE SEMI-STRUCTURED QUESTIONNAIRES 116
APPENDIX 6.2. QUESTIONNAIRE FOR HOSPITAL PHARMACIST 118
APPENDIX 6.3. QUESTIONNAIRE FOR INTERVIEWS FOR SICKNESS FUNDS 118
APPENDIX 6.4. QUESTIONNAIRE FOR INTERVIEWS FOR PHYSICIANS 119

APPENDIX 6.5. QUESTIONNAIRE FOR INTERVIEWS FOR PHARMACEUTICAL COMPANIES 120
APPENDIX 6.6. QUESTIONNAIRE FOR INTERVIEWS FOR HOSPITAL DIRECTORS 120
APPENDIX 7. WEB SURVEY 122
APPENDIX 7.1. QUESTIONNAIRE 122
APPENDIX 7.2. RESPONSE RATE 125
APPENDIX 7.3. RESULTS 126

LIST OF FIGURES

Figure 1 – Percentage of sales in DDD of biosimilars on total market (biosimilars, reference product and non reference product) 58
Figure 2 – Biosimilar uptake process and decision makers involved 73
Figure 3 – Biosimilar uptake process and key players included in face-to-face interviews 74
Figure 4 – Flow chart for studies used in the structured literature review 113

LIST OF TABLES

Table 1 – Biosimilars currently approved in the EU (situation on 29 January 2012) 23
Table 2 – Differences between EMA and FDA guidelines for biosimilars 37
Table 3 – RIZIV – INAMI Pharmaceutical expenses in community and hospital pharmacies 2005-2010 (in million euros) 44
Table 4 – Top 20 pharmaceutical expenses (in €) for RIZIV – INAMI 45
Table 5 – Information on therapeutic class, pricing and market share for available biosimilars in Belgium 48
Table 6 – DDD and RIZIV – INAMI expenses for all available epoetins in Belgium 49
Table 7 – DDD and RIZIV – INAMI expenses for filgrastim (biosimilar and reference product) as well as for pegfilgrastim 50
Table 8 – DDD and RIZIV – INAMI expenses for somatropin (biosimilar and reference product) 51
Table 9 – Prices and reimbursement basis for different erythropoietin 53
Table 10 – Measures to stimulate biosimilar uptake in selected Member States and EEA countries 59
Table 11 – Products admitted for reimbursement in a selected number of countries 61
Table 12 – Price reductions between the reference product and biosimilar prices 62
Table 13 – Prescription conditions/guidelines 63
Table 14 – Measures for physicians potentially influencing biosimilar prescription in outpatient settings 64
Table 15 – Measures for pharmacists potentially influencing biosimilars dispensing 66
Table 16 – Measures for the patients concerning outpatient pharmaceuticals 67
Table 17 – Hospital financing for inpatient pharmaceuticals (for biological products having a biosimilar) 68
Table 18 – Other measures in hospitals possibly influencing biosimilar prescription 69
Table 19 – Erythropoiesis-stimulating active substances: minimal prescription quotas and actual DDD in 2010 (for Barmer GEK) 72
Table 20 – Response rate to the web survey on biosimilars 75
Table 21 – Barriers for biosimilar uptake at the different levels of the uptake process 76

Tables in the Appendix

Table 22 – EMEA Guidelines for biosimilars 101
Table 23 – Community pharmacy and wholesaler margins 104
Table 24 – Cost-sharing mechanisms in community pharmacies 104
Table 25 – Cost-sharing mechanisms for outpatient pharmaceuticals dispensed by the hospital pharmacy . 106
Table 26 – Cost-sharing mechanisms for inpatient pharmaceuticals 107
Table 27 – Thresholds for procedures for the purchase of pharmaceuticals 110
Table 28 – Search strategy 112
Table 29 – Sample of face-to-face interviews among health care providers 116
Table 30 – Main issues covered during the face-to face interviews 117
Table 31 – Response rate to the web survey on biosimilars 125
Table 32 – Setting of respondent (per specialty) 126
Table 33 – Knowledge of the definition of a biosimilar (per specialty) 126
Table 34 – Attitude on using a biosimilar to start a new treatment (i.e. primary substitution) (per specialty) . 127
Table 35 – Attitude on using a biosimilar to switch a treatment (i.e. secondary substitution) (per specialty) . 127
Table 36 – Summary of results for primary and secondary substitution 128
Table 37 – Awareness of biosimilar on hospital formulary (per specialty) 128
Table 38 – Biosimilars prescription habits (per specialty) 129
Table 39 – Attitude on the importance of biosimilars (per speciality) 129
Table 40 – Reasons not to prescribe a biosimilar (per specialty) 130
Table 41 – Summary: Reasons not to prescribe a biosimilar (percent of respondents of specialty who checked that reason) 131
Table 42 – Interventions to increase the uptake of biosimilars 132
Table 43 – Summary of interventions to increase the uptake of biosimilars 133
Table 44 – Lump sum to increase the uptake of biosimilars 133
Table 45 – Effectiveness of quota at hospital level to increase the uptake of biosimilars 134
Table 46 – Effectiveness of quota at prescriber level to increase the uptake of biosimilars 134
Table 47 – Main source(s) of information on biosimilars 135
Table 48 – Subjects around biosimilars on which more information is requested 136

LIST OF BOXES

Box 1 – Examples of biologicals 20
Box 2 – Definition data exclusivity 27
Box 3 – Opening a possibility for global development 28
Box 4 – Selecting appropriate endpoints 29
Box 5 – Examples of specific points for clinical efficacy studies per product class 31
Box 6 – Differences EU versus USA 38
Box 7 – Success factor biosimilar market penetration in Germany 71

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADA	Anti-drug antibody
ANDA	Abbreviated New Drug Application
ATC	Anatomical Therapeutic Chemical classification
BFM – BMF	Budget of Financial Means – Budget Financiële Middelen (BFM) – Budget des Moyens Financiers (BMF)
BMWP	The Biosimilar Medicinal Products Working Party
CHMP	Committee for Medicinal Products for Human Use
BCFI – CIBP	Belgian Centre for Pharmacological Information – Belgisch Centrum voor Farmacotherapeutische Informatie – Centre Belge d'Information Pharmacothérapeutique
CTG – CRM	Drug Reimbursement Committee – Commissie voor Tegemoetkoming Geneesmiddelen – Commission de Remboursement des Médicaments
CTD	Common technical document
DNA	Deoxyribonucleic acid
EEA-EFTA	The European Economic Area: unites the 27 EU Member States and the three EEA EFTA States (Iceland, Liechtenstein, and Norway) into an internal market governed by the same basic rules
EGA	European Generic Association
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPO	Erythropoietin = epoetin
EU	European Union

FAMHP – FAGG – AFMPS	Federal Agency for Medicines and Health Products – Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten – Agence Fédérale des Médicaments et des Produits de Santé
FDA	Federal Drug Agency
G-CSF	Granulocyte colony-stimulating factor
IFPMA	International Federation of Pharmaceutical Manufacturers Associations
IGES	IGES Institut
RIZIV – INAMI	National Institute for Health and Disability Insurance – Rijksinstituut voor Ziekte- en Invaliditeitsverzekering – Institut National d'Assurance Maladie-Invalidité
MA	Market Authorization
MAA	Market Authorization Application
mAb	Monoclonal antibodies
MPA	Medical Products Agency - Sweden
PASS	Post-authorization Safety Studies
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan
PR	Preferential Reimbursement
PRAC	Pharmacovigilance Risk Assessment Committee
RAC	Risk Assessment committee
PSUR	Periodic Safety Update Report
PTC – MFC – CMP	Pharmaceutical Therapeutic Committee – Medisch-farmaceutisch comité – Comité médico-pharmaceutique

RB	Reimbursement basis
RMP	Risk management plan
RNA	Ribonucleic acid
RP	Reference product
SEB	Subsequent Entry Biologics
SPC	Summary of Product Characteristics
US	United States

GLOSSARY

TERM	DEFINITION	SOURCE
Active Ingredient	Ingredient that alone or in combination with one or more other ingredients is considered to fulfil the intended activity of a pharmaceutical. Also called: Active substance, compound, active pharmaceutical ingredient.	PHIS glossary
Automatic substitution	Refers to the practice whereby a health care provider, usually a pharmacist is obliged to dispense one medicine instead of another equivalent and interchangeable medicine due to national or local requirements.	Rovira *et al*. [1]
Bioavailability	The rate and extent to which the active ingredient or active moiety is absorbed from a medicinal product and becomes available at the site of action.	EMA glossary
Bioequivalence	The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of action when administered at the same molar dose under similar conditions in an appropriately designed study.	EMA glossary
Biological medicinal product	It is a product that contains a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterization and the determination of its quality a combination of physico-chemical-biological testing together with the production process and its control. Also called: “biological medicine” or “biopharmaceutical”	PHIS glossary
Biological	See definition of “biological medicinal product”. In the report, the term biological will be used.	
Biosimilar	See definition of “Similar biological medical product”. In the report, the term biosimilar will be used.	
Biotechnology	A process using biological systems to create or modify products.	EMA glossary
Bundling	Is a marketing strategy that involves offering several products for sale as one combined product, sometimes referred to as portofolio contracts.	PHIS glossary
Claw-back	A system allowing third party payers to recoup (part of the) discounts/rebates granted in a reimbursement system between various stakeholders, e.g. wholesalers and pharmacists.	PHIS glossary

Community pharmacy	Health care facility dispensing medicines (Prescription only medicines and over-the-counter medicines, reimbursable and non-reimbursable medicines) to outpatients. Pharmacies are subject to pharmacy legislation (e.g. national legislation regarding establishment and ownership of pharmacies). In many countries, community pharmacies are private facilities, but public pharmacies (i.e. in public ownership) also exist. Pharmaceutical provision for inpatients is provided for by hospital pharmacies or pharmaceutical depots; in some cases hospital pharmacies also act as community pharmacies.	PHIS glossary
Comparability exercise (referring to batch-to batch comparability)	The activities, including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable.	ICH [2]
Comparability exercise (referring to biosimilars)	For biosimilar: The comparability exercise should be a robust head-to-head comparison between the similar biological medicinal product and the reference medicinal product performed at the levels of quality, safety and efficacy.	EMA [3]
Cost-free medicines	Are products which are given to hospitals/hospital pharmacies in the course of delivery without need for payment.	PHIS glossary
Data exclusivity	Refers to protection of clinical test data required to be submitted to a regulatory agency to prove safety and efficacy of a new pharmaceutical, and prevention of generic/ biosimilar pharmaceutical manufacturers from relying on this data in their own applications. Market exclusivity means that competitors are really forbidden to make a MAA even if they have generated their own data. As such, data exclusivity and market exclusivity are independent from the patent exclusivity period, but might be more relevant from a biosimilar entry perspective, since biosimilars rely on their own production processes and often have slightly different products.	IFPMA [4]
Discount	Is a price reduction granted to specified purchasers under specific conditions prior to purchase.	PHIS glossary
Discounted price	Price paid for a given pharmaceutical by the hospital to the manufacturer after taking into account any discounts or rebates.	Own definition

Efficacy study	A study to evaluate whether a medicinal product works in the desired indication.	EMA glossary
European Public Assessment Report (EPAR)	Full scientific assessment report for every medicine granted a central marketing authorisation by the European Commission. The EPAR is prepared by the EMA with the CHMP members who evaluated the MAA. EPARs are prepared for all dossiers evaluated via the centralised procedure in all cases where the CHMP formulates positive final opinions. They are publicly available to third parties on request (and available via the Internet). They include the approved Summary of Product Characteristics plus information on labelling and package leaflets.	EMA glossary
Extrapolation	Extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product.	EMA [5]
Generic medicinal product	A medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. (Reg. 726/2004, Art 10, 2b) Generic "copies" can only be marketed after the originator's patent protection and/or marketing exclusivity has expired.	EMA glossary
Generic substitution	Practice of substituting a pharmaceutical, whether marketed under a trade name or generic name (branded or unbranded generic), by a pharmaceutical, often a cheaper one, containing the same active ingredient(s).	PHIS glossary
In-patient care	An in-patient is a patient who is formally admitted (or “hospitalised”) to an institution for treatment and/or care and stays for a minimum of one night in the hospital or other institution providing in-patient care. In-patient care is mainly delivered in hospitals, but partially also in nursing and residential care facilities or in establishments that are classified according to their focus of care under the ambulatory-care industry but perform in-patient care as a secondary activity.	PHIS glossary

	It should be noted that the term “in-patient” used in the OECD-SHA has a wider meaning compared to some national reporting systems where this term is limited to in-patient care in hospitals. Included are services delivered to in-patients in prison and army hospitals, tuberculosis hospitals, and sanatoriums. In-patient care includes accommodation provided in combination with medical treatment when the latter is the predominant activity provided during the stay as an in-patient. On the other hand, accommodation in institutions providing social services, where health care is an important but not predominant component should not be included in the health function. Examples might include institutions such as homes for disabled persons, nursing homes, and residential care for substance abuse patients.	
Interchangeable pharmaceutical product	An interchangeable pharmaceutical product is one which is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice.	PHIS glossary
International non-proprietary name (INN)	The INN identifies pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognised and is public property. A nonproprietary name is also known as a generic name.	EMA glossary
List price	Official price of the medicine as fixed by the national pricing and reimbursement authorities. In the report the list price refers to prices for reimbursable pharmaceuticals.	Own definition
Low cost pharmaceutical	Low cost pharmaceuticals include: (1) original pharmaceuticals for which the reimbursement basis has been decreased because a generic alternative exists, and which have lowered their public retail price to the reimbursement basis (so that there is no reference supplement to be paid), (2) generics and copies.	RIZIV – INAMI
Marketing exclusivity	A mechanism by which an innovative medicinal product is protected from generic competition beyond that conferred by the patent, in order to compensate for the time taken to develop the product. The EU scheme is described under SPC (Supplementary Protection Certificate) and Abridged MAA.	EMA glossary

Me-too pharmaceutical	A me-too medicine is approved after a pioneering product and is defined as comparable or similar but not clinically superior product.	PHIS glossary
Original product (Originator)	The first version of a medicine, developed and patented by an originator pharmaceutical company which has exclusive rights to marketing the product (in the European Union for 20 years). An original product has a unique trade name for marketing purposes, the so-called brand name. Also called: “First-in-class product”, “innovator product”	PHIS glossary
Outpatient care	Also called: “ambulatory care”	
Pharmacovigilance	Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.	EMA glossary
Primary substitution	The use of a biosimilar rather than its original when starting a treatment.	CPME
Rebate	Is a payment to the purchaser after the transaction has occurred. Purchasers (either hospitals or pharmacies) receive a bulk refund from a wholesaler, based on sales of a particular product or total purchases from that wholesale over a particular period of time.	PHIS glossary
Reference medicine	See “Reference medicinal product”	
Secondary substitution	The replacement of an original pharmaceutical by a biosimilar already in use in a patient. also referred to as: “switching”	CPME
Second-generation biological	Biological that has been structurally and/or functionally altered to achieve an improved clinical performance also called: “next-generation biological”	BMWP [6]
Similar biological medicinal product	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	EMA [7]

	reference medicinal product. A biosimilar medicine and its reference medicinal product are expected to have the same safety and efficacy profile and are generally used to treat the same conditions. Also called: "biosimilar" Means that "the biological product is highly similar to the reference product nothwithstanding minor differences in clinically inactive components" and that there are now clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product"	FDA [8]
Substitution	Practice of dispensing one medicine instead of another equivalent and interchangeable medicine.	CPME
Switching	The practice of replacing one pharmaceutical with another in course of a treatment that is expected to have the same clinical effect.	CPME (adapted)

Source: Terms in this glossary are reproduced from different sources. For terms having different definitions, we selected the definition provided by official regulatory authorities: 1) European Medicines Agency (EMA) glossary [9] 2) Pharmaceutical Health Information System (PHIS) Glossary [10]; 3) CPME [11] RIZIV – INAMI [12]. Own definitions were set here to increase the understanding of the content of the report.

SCIENTIFIC REPORT

1. INTRODUCTION

1.1. Background

According to the Belgian national social report 2012, accessibility, quality and sustainability remains the three main objectives of the health system, in line with the framework of the open method of coordination on social protection and social integration developed by the European Union. [13] Concerning price and reimbursement policies on pharmaceuticals, national authorities should therefore ensure to eliminate barriers that limit the use of the least expensive alternative among equally high quality treatment options. The apparition of biosimilar pharmaceuticals is worldwide seen as a new opportunity to guarantee accessibility to affordable treatments and to enhance financial sustainability of national health systems. However, even if biosimilars seem to be increasingly adopted in many European countries, Belgium has one of the lowest biosimilar uptake rates in Europe. Sales are generated only for one active substance, i.e. somatropin (=biosynthetic growth hormone (rhGH) further referred to as somatropin). Biosimilars for epoetin (=biosynthetic erythropoetin (rEPO), further referred to as epoetin) and filgrastim (=biosynthetic granulocyte colony-stimulating factor (rG-CSF) further referred to as filgrastim) have not been able to penetrate the market.

1.2. Research questions and scope of the study

Against this background, the Minister of Social Affairs and Public Health asked the KCE to identify barriers and measures, which may influence uptake of biosimilars in Belgium. In order to do so, three different research questions were addressed:

- Based on the literature, what is the impact of the introduction of biosimilars on the health system in terms of price reduction (with respect to the reference product), uptake and savings for the third-party payer?
- What is the experience in European countries concerning policy measures relating to biosimilar uptake?
- Based on the literature and on stakeholder views, what are the specific barriers to market penetration 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. An overview of the European Medicine Agency (EMA) market authorization procedure for biosimilars is also included in the report. The aim of this section is to allow the reader to have a general perspective on biosimilar regulation in Europe. Evaluation of the EMA regulatory pathway for biosimilars as well as clinical research questions on effectiveness, safety, and interchangeability of biosimilars are out of scope.

1.3. Structure of the report

The next parts of this report are structured as follows:

- Chapter 2 describes the key concepts and definitions for pharmaceuticals and an overview of currently approved and forthcoming biosimilars.
- Chapter 3 highlights Key Points of the regulatory framework for biologics and biosimilars in the European Union (EU) as defined by the EMA.
- Chapter 4 focuses on the Belgian situation regarding pricing and reimbursement procedures with a focus on biosimilars.
- Chapter 5 aims at providing evidence, from a structured literature research, on the impact of biosimilar competition on price reduction, market uptake and savings for the third-party payer.
- Chapter 6 describes measures adopted in selected foreign countries (i.e. France, The Netherlands, Germany, and Sweden) to stimulate biosimilar uptake. The objective of this chapter is not to determine if these policies are effective in terms of cost-containment but rather to list measures (incentives or constraints) that could potentially stimulate biosimilar uptake.
- Chapter 7 aims at building on-the-ground evidence on factors determining biosimilar uptake in Belgium.
- Chapter 8 contains the conclusions, limitations and discussion of this report.

2. DEFINITIONS

2.1. Biological medicines

2.1.1. Definition

According to Part I of Annex I of Directive 2001/83/EC (annex I, part I, 3.2.1.1. b) [14], a biological medicinal product or biological is a product that contains a biological substance. A biological substance is a substance that is produced by or derived from a living organism. A biological is per definition a heterogeneous mix that can be characterized by a range of physical, (bio)chemical testing procedures. Biologicals are also referred to as biopharmaceuticals, biopharmaceutics or biologics. Biologicals can consist of a broad range of molecule types including proteins (i.e. hormones, enzymes, insulins and erythropoetins), deoxyribonucleic acid (DNA), ribonucleic acid (RNA), monoclonal antibodies, blood products, or immunological medicinal products like vaccines and allergens. [15]

2.1.2. Biologicals versus small molecule chemical pharmaceuticals

The biopharmaceuticals are inherently different from small molecule chemical medicines as they are in general larger and more complex than small molecule pharmaceuticals. Biologicals are made of naturally occurring building blocks or variations thereof, while small molecule pharmaceuticals have basic atomic units. For example, proteins are build of a chain of ten to hundreds or more glycoproteins (i.e. amino acids and sugar molecules), each of them more or less the size of a small molecule. That chain is compacted in a specific three-dimensional structure and modified by various biochemical reactions (for example cysteine-cysteine bridges, glycosylation, phosphorylation). Biologicals are designed by nature to target specific human factors (for example the human growth factor binds to the human growth factor receptor), while in general small molecules are made synthetically at random, screened for binding to a specific target and then analyzed on mechanisms of action when possible. Usually, biologicals are produced in industrial laboratories via complex processes starting from living microorganisms that have first been “engineered” to fulfil the best possible production and delivery characteristics. Such engineered cellular clones (the “production clones”) are not commercially available and each company has to produce its own

in-house, which per se represents an important variability factor. The bio(techno)logical molecules can undergo variable post-translational modifications (e.g. glycosylation or sulphation), leading to a heterogeneous mixtures of several "isoforms" with distinct biological properties. The final biopharmaceutical product is influenced by many production- and/or batch variables, such as the type of expression system (bacteria, yeast, and mammalian cells) and production clones, the growth conditions (cell medium, pH, cell density, temperature), the purification process, the actual formulation and the conditions during storage and transport. Per definition, a batch is a specific quantity of an intermediate or active pharmaceutical ingredient intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. [16] Manufacturers and regulators expect and tolerate batch-to-batch quality differences within defined limits. Since small molecules have a well-defined chemical structure, the chemical structure can be analyzed, characterized and exactly reproduced when identical raw materials are used. For biologicals, the final products cannot be exactly reproduced between subsequent batches. [17, 18] In addition, due to its complexity, biologicals are more difficult to characterize than small molecules. Recent state-of-the art high technological analytical methods and expertise are used to determine physicochemical, immunochemical and purity characteristics in combination with biological effects. However, the interpretation of the product quality based on the analytical profile remains difficult.

Box 1 – Examples of biologicals

In 1982, the first biologic approved by a regulatory agency (Food and Drug Administration (FDA)) for therapeutic use was "human" insulin (Humulin), which was in made E.coli via recombinant DNA technology. Since then, biologics have been developed for different therapeutic areas (including cancer, multiple sclerosis, rheumatoid arthritis and orphan diseases such as Gaucher's, Pompe) and different pharmaceutical classes including blood factors (Factor VIII and Factor IX), thrombolytic agents (tissue plasminogen activator), hormones (insulin, glucagon, growth hormone, gonadotrophins), haematopoietic growth factors (erythropoietin, colony stimulating factors), interferons (Interferons-α, -β, -γ), interleukin-based products (interleukin-2), vaccines (hepatitis B surface antigen, HPV), monoclonal antibodies (anti-TNF) and therapeutic enzymes. [15]

2.1.3. Me-too biologicals and biobetters

As for all pharmaceuticals, a new alternative for the treatment of an illness can be related to a pioneering medicinal product. "Me-too[a] biologicals" are biologicals that have been developed independently and are not directly compared and analyzed against an existing licensed reference product, which may or may not be clinical comparable. [6] Examples among epoetins are Biopoin[b] (epoeitin theta from CT Arzneimittel) and Eporatio (epoetin theta from Ratiopharm). [19] Biobetter or second-generation biologicals (sometimes referred to as "best-in-class") are biologicals which have been structurally and/ or functionally altered to achieve an improved therapeutic value in one or more specific indications. [6] For example, for darbepoetin alfa (commercialised as Aranesp by Amgen) 5 amino acids are substituted which creates a 3 fold longer half-life of the molecule and higher potency as the comparator epoetin-alfa. Therefore, a less frequent dosing is possible as compared to first generation epoetin (Eprex) (3 weekly as compared to once weekly). Both me-too as second-generation biologicals

[a] The term me-too drug or me-too pharmaceutical is also used for small molecule medicinal products

[b] Brand name products are written in the report in capitalised names

are authorized through the normal full clinical development approval pathway for biologics.

2.2. Biosimilars

2.2.1. Definition

In analogy with the introduction of generics for small molecules, the expiration of patents of first biologics opened new hopes for affordable copies and increased competition. However, whilst generics are exact copies of the original small molecule pharmaceutical, the replicate versions of biologics, "the so-called biosimilars", do not meet the conditions in the definition of generic medicine products, because they are not identical but rather similar to the originator (art. 10.2.b. Directive 2001/83/EC). [14] In Europe, initially the legislation did not provide an exact definition but the legal basis of the *"biosimilar approval pathway has been set"* (Directive 2001/83/EC (as amended), Article 10, point 4). [14] It states that where there are differences (particularly) in raw materials or manufacturing processes of a biosimilar and its reference product, then results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. In 2012, The EMA provided the first definition for a Biosimilar:

"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 biosimilar medicine and its reference medicinal product are expected to have the same safety and efficacy profile and are generally used to treat the same conditions". [3]

The reference medicinal product (further referred to as RP or reference product) refers to an original medicinal product (referred also as innovator or originator) which has been granted a marketing authorisation by a Member State or by the Commission on the basis of a complete dossier, i.e. with the submission of quality, pre-clinical and clinical data and in accordance with the provisions applicable to originator products. The biosimilar expression system (*E. Coli*, different mammalian cell lines), may differ from that of the innovator. For example, an approved somatropin, valtropin has an alternative expression system compared to the reference product (*S. Cerevisiae* vs. *E.coli*), however was proven similar in clinical efficacy and safety. [20]

In order to get approval, biosimilars have to go through a step-by-step comparability exercise with the reference product (see paragraph 3.2.2). Comparability between the reference and the biosimilar product is the core principle of a biosimilar development. The scientific concept of "comparability" is well established and regulated in guidelines such as international conference on Harmonization (ICH)Q5E. [2] In principle, new batches of an approved biological or originator itself can be regarded as (bio)similar as these are never identical, but can vary in quality attributes (such as relative isomers contents, relative glycosylation and fucosylation, N- and C-term heterogeneity). [18, 21] Different quality profiles are accepted within a pre-defined, product-specific range, without new clinical trials. Changes in the manufacturing process can exist for any product. The extent to which the comparability after changes needs to be documented by (clinical) evidence and checked by the scrutiny of regulators is assessed in a case-to-case manner based on the scientific knowledge and totality of evidence around the product and the batches. [22] The demonstration of comparability does not necessarily mean that the quality attributes need to be identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the medicine. [22] The principles underlying the comparability exercise required for changes in the manufacturing process of a given biological product and for the development of a biosimilar product are the same. However, data requirements for biosimilars are higher than when assessing a process change for the same product. [6]

As "biosimilar" is a recent concept, the terminology used worldwide is not always homogenous. In the USA, biosimilars are rather referred to as follow-on biologics in publications, but the FDA has officially adopted the name biosimilar (www.fda.gov). In Canada, biosimilars are referred to as subsequent entry biologics. [23] Biosimilars should not be confounded with the biogenerics or non-comparable biologics (often referred to as biosimilars anyways) that have been marketed in countries such as China and India, without the rigorous regulatory scrutiny as used in Europe.

2.2.2. Current available biosimilars

Biosimilars are available in Europe since 2006 and 14 biosimilars have been approved in three product classes: Erythropoiesis-stimulating agents (epoetins), granulocyte-colony stimulating factors (filgrastim) and growth hormones (somatropin) (see Table 1). While there are five epoetin biosimilars on the market (Retacrit, Silapo, Abseamed, Binocrit and Epoetin alfa Hexal), these are produced by only 2 different manufacturers (Rentschler Biotechnologie and Norbitec). The same is true for the filgrastim biosimilars for which 6 products are currently commercialized (Biograstim, Ratiograstim, Tevagrastim, Nivestim, Zarzio, Filgrastim and Hexal) are produced by only 3 manufacturers (Sicor Biotech, Hospira Zagreb and Sandoz). [19] Filgrastim Ratiopharm was voluntary withdrawn from the market in 20/07/2011. For somatropin, both omnitrope (Sandoz) and Valtropin (Biopartners) were authorized. Valtropin was recently withdrawn from the market. The majority of the applications for biosimilars gained approval; however, several applications have been rejected. [19] For example, Insulin and interferon- alfa biosimilars have not obtained MA given incomplete data (no stability, insufficient immunogenicity testing, quality issues), issues on comparability or non-validated analytical tools. [24] Recently, the MA of the first biosimilar (Omnitrope) was renewed after 5 years based on CHMP's opinion that the quality, safety and efficacy was adequate and sufficiently demonstrated and therefore considered that the risk-benefit profile of Omnitrope continues to be favorable. [25] No major safety issues with biosimilars have been reported, however clear data on patient safety years in real world conditions are lacking. Currently, two biosimilars for infliximab, two for follitropin alfa and one for filgrastim are being evaluated by the European Medicines Agency. [26] Biosimilars naming and International Non-Proprietary Names (INN)

The International Non-Proprietary Names (INN) system, administered by the World Health Organisation (WHO), identifies pharmaceutical substances or active pharmaceutical ingredients. [27] Each INN is a unique name that is globally recognised and public property (also referred to as "generic name"). In principle, the INN is selected only for a single, well-defined substance that can be unequivocally characterized by a chemical name (or formula). [27] In general, INN names for biologicals are more problematic than for small chemical molecules, because of the lack of a homogenous chemical structure. [28]

There is a debate within the medical and pharmaceutical community whether biosimilars need a distinct INN (from their originator and/or from each other). According to the EMA, different biotech products (originator and biosimilar versions) need to be distinguishable for patient safety reasons. The INN has been historically a key tool in both adverse event reporting and substitution. The European innovative biotechnology and pharmaceutical industry associations plead in favour of a distinct INN for biosimilars in order to have: clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists worldwide. [29] According to the FDA, however, there is no need to modify the current INN system, since in the USA alternative methods such as lot number and national pharmaceutical code exist to avoid inappropriate substitution of products with the same INN. [30] In the FDA's view, the assignment of INNs should be independent of the regulatory process or of considerations of prescribing interchangeability or the use of INNs in pharmacovigilance. Indeed, in practice, the INN is proposed by the developer and requested before the regulatory process is finalized and thus there is no link between interchangeability and INN.

Table 1 – Biosimilars currently approved in the EU (situation on 29 January 2012)

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

Source:Mighetti (2011) [31], updated using official information from the EMA.

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000602/human_med_001125.jsp&mid=WC0b01ac058001d12 4

[2] http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2011/07/WC500109157.pdf

However, due to generic regulation and substitution, the same INN is an important signal to physicians and pharmacists that the active substance of biosimilar and reference product is indeed comparable. For pharmacovigilance purposes, the lot number and the manufacturers name should be added in any case, ensuring the traceability and distinguishability (Article 102 of the medicinal products Directive 2001/83/EU, as amended by Directive 2010/84/EU). [32]

The European Generics Association (EGA) agrees with the position to maintain the INN naming system. In their opinion, comparability of two biologicals is sufficient to assign the same INN. [33]

For current available biosimilars in Europe, the naming situation is rather complex. There are multiple biosimilars to the originator version of epoetin-alfa (Eprex). Epoetin-alfa is a glycosylated protein and thus these post-translational modifications tend to differ between manufacturers because of the cells used and the processing steps. Although all of the biosimilars approved using epoetin-alfa as a reference product have differences in glycosylation from the reference product, they do not all have different INNs. Some of these use the INN of the reference product (epoetin-alfa), while some have their unique INN (epoetin-zeta) (see Table 1). Since INN is assigned independently from the regulatory MA process, the naming is more likely to be guided by strategic and marketing goals of the developer, rather than differences in product profiles. [28]

Key Points

- **A "generic" is a pharmaceutical that has the same qualitative and quantitative composition in active substances, the same pharmaceutical form as its reference medicine, which is a small molecule. Bioequivalence between the two products is demonstrated by appropriate bioavailability studies.**
- **A "Biosimilar" is a pharmaceutical that has a similar qualitative and quantitative profile as its reference medicine, which is a biological medicine that has already been authorised. Similarity between the two products is established based on a step-wise comparability exercise.**
- **Biosimilars are not generics, nor me-too biologics.**
- **In Europe, a biosimilar is approved by the regulatory authorities as being similar in terms of quality, efficacy and safety to a reference biological medicine for at least one indication.**
- **Currently, in Europe biosimilars on the market include erythropoiesis-stimulating agents (epoetins), granulocyte-colony stimulating factor (filgrastim) and growth hormone (somatropin).**
- **Biosimilar medicines have been used in clinical practice in the European Union since 2006. Until now, no major safety issues after using biosimilars were reported.**

3. REGULATORY FRAMEWORK FOR THE EUROPEAN UNION

This chapter highlights Key Points from regulatory framework in the European Union (EMA) for biologics and biosimilars.

3.1. Market authorization of biologicals

Market authorization can be granted by the European Commission following an opinion by the European Medicines Agency (EMA) via the centralised procedure or by the Federal Agency for Medicines and Health Products (FAMHP) using a national procedure, decentralized procedure or a mutual recognition procedure. Within the EMA, the Committee for Medicinal Products for Human Use (CHMP)[c] is responsible for preparing the agency's opinions on all questions concerning medicines for human use. Since 2004 technologically advanced medicinal products and medicines involving biotechnology[d], including biopharmaceuticals, should request a MAA for a new biological entity (NBE) through a centralized procedure in the EU. [34] A single application, a single evaluation and a single authorisation allows a market authorization for the European Union and EEA-EFTA states (Iceland, Liechtenstein and Norway). The market authorization (MA) holder needs to hand in a dossier called the common technical document (CTD), which contains the required data in a standardized format. The CTD comprises five modules:

- Module 1 provides specific administrative data
- Module 2 provides a summary on the quality, nonclinical and clinical data
- Module 3 provides chemical, pharmaceutical and biological information (i.e. quality)
- Module 4 provides nonclinical reports
- Module 5 provides clinical study reports.

The evaluation of the MAA is published in the form of European public assessment reports (EPAR). The EMA continues to monitor the safety of medicines once they are on the market.

3.1.1. Pharmacovigilance and the risk management plan

In line with article 8(3) (ia) of Directive 2001/83/EC, a MAA for a new active substance should contain a detailed risk management plan. A risk management system is a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions[e]. The aim of a risk management system is to ensure that the benefits of a particular medicine (or a series of medicines) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. The description of a risk management system should be submitted in the form of a EU-Risk management Plan (EU-RMP), which contains 2 parts:

- Part 1: A safety specification and pharmacovigilance plan
- Part 2: A risk minimisation plan: An evaluation of the need for additional (i.e. non- routine) risk minimisation activities
- The legal framework of pharmacovigilance for medicines marketed within the EU is provided for in Regulation (EC) No 726/2004 with respect to centrally authorised medicinal products. [34] The EU pharmacovigilance legislation has been subject to a major review that

---

c Replaced the former Committee for Proprietary Medicinal Products (CPMP) by Regulation (EC) No 726/2004

d For medicinal products that have been made using biotechnology (such as genetic engineering), advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines, new medicinal products intended to treat treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other, immune dysfunctions, and viral diseases and 'orphan medicines' the centralized procedure is mandatory. For other products the decentralized procedure or the mutual recognition procedure can also be used. (http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp).

e Detailed information in: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000306.jsp&mid=WC0b01ac058017e7fc

lead to the adoption of new legislation in 2010 (Regulation (EU) No 1235/2010 [35] and Directive 2010/84/EU [32]). [36] According to the EMA, this legislation reform is the biggest change to the regulation of human medicines since 1995[f]. The new legislation, which came into effect in July 2012, strengthens and rationalises the system for monitoring the safety of medicines on the European market. It improves patient safety and public health through better prevention, detection and assessment of adverse reactions to medicines and promises to put a stronger link between safety assessments and regulatory action. The newly founded Pharmacovigilance Risk Assessment Committee (PRAC) will advise the CHMP on risk management procedures:

- Collection of key information on medicines through risk-proportionate, mandatory post-authorization safety (PASS) and efficacy studies (clinical trial or observational studies) including off-label use. [37]
- The Committee will publish the agendas and minutes of PRAC meetings, any high-level outcomes of the PRAC's main scientific discussions, and the PRAC's Recommendations and Advice, strengthened transparency, communication and patient involvement

In addition, Commission Implementing Regulation (EU) No 520/2012 [38] on the performance of pharmacovigilance activities clarifies the role and responsibilities of the stakeholders by stipulating operational details in relation to certain aspects of pharmacovigilance to be respected by marketing authorisation holders, national competent authorities and EMA. Finally, the EMA has released good pharmacovigilance practice guidelines (GVP) in order to facilitate the performance of pharmacovigilance activities. These GVP modules replace parts of the Volume 9A of, "The rules governing medicinal products in the European Union - Pharmacovigilance" of which the remaining chapters are in review.

With regard to the reporting of adverse events, Directive 2010/84/EU now amends Article 102 of the medicinal products Directive 2001/83/EU, by requiring that Member States record the name and batch number of any dispensed medicinal product. This is to ensure "that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of an adverse reaction report". [32] In this way, it should be possible to determine which product a patient has taken before suffering an adverse event, and not only which active substance the medicine contained. Physicians, pharmacists and other health-care professionals will be subject to "specific obligations" in order to comply with Article 102 of Directive 2010/84/EU. Doctors are required, therefore, to maintain accurate records of prescribing and dispensing, so that if a pharmacist does make a substitution, and the patient has an adverse event, it will be possible to trace the product responsible for the adverse event.

Adoption of the new pharmacovigilance legislation in Belgium was done by the Health care act published on 11 September 2012 modifying the Health care act of 25 March 1964 on pharmaceuticals. [39] In line with this, the Royal Decree of 14 December 2006 relating to medicines for human and animal use will also be modified. [40]

3.1.2. Comparability exercise for changes in manufacturing procedures

The characteristics of biologicals are directly related to the manufacturing process and cannot be precisely duplicated. Originator companies often have to change their processes due to improvements in efficiency (changes of cell and seed strains or fermentation and purification processes) or manufacturing site changes, and regulatory bodies have established pathways for the approval of such process changes. For such changes in manufacturing procedures, occurring after the market authorization approval, the FDA introduced a "comparability exercise". [41] The comparability exercise is a side-by-side comparison of the new versus the old versions of biological medicinal products to provide evidence for the similarity of the essential quality, efficacy and safety characteristics. The EMA adopted this comparability exercise for changes in manufacturing processes. Guidelines issued in 2000 (quality) and 2002 (clinical and non-clinical issues) allowed manufacturers of "well-characterized biopharmaceutical products" (i.e. proteins whose identity, purity, impurities, potency and quantity can be determined and controlled) to implement changes in the manufacturing, usually without any additional clinical trials. Both were updated in 2003 and 2006 respectively. The guidelines have been frequently applied and the occurrence of such

f http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000492.jsp&mid=WC0b01ac058033e8ad

evaluation procedures will be notified on the EMA webpage. As such, substantial experiences have been gained successfully over the years within the EMA, although the evaluation dossier is not publicly available.

3.2. Market authorization of biosimilars

3.2.1. Legal biosimilar approval pathway

A biosimilar can only be authorised after expiry of data exclusivity of the reference product. In general, this means that the biological reference medicine must have been authorised for at least 10 years before that biosimilar can be made available by another company (unless agreed otherwise). A scaled down market authorization procedure for biosimilars was established by the EU in 2005. The motivation mentioned for an abbreviated regulatory pathway included:

- First, economical need for less expensive alternatives to expensive biologicals to expand patient access, to increase competition, and decrease cost for health care systems and patients. A scaled-down biosimilar development pathway could keep development cost for companies under control, increasing the likelihood that companies will enter the market and disrupt existing monopolies. [42]
- Second, a full clinical development program as for a new biological application was deemed unnecessary (and arguably therefore unethically) since scientific arguments are strong enough not to expect therapeutic difference between a biosimilar and the reference product. [42] Conducting "duplicative" studies would: i) divert R&D investment from innovative pharmaceuticals, ii) increase the cost of pharmaceuticals iii) slow down approval and delay access to less expensive pharmaceuticals to the public and iv) strain already stretched capacity of regulators.
- Furthermore, the development of a separate authorization for biosimilars was pushed by the realization that the authorization procedures required for a generic medicine were not sufficient for biosimilars due to the inherent differences between small molecule pharmaceuticals and biopharmaceuticals (see section 2.2.1). [43]

Box 2 – Definition data exclusivity

Data exclusivity refers to protection of clinical test data required to be submitted to a regulatory agency to prove safety and efficacy of a new pharmaceutical, and prevention of generic/ biosimilar pharmaceutical manufacturers from relying on this data in their own applications. Market exclusivity means that competitors are really forbidden to make an MAA even if they have generated their own data. As such, data exclusivity and market exclusivity are independent from the patent exclusivity period, but might be more relevant from a biosimilar entry perspective, since biosimilars rely on their own production processes and often have slightly different products.

As the implications of extensive process changes by originators can be similar to those of introducing a new process for the production of a biological, biosimilars companies have argued that the regulatory guidance approving comparability after a process change (i.e. by use of the comparability exercise) can also be applied to the approval of biosimilar versions of the biological. [42]

The legal basis for a new market authorization application (MAA) procedure specific for biosimilars was set in the EU Directive in 2001 (article 10 Directive2001/83/EC), which lays down the requirements for the MAA based on the demonstration of the similar nature of two biological medicinal products from different manufacturers based on the comparability exercise to the reference product. All currently marketed biosimilars have submitted a marketing authorization application via the centralised procedure at the EMA. The EMA Biosimilar Medicinal Products Working Party (BMWP) was set up to provide recommendations to CHMP on clinical or non-clinical matters relating directly or indirectly to biosimilar medicines. The BMWP's work covers both products that are already authorised through the centralised or mutual-recognition procedures, and those being developed. It works together with other CHMP working parties and scientific advisory groups, and co-operates with regulatory authorities in the Member States. The evaluation of the MAA is published in the form of European public assessment report (EPAR) and can be publicly assessed. [44]

From a scientific point of view, the procedures for biosimilars is not "abridged" such as for generics, but rather "tailored" in the form of a comparability exercise to an approved new biological entity. The biosimilar paradigm requires that the biosimilar is developed with respect to the original "reference" biological medicine already licensed in the European Economic Area (EEA). In general, the pharmaceutical form, route of administration and strength should be the same, although exception can be made when sufficiently justified.

Box 3 – Opening a possibility for global development

To facilitate the global development of biosimilars and to avoid unnecessary repetition of clinical trials, Commissioner Dalli announced in 18th European Generic Medicines Association (EGA) that the European Commission intends accept "batches of reference medicinal products sourced from outside the EEA in certain preclinical and clinical studies for the comparability exercise". [45] Use of batches outside the EEA will be possible under the condition that they are representative of the reference medicinal product authorised in the EEA. As a consequence, additional comparative pharmacokinetic and pharmacodynamic data may be required to be included in the market authorization application. [46]

3.2.2. The biosimilar paradigm and the comparability exercise for biosimilars

The aim of a biosimilar development program is not to establish therapeutical benefit of a treatment for the patient – since this had been established before for the reference product but to assess comparability to the reference product (guidelines biosimilars). [47]

The "comparability exercise" includes three main steps: 1) Quality comparability (physicochemical and biological comparability); 2) Non-clinical comparability (comparative non-clinical studies); 3) Clinical comparability (comparative clinical studies). Quality comparability between the reference product and the biosimilar is established for the molecular structure as well as for functionality (for example by means of relevant receptor binding studies). The non-clinical and clinical comparability aim at proving that quality differences between the biosimilar and the reference product, have no impact on the safety and efficacy of the biosimilar. As a consequence, trial design, including clinical endpoints, might be different from the guideline principles for a new biological entity.

3.2.3. From bench to approval

The development of a biosimilar starts with a thorough physicochemical and biological characterization by a broad range of assays of the original product, chosen as a reference product, which aims at setting the criteria to which a biosimilar should adhere (i.e. range of quality profile and biological activity of the reference product). In practice, several batches of the reference product are procured over a broad period of time and characterized to create a "fingerprint" profile of the product. Often changes in manufacturing process can be detected by a shift in the quality profile of the original product, [18] broadening the target range for the biosimilar. In analogy to a fingerprint comparison, the newly developed biosimilar is compared head-to-head in a stepwise approach in the same range of analytical (tests addressing quality, biological and toxicity characteristics), PK/PD characteristics and clinical tests. At each step, the residual uncertainty of similarity or specific detected difference determines the extent and design of the next step. As such, *"quality attribute values which are outside the range of variability measured in the different profiles of the reference medicinal product should be appropriately justified with regards to their potential impact on safety and efficacy".* [48] For clinical trials, the study population should be as homogeneous and as sensitive as possible to the effects of the biological. The end-points should ideally reflect the unconfounded pharmacologic action of the product and be able to detect potential pharmaceutical-related differences in efficacy and safety, while minimizing variability caused by disease or patient-related factors. [47] Thus, the clinical study indication is selected to represent the most sensitive test model to study differences. For example, the EMA recommended that the target population for epoetins should be patients with renal anaemia*: "Sensitivity to the effects of epoetin is higher in erythropoietin-deficient than non erythropoietin-deficient conditions and is also dependent on the responsiveness of the bone marrow. Patients with renal anaemia are therefore recommended as the target study population as this would provide the most sensitive model."* [48] Weise pointed out that *"the focus of biosimilar development is not to establish patient benefit per se – this has already been done for the originator product– but to convincingly*

demonstrate high similarity to the reference product as basis for relying, in part, on its efficacy and safety experience. For these reasons, the study design, study population, and/or end points used in studies comparing the biosimilar with the reference product may be different from those previously used to establish therapeutic benefit of the reference product." [47] This paradigm leads to important differences between the biological pathway and biosimilar pathway: a higher similarity in analytical and PK/PD data leads to lower risk in clinical difference and thus may allow more selective and targeted clinical trials. [49]

Box 4 – Selecting appropriate endpoints

Endpoints measuring activity of the pharmaceutical are usually more sensitive for detecting product-related differences than hard end points evaluating patient benefit and may be acceptable if they are clearly related to the desired clinical effects. Examples of pharmacodynamic parameters that have been accepted as surrogate end points for the evaluation of efficacy of biosimilars in the EU include glucose infusion rate in clamp studies for insulins, absolute neutrophil count for G-CSF, and number of oocytes retrieved (in the context of in vitro fertilization) for follicle-stimulating hormones. [47]

As with all biologicals, immunogenicity is of greatest concern. Immune reactions, in particular antibody formation (ADA= anti-drug antibody) can have consequences, which can range from irrelevant for therapy, to loss of efficacy, to serious and life-threatening situations [50], but are rarely detected. Therefore, for all biologicals, immune reactions and antibody formation should not only be monitored during clinical trials, but also after market authorization. [51] Testing for such antibodies can be technically challenging due to several factors such as low titres of antibodies, cross-reactivity with the product itself, interferences from serum proteins, etc. Specific guidelines on immunogenicity assessment of biologicals and more specific for monoclonal antibodies (mAb) have been published. [52] As for all biologicals, biosimilars are subjected to the new pharmacovigilance in application since July 2012.

3.2.4. Guidelines for comparability exercise

The EMA has published guidelines on how to address similarity (see Table 22 in the appendix 1). The guidelines are not legally binding and each application is evaluated on a case-to-case basis by the EMA. Currently for seven product classes guidelines are available (epoetins, filgrastim, somatropin, low-molecular-weight heparins, interferon-alfa, insulin and monoclonal antibodies) and for two there are guidelines in development (interferon beta, recombinant follicle stimulation hormone). Only in three product classes, biosimilars have been approved. Currently five biosimilars are in evaluation by the EMA (i.e. two for infliximab, two for follitropin alfa and one for filgrastim). [26]

The EMA guidelines built on the experience with similar biological medicinal products for manufacturing changes, but added the need for minimal clinical comparability evidence in terms of safety and efficacy. Residual uncertainties about the similarity of the two products, based on the totality-of-evidence (the pre-clinical structural and functional characterization, human PK and PD data, and clinical immunogenicity) assessment will have to be addressed in comparative safety and effectiveness studies. The EMA stated that "the clinical comparability exercise is a stepwise procedure that should begin with pharmacokinetic (PK) and pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, pharmacokinetic/pharmacodynamic (PK / PD) studies for demonstrating clinical comparability (...)". [43] For efficacy trials, the EMA states that *"comparative clinical trials will be necessary to demonstrate clinical comparability between the similar biological and the reference medicinal product. Clinical comparability margins should be pre-specified and justified, primarily on clinical grounds."* [43]

Generally, clinical study or studies (including an assessment of immunogenicity and PK or PD) are necessary to demonstrate safety, purity, and potency as compared to the reference product in an equivalence or non-inferiority design, covering one or more appropriate conditions of use for which the reference product is licensed. The argumentation of a sponsor that certain clinical safety and effectiveness studies (for example for certain indications) are redundant may be followed if a sound scientific justification is given. Hence, the CTD for biosimilars comprise of full modules 1, 2 and 3, but need the comparability exercise for modules 3, 4 and 5 decreasing the number of clinical trials required.

However, the sample size is typically larger for equivalence trials and non-inferiority trials compared with superiority trials.

Nevertheless, the extent of (clinical) data requirements is determined on a case-by-case basis and might vary between individual firms for the same type of biosimilar.

The process might dependent on several issues including: [47]

- the product type and class of the active substance, which determines the complexity of the molecule, the knowledge around the molecule and the reference product and how well it can be characterized
- the previous experience with RP and/or biosimilars within the specific product class: for example on the type and seriousness of safety concerns that have been encountered with the reference product or the substance class
- the availability of an accepted surrogate end point to compare efficacy
- the possibility to extrapolate efficacy and safety data to other indications of the reference product
- the residual uncertainty about biosimilarity after the structural and functional characterization (Scientific considerations in demonstrating biosimilarity to a RP).

The members and experts of the Working Party on Similar Biologic Medicinal Products of the European Medicines Agency (EMA) address the concerns on the acceptance range or comparability margins (too wide or not specified) as follows:

"The basis for considering the efficacy of a biosimilar to be comparable to that of the reference product has been questioned. Specifically, the acceptance range for therapeutic equivalence for biosimilar epoetins was considered wide. In a statistical and regulatory sense, therapeutic equivalence infers that the test drug does not have better or worse efficacy than the reference product, thus allowing the use of the same dosage for the same indication, as is intended for biosimilars. When defining comparability margins, clinical considerations need to be taken into account; the selected margins should represent the largest difference in efficacy that would not matter in clinical practice. Treatment differences within these margins would thus be acceptable because they have no clinical relevance. The principles of margin selection are not unique to biosimilar testing but are used in any clinical trial comparing treatment alternatives or prechange and postchange product in case a biological has undergone a change in its manufacturing process and clinical data are required for assessment of comparability. Comparability margins proposed for licensing studies for a given medicinal product, including biosimilars, will always need sound scientific justification to be acceptable for regulators (...) It should be noted that, not only the observed mean treatment difference (between biosimilar and reference product) but also the 95% confidence interval of this difference needs to be fully contained within the equivalence margins, thus providing sufficient statistical reassurance that efficacy is indeed similar. The assumption that patients switched from an originator product to the respective biosimilar may need to change dosage, dosage intervals, or route of administration is unsubstantiated". [47]

3.2.5. Product class-specific guidelines

Product class-specific guidelines have been developed for several therapeutic proteins, providing guidance on appropriate non-clinical (pharmacodynamic and toxicological studies) and clinical (pharmacodynamic, pharmacokinetic, efficacy and safety) studies (website EMA). The guidelines are regularly updated based on the experience with the specific biosimilar products, which were evaluated or approved. Therefore biosimilar developers are recommended to contact the CHMP early in the development process to allow recognition of the development path and to address the requirements of the EMA by a step-wise approach based on the accumulated evidence (each of which confirmed by the CHMP).

Over time, the regulatory decisions on what is needed in a specific product-class might be more pragmatic for the requirements for the demonstration of clinical comparability. For example in 2008, the biosimilar (Tevagrastim) obtained approval after conducting a full three-arm phase III trial on 384 patients with breast cancer. [53] Six months later, Zarzio was approved with a phase I pharmacodynamic study on 146 healthy volunteers, without any clinical tests on patients. In this case, the regulators judge this to be sufficient for approval on the particular disease state, based on the validity of the pharmacodynamic marker as a surrogate marker for efficacy (as stated in the guidelines on similar biological

products: clinical and non-clinical issues and product-specific guidelines. [54, 55]

Box 5 – Examples of specific points for clinical efficacy studies per product class

Epoetin: "*Equivalent therapeutic efficacy between the similar and the reference product should be demonstrated in at least two adequately powered, randomised, parallel group clinical trials. Confirmatory studies should preferably be double-blind to avoid bias. If this is not possible, at minimum the person(s) involved in decision-making (e.g. dose adjustment) should be blinded to treatment allocation.*" [48]

Filgrastim: *"The recommended clinical model for the demonstration of comparability of the test and the reference medicinal product is the prophylaxis of severe neutropenia after cytotoxic chemotherapy in a homogenous patient group (e.g. tumour type, previous and planned chemotherapy as well as disease stage). (…) Demonstration of the clinical comparability in the chemotherapy-induced neutropenia model will allow the extrapolation of the results to the other indications of the reference medicinal product if the mechanism of action is the same. Alternative models, including pharmacodynamic studies in healthy volunteers, may be pursued for the demonstration of comparability if justified. In such cases, the sponsor should seek for scientific advice for study design and duration, choice of doses, efficacy / pharmacodynamic endpoints, and comparability margins."* [55]

mAb: "*Comparative clinical studies between the biosimilar and reference medicinal product should always be conducted. The number and type of studies might vary according to the reference product and should be justified based on a sound scientific rationale. A stepwise approach is normally recommended throughout the development programme, and the extent and nature of the clinical programme depends on the level of evidence obtained in the previous step(s). During the clinical development programme, patients are normally enrolled commensurate with the level of evidence obtained from preceding steps which support comparability.*" [56]

The pharmacodynamic marker was accepted on the following basis: "Normally comparative clinical trials are required for the demonstration of clinical comparability. In certain cases, however comparative PK/PD studies between the similar biological medicinal product and the reference medicinal product may be sufficient to demonstrate clinical comparability, provided that all the following conditions are met:

- The PK of the reference medicinal product are well characterised.
- There is sufficient knowledge of the pharmacodynamic properties of the reference medicinal product, including binding to its target receptor(s) and intrinsic activity. Sometimes, the mechanism of action of the biological product will be disease-specific.
- The relationship between dose/exposure and response/efficacy of the reference medicinal product (the therapeutic "concentration-response" curve) is sufficiently characterized.
- At least one PD marker is accepted as a surrogate marker for efficacy, and the relationship between dose/exposure to the product and this surrogate marker is well known. A PD marker may be considered a surrogate marker for efficacy if therapy-induced changes of that marker can explain changes in clinical outcome to a large extent. Examples include absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor (G-CSF), and early viral load reduction in chronic hepatitis C to assess the effect of alfa interferons. The choice of the surrogate marker for use in PK/PD studies should be thoroughly justified. If PK/PD studies are used to demonstrate comparability of the biological medicinal products, care should be taken to investigate a relevant dose range to demonstrate assay sensitivity (see ICH topic E10). The margins defining clinical comparability of PK and PD parameters must be defined a priori and justified." [54]

3.2.6. Pharmacovigilance requirements are the same for all biologicals

As for all biologicals, the EMA continues to monitor the safety of biosimilar medicines once they are on the market. Each application for a biosimilar MAA contains a EU-Risk management Plan (EU-RMP). Within the new pharmacovigilance legislation, the Regulation (EU) No. 1235/2010, [35] recital 17 states that : "It is essential that a strengthened system of

pharmacovigilance not lead to the premature granting of marketing authorisations. However, some medicinal products for human use are authorised subject to additional monitoring. This includes all medicinal products for human use with a new active substance and biological medicinal products, including biosimilars, which are priorities for pharmacovigilance". Therefore, it is clearly mentioned that new pharmacovigilance rules apply to the biosimilar in the same way as for other new biologicals (see 3.1.1). As a result, manufacturers must include a "black symbol" (cfr. a black triangle in the UK) in the product information. In addition, "any biological medicinal product" authorised after 1 January 2011, which include biosimilars, are included in an additional monitoring list. The PRAS can decide to remove certain products of the list.

The members and experts of the Working Party on Similar Biologic Medicinal Products of the European Medicines Agency (EMA) address the concern of insufficient safety data at time of approval as follows:

"… The risk for detection of new (serious) adverse effects after licensing is considered much lower for a biosimilar than for a biological containing a new or modified active substance. Immunogenicity, on the other hand, is an ongoing concern, especially for biologicals for which immune responses have been linked to serious safety issues, the most quoted example being pure red cell aplasia caused by cross-reacting neutralizing antibodies against erythropoietin. Immunogenicity may be influenced by patient-, disease-, or product-related factors. Patient- and disease-related factors are already known from the experience gained with the originator product and therefore do not need to be reinvestigated for the biosimilar. The focus of the evaluation is thus on potential product-related factors, such as structural alterations (e.g., aggregation, which has been implicated in the immunogenicity of epoetins) or impurities/contaminants, most of which are readily detected by state-of-the-art analytical methods. However, even seemingly small differences may have an impact on immunogenicity, and analytical or animal data cannot predict immune responses in humans. Therefore, human immunogenicity data are generally necessary before licensing to exclude a marked increase in immunogenicity of the biosimilar compared with the reference product. If the incidence of the immune response is known to be rare and thus unlikely to be captured before licensing, an additional post-marketing study designed to detect more subtle differences in immunogenicity may be requested, which, as in the case of biosimilar epoetins, can be of substantial size.

The current prelicensing requirements are supported by the finding of excessive immunogenicity for a biosimilar somatropin because of the presence of increased amounts of host-cell-protein, which could be eliminated by introduction of an additional purification step and, more recently, the observation of 2 cases of neutralizing anti-epoetin antibodies associated with the subcutaneous use of a biosimilar epoetin alfa in a clinical trial in patients with renal anaemia, resulting in premature study termination. A thorough root-cause analysis of the latter cases identified tungsten-mediated unfolding and aggregation of the epoetin alfa as a potential cause for the increased immunogenicity. Because the soluble tungsten found in some of the syringes used for the product is not present in the drug product per se but stems from the manufacture of the syringes, this problem, if confirmed, could also be relevant to other epoetin-containing products. It should be emphasized that immunogenicity is a potential concern for all biologicals, not just for biosimilars". [47]

3.2.7. Extrapolation to other indications and route of administration

Biosimilars clinical development does not necessarily include trials for all indications approved for the reference medicine. However, as opposed to generics, biosimilars cannot automatically claim all indications of the reference product. Extending the findings from one set of conditions to another (such as extending and applying the data from clinical studies regarding one medical condition to another medical condition or extending data from clinical studies in adults to children), also referred to as extrapolation, can be demanded by the MA holder possibly without any additional clinical tests. The demand will require sound scientific justification and will be assessed on a case-to case basis keeping in consideration the existing knowledge and experience in the field, clinical experience, the mechanism of action of the molecule, the specific patient groups, etc. The EMA states that *"in case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. In certain cases, it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal*

product. Justification will depend on e.g., clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications. Possible safety issues in different subpopulations should also be addressed". [54]

Extrapolation, however, remains a matter of debate especially when different indications imply the use of significant different doses, children versus adults, the use of cytotoxic or immunosuppressive co-medication or when extrapolation to use in healthy individuals is concerned. For example, use of biosimilar filgrastim for stem cell mobilisation and collection in healthy donors is controversial since filgrastim is only studied extensively in patients with a suppressed immune system (i.e. undergoing chemotherapy) decreasing the risk for immune related side effects [57, 58] and the use of biosimilar in patients with cancer. In addition, there is growing concern in the rheumatology, gastroenterology, and dermatology communities regarding the future use of biosimilar anti-inflammatory monoclononal antibodies based on extrapolation of data.

The members and experts of the Working Party on Similar Biologic Medicinal Products of the European Medicines Agency (EMA) address the concerns on extrapolation of indication as follows:

"For extrapolation of data to be considered, several requirements need to be fulfilled:

A. Similarity with the reference product must be convincingly demonstrated, based on the totality of the evidence from a thorough comparability exercise. Clinicians need to be aware that clinical data are not the only cornerstone of a biosimilar development to be relied on. Extensive characterization and comparison of the physicochemical properties and biologic activity of the biosimilar and the originator product play a fundamental role in this, and close similarity in these aspects is a prerequisite for any reduction in the amount of nonclinical and clinical data requirements. Clinical data provide complementary information (e.g., regarding the clinical relevance of any observed differences and on immunogenicity).

B.(....) If the mechanism of action is different or unknown, additional convincing data [e.g., on pharmacodynamic parameters and/or specific and sensitive functional assays reflecting the respective pharmacologic action(s)] are necessary to provide further reassurance that the biosimilar will behave as the originator product in these indications. In this sense, comparative pharmacodynamic studies in healthy subjects are required for biosimilar G-CSF, evaluating, in addition to absolute neutrophil count, the CD34+ cell count to assess mobilization of stem cells from the bone marrow. Such data should not be considered in isolation but as a further building block in the overall proof of biosimilarity. (...)

C. Another prerequisite for extrapolation is that the safety profile of the biosimilar must have been properly characterized and unacceptable immunogenicity excluded. Extrapolation of immunogenicity data is only possible from high-risk to low-risk patient populations and clinical settings. For example, pure red cell aplasia resulting from neutralizing anti-epoetin antibodies is a potential concern for subcutaneous use of epoetins in patients with renal anemia but less for intravenous administration or use in cancer patients receiving chemotherapy. Therefore, extrapolation of immunogenicity data is considered possible from subcutaneous use in renal anemia patients to intravenous use in the same population or to subcutaneous use in immunocompromised cancer patients but not vice versa. In this respect, the concern expressed in a recent review, that immunogenicity data collected for intravenous use of epoetin could be extrapolated to subcutaneous use, is not substantiated because the respective guideline clearly states that comparative immunogenicity data will always be required for subcutaneous use, if applied for.

In this context, it should be emphasized that the scientific principles of extrapolation of data are not new for biosimilars but also apply to the comparison of prechange and postchange product on a change in the manufacturing process of a biological, which is already licensed for use in several indications. To the knowledge of the authors, up to now, there has not been a case, even with extensive changes to the manufacturing process, where new clinical data have been generated or requested in every indication because the overall data from the comparability exercise already conclusively demonstrated that the manufacturing change has no adverse impact on efficacy and safety. In conclusion, extrapolation of data to other indications of the reference product, and thus formal lack of a clinical trial in the respective clinical indication, does not imply less reassurance as regards efficacy and safety of the biosimilar if all the aforementioned considerations are taken into account, and represents a logical consequence of the scientific concept. Therefore, clinicians should

have confidence in using biosimilars for all indications for which they have been licensed." [47]

3.2.8. Interchangeability and substitution

Interchangeability refers to the medical practice of changing one medicine for another that is equivalent, in a given clinical setting on the initiative or with agreement of the prescriber. Interchangeability does not necessarily imply a change during the course of treatment, as the physician may decide to start a treatment with a given molecule. Primary substitution for biosimilars would imply that they are used rather than the reference product when starting treatment. Patients using a biosimilar are expected to have the same clinical benefit and the same risk for side effects as when starting on the reference product and hence there should be no meaningful clinical arguments to start on one or the other (other than the risk on the uncertainty or other co-indications). Secondary substitution implies a change from one molecule to another after initiating a treatment. Switching or secondary substitution is defined by replacement of an already existing treatment for a patient from a reference product to a biosimilar or visa versa with the consent of the physician (replacement of an original biological by a biosimilar already in use of the patient).

Automatic substitution is referred to when a reference product must automatically be exchanged by the biosimilar (or vice versa) usually by the pharmacist, without the explicit approval of the care provider.

The decision of interchangeability and substitution of medicines relies on national competent authorities [59], however it is unclear if they have full access to study reports or should be basing themselves on the EPAR. So far, automatic substitution is forbidden in most countries, like in Belgium. Secondary substitution is not recommended in most countries. [60]

The members and experts of the Working Party on Similar Biologic Medicinal Products of the European Medicines Agency (EMA) address concerns on interchangeability as follow:

"The question has been raised whether biosimilars could be considered interchangeable (in the sense of a therapeutic alternative initiated by, and under surveillance of the treating physician) with the respective reference product and, consequently, the concern that automatic substitution at the pharmacy level (without the knowledge of the physician) might follow. Undoubtedly, biosimilars developed in line with EU requirements can be considered therapeutic alternatives to their respective reference products. Interestingly, it has been stated that the originator products epoetin-alfa and epoetin-beta are considered as interchangeable by healthcare professionals because of the long medical experience with both products Although both epoetins can undoubtedly be considered efficacious and safe, similarity has never been demonstrated in a head-to-head comparison and dosage recommendations are not fully identical as would be required for a biosimilar." [47]

Key Points

- **Development process for biosimilars is determined by the choice (of the batches) of the reference product.**
- **Mandatory Centralized Market Authorization application procedure for biosimilars through EMA.**
- **Biosimilar approval pathway is based on a comparability exercise with the reference product:**
- **The scientific principles for establishing biosimilarity are the same as those for demonstrating comparability after a change in the manufacturing process of an already licensed biological.**
- **Similarity between biosimilar and reference product needs to be showed in the evaluation of physicochemical and functional characteristics, and clinical performance.**
- **Range of comparability that is acceptable is defined by the reference product and differences needs to be justified on scientific and clinical basis by indication.**
- **The demonstration of similar safety and efficacy to a reference product is generally done through a well-controlled, randomized, double-blind and parallel clinical study that includes: primary endpoints reflecting clinical benefits, a duration long enough to confirm the lack of difference in safety profile, and a sample size statistically powered for equivalence.**
- **Overarching guidelines exist which are specified in quality, non-clinical and clinical guidelines for biosimilar development.**

- Product-class specific guidelines define specifics for particular product classes where available.
- Extrapolations of indications can be made on a case-by-case base based on scientific evidence.
- Decision-making of the regulatory authority is based on the totality of the evidence provided by the applicant in support of biosimilarity.
- Regulatory experience will lead to evaluating guidelines and assessments.
- Good Manufacturing Practices (GMP) and standards apply to the manufacturing of biosimilar products in the same way as for any other biological medicinal product. Compliance is subject to inspections by national competent authorities.
- Traceability and strict pharmacovigilance regulation is set for all biologicals, including biosimilars.
- Biosimilars are therapeutic alternatives to the reference product.

3.3. EMA guidelines and FDA draft guidelines: main differences

The principles introduced in the EMA guideline have been adopted by various countries like Japan, Korea, Canada, Australia, Singapore and the WHO. The latter has been an important step, since the WHO also contains developing countries with unregulated approval processes, clearing the way for global acceptability and harmonization. In the USA, the Biologics Price Competition and Innovation Act (BPCI Act) was passed as part of the Affordable Care Act that President Obama signed into law in March 2010. The BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to or "interchangeable" with an US Food and Drug Administration (FDA)-licensed reference product [section 351(k) of the Public Health Service Act]). [61]

Biosimilar or biosimilarity means that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product". [8]

The draft guidelines for biosimilars, which were released in February 2012, are mostly adapted from the EMA with a few specifications (Table 2), but have not yet been implemented. Nevertheless, a couple of "biosimilar" products have gained market approval in the USA through different approval pathways. [62] The low molecular weight heparin enoxaparin sodium was authorized in 2010 through an abbreviated new drug application (ANDA) normally used for generics. Hence, a minimum of pharmacokinetics evidence were used to extrapolate safety and efficacy and resulted in a "AB interchangeable" rating (the US term for substitution). In contrast, the biosimilar pathway for heparins in the EU requires extensive PK, PD, immunogenicity and efficacy studies. In addition, Omnitrope has been approved as a follow-on protein product meaning it was deemed sufficiently similar to another approved protein product (Genotropin) to allow the manufacturers to rely on findings from clinical data regarding the safety and effectiveness of the other protein product. However, Omnitrope was not determined to be therapeutically equivalent to Genotropin and thus was not "AB rated."

In the US, a biosimilar is defined legally to be interchangeable with the reference product if (i) the biological product is biosimilar to the reference product; and (ii) it can be expected to produce the same clinical result in any given patient. In addition, for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. [61] As such, interchangeability is stricter than biosimilarity: biosimilarity plays on population level, while interchangeability at individual level and it implies potential interaction between the two different products. In the draft guidelines from the US, FDA can declare a biosimilar to be interchangeable (in the US per definition both primary and secondary substitution), but the agency has stated that it will require crossover (switching) studies to do so. Crossover (switching) studies are parallel-group studies (in which each pharmaceutical is administered to a different group of subject) usually designed to determine comparability. They only provide an estimate of total variance, and not of within-subject variation.

In crossover studies, there are 2 groups of patients that will start either on the originator or biosimilar product and then switch to the other product after a certain time period giving an estimation of within-subject variation.

For some biologicals, which have long half-lives, cross-over studies would be ineffective and unethical for assessing bioequivalence (PK/PD or efficacy). This is due to the fact that a crossover study requires a wash-out period (which would be long for pharmaceuticals with long half-lives) where the patient is not allowed to take the pharmaceutical and therefore will have no treatment for their condition. This makes an evaluation of interchangeability on efficacy difficult, however safety studies on switching can be performed. [63, 64] Interchangeability assessments between the biosimilar and the reference product in the US (product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product i.e. substitutable), is not automatically conferred for biosimilars, could arguably result in an decreased perception of risk of biosimilars in the US Moreover, especially in the US, substitution might be payer-driven.

Table 2 – Differences between EMA and FDA guidelines for biosimilars

	EU (EMA)	USA (FDA)
Data-exclusivity for biologicals	8 years data exclusivity and 2 years market exclusivity (+1 year for new indication) = 10 years + 1	4 year data exclusivity + 8 years market exclusivity = 12 years First interchangeable biosimilar = up to 1 year to other biosimilars
Quality	Must be same formulation unless stated otherwise	Allow differences in formulation, presentation
	Different expression systems are acceptable	Different expression systems are acceptable
Reference product (RP)	RP must be authorized in EU Since June 2012: RP must be authorized in EU, but can be sourced somewhere else (J. Dalli speech)	Accepts RP from other regions (such as EU)
Clinical	Equivalence studies for efficacy in selected indication(s), non-inferiority for immunogenicity accepted	Both equivalence and non-inferiority accepted (in selected indication(s))
Immunogenicity	Homogeneous, most sensitive population (can be healthy persons e.g. GCSF)	Most sensitive population
Pharmacovigilance	same post-marketing monitoring procedures as the innovator reference product: Risk management plan (RMP)	Risk evaluation and mitigation strategy (REMS)
Interchangeability	No opinion given by EMA, Responsibility for national agencies	Accepted biosimilars can be labelled “interchangeable” (meaning substitutable) by FDA
	Exempted from Paediatric Investigation Plan (PIP)	When not interchangeable, a biosimilar is viewed as a new active ingredient and requires Paediatric Investigation Plan (PIP)
Switching	No opinion given by EMA, Responsibility for national agencies	
Indication	Extrapolation of indication allowed on a case-by- case basis by scientific justification	Extrapolation of indication allowed on a case-by-case basis by scientific justification

Source: Adapted from Dowlat (2012) [25]

Box 6 – Differences EU versus USA

FDA can decide on interchangeability and substitution, while EMA chooses to leave this responsibility to national agencies, which mostly have not taken up this responsibility.

FDA explicitly accepts differences in formulation, presentation.

Shorter data exclusivity period for biologicals in EU.

FDA and EMA will accept reference product from other regions (US) under certain conditions, possibility of accepting clinical trials done in other regions.

4. BIOSIMILARS IN THE BELGIAN CONTEXT

Chapter 0 provided an overview of the regulatory pathway leading to market authorization of biological medicines in Europe. In this chapter, we focus on the Belgian situation regarding pricing and reimbursement decisions as well as on use of biosimilars. The first section of the chapter includes an overview of the pharmaceuticals reimbursement decision processes. Because biologicals are delivered by hospital pharmacy, a brief description of procurement in hospital settings is provided in section 4.2 and 4.3. For further details on pricing and reimbursement conditions for pharmaceuticals in Belgium we refer to KCE report 147B [65] and for detailed description of the functioning of the hospital pharmacy we refer to KCE report 126B. [66] Section 4.4 presents data on pharmaceuticals in Belgium. The last section addresses the introduction and use of biosimilars within the previously described framework.

4.1. Reimbursement pathway

The request for market authorization and reimbursement for medicinal products in inpatient and outpatient settings follows the same pathway in Belgium. Market authorization can be granted by the European Commission following an opinion by the European Medicines Agency (EMA) via the centralised procedure or by the Federal Agency for Medicines and Health Products (FAMHP) using a national procedure, decentralized procedure or a mutual recognition procedure[g]. Request for reimbursement is possible only after obtaining marketing authorization. The Drug Reimbursement Committee (CTG – CRM) reviews the reimbursement request file of a new medicinal product and submits an advice to the Ministry of social affairs. At the same time, the pharmaceutical company sends a price request to the Ministry of economic affairs. The requested price might not correspond to that advised by the CTG – CRM. The final appraisal report by the CTG – CRM includes the reimbursement basis and price (here addressed as list price), the reimbursement category (patient cost-sharing), specific conditions for patient reimbursement and the reimbursement group according to the therapeutic chemical classification[h].

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. Within this class, three sub-groups are defined: 2A covers new dosages for already reimbursed pharmaceutical; 2B covers medicinal products not corresponding to the category 2A, 2C or to Class 3 and 2C covers medicinal products obtaining market authorization based on scientific literature.

---

g In French, Agence Fédérale des medicaments et des Produits de Santé (AFMPS) and in Dutch Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG)

h We only provide details on the first two points. Specific reimbursement conditions are defined in seven *Chapters.* Conditions may include “a priory” approval by the medical officer (Chapter IV) or ex-post controls (Chapter 2). For more information please refer to KCE report 147B[65] or to the INAMI–RIZIV website http://www.inami.fgov.be/drug/fr/drugs/general-information/refunding/index.htm

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. [65, 67] Class 3 also include three sub-groups that include generic medicinal products who obtained market authorization based on different prerequisites[i]. [67]

The reimbursement basis usually corresponds to the pharmaceutical pharmacy list price. Exceptions mainly concern:

- Reference medicinal products included in the reference price system, for which the retail price may be higher than the reimbursement basis.
- Pharmaceuticals in category F, for which the reimbursement basis is a flat rate that may be below the retail price.

The reimbursement category determines patient cost-sharing. Since April 2012, there are 7 reimbursement categories (A, B, C, Cs, Cx, Fa and Fb). [68] 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 4.7 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. Cost-sharing mechanisms according to different categories in community pharmacies are described in detail in the appendix 2).

4.2. Functioning and reimbursement of pharmaceuticals dispensed by the hospital pharmacy

In broad terms, hospitals have three main sources of funding: the budget of financial means[j], physician fees and pharmaceutical products. These three funding sources represent approximately 95% of total hospital resources. [69] Other sources of funding include specific lump sums for day hospital activities (i.e. mini-lump sum covering urgent admission and intravenous therapy), conventions covering specific chronic disorders (i.e. financing of haemodialysis, rehabilitation conventions), budgets for laboratory testing and medical imaging, federal or regional level funding for infrastructure and patients out-of-pocket payments[k]. [66]

There are four main financing sources for pharmaceuticals in hospital (besides patient co-payments). First, the hospital pharmacy budget is directly dependent of the hospital resources as functioning cost are mainly funded by the subpart B5 of the budget of financial means (corresponding approximately to 2% of total budget). No margin for the pharmacists can be added to the ex-factory price for inpatient reimbursed pharmaceuticals. Second, in 2006 a prospective budget was introduced to cover the cost of pharmaceutical for hospitalised patients. The prospective budget applies neither to psychiatric or chronic hospitals, nor for one-day hospitalizations. Moreover, these budget excludes: 1) pharmaceuticals highly relevant to medical practice, in terms of therapeutic needs, social values and innovative character; 2) pharmaceuticals whose high costs can strongly delay their administration to a hospitalized patient if it is included in the prospective budget and 3) other specific products excluded by law (e.g. orphan pharmaceuticals, cytostatics, immunoglobulins and albumins, retroviral pharmaceuticals, radioisotopes, etc.). Third, for pharmaceuticals excluded of the prospective budget, the hospital invoicing is set according to the pharmaceutical category (using the full reimbursement basis). A delivery margin for the pharmacist of 21.746% with a maximum of € 7.11

[i] For medicinal products proving efficacy and safety proves based on scientific literature and not on pharmacological and toxicity trials, nor on results from clinical studies as determined by Article 2, 8°, a), second hyphen of the Royal Decree of 3 July, 1969 or by Article 6bis, § 2 of the Law on medicinal products of 25 March, 1964

[j] In French Budget des Moyens Financiers (BMF) and in Dutch Budget Financiële Middelen (BFM)

[k] Out-of-pocket payments include patients' official co-payments (difference between official fees and the third party-payer intervention) as well as additional charges or supplements not covered by the health insurance.

per package per large package can only be added for non-reimbursed pharmaceuticals or for reimbursed outpatient pharmaceuticals (e.g. pharmaceuticals for patient in day hospitalisation, in medical imaging, or in nuclear medicine). Therefore, unit prices for pharmaceuticals dispensed in hospitals differ between hospitalised and ambulatory patients for reimbursed pharmaceuticals (see details in the appendix 2). Finally, procurement of pharmaceuticals via direct negotiations between hospital pharmacists and pharmaceutical companies lead to discounts on list prices that are fully received by the hospital (see section 4.3.1 for details)

4.3. Changes in procurement policies in hospital settings: from direct negotiations towards public tendering

4.3.1. Procurement of pharmaceuticals, the hospital pharmaceutical formulary and the pharmaceutical and therapeutic committee

In Belgium, there is no specific hospital only medicines list. However, reimbursement of pharmaceuticals may be linked to its delivery at a hospital pharmacy and it is therefore clearly stated in the conditions for reimbursement. [70] Expensive pharmaceuticals have been historically delivered by hospitals pharmacies as means to guarantee their proper use. All pharmaceuticals used in hospitals for the diagnosis or treatment of patients need to be distributed by the hospital pharmacy (art.7. RD 4 March 1991 [71]). The pharmaceuticals that are preferentially used in the hospital are included in a list, the hospital pharmaceutical formulary (Article 24 RD 4 March 1991 [71]). Selection of pharmaceuticals needs to be performed "on a balanced and economically justified way by the pharmaceutical and therapeutic committee (MFC – CMP[l]) (art. 25 § 1, 1° RD 4 March 1991 [71]). This committee is composed of the hospital director or his/her representative, the chief hospital pharmacists and one or more hospital pharmacists if available, the chief physician, physicians appointed by the medical council, if necessary other physicians-specialists (for instance because of the discipline-specificity of a pharmaceutical) and the chief nursing services. [71] The pharmaceuticals in the pharmaceutical formulary are deemed to be permanently available to cover patient therapeutic needs. If a pharmaceutical is not mentioned in the pharmaceutical formulary, prescription and administration to the patient are solely allowed if the MFC – CMP gives its explicit permission.

The MFC – CMP tasks are clearly defined in the RD of 4 March 1991. They include: i) organisation and decision-making on the articles of the association, ii) storage and organization of pharmaceuticals purchased by the hospital iii) update of the hospital pharmaceutical formulary. [70] The MFC – CMP meets at least once a year.

In principle, the MFC – CMP is free to include pharmaceuticals on the list if it can be argued that the choice was "balanced and economically justified". Legislation, however, does not clarify whether the choice should be economically justified for the patient, the third-party payer or the hospital. In line with the task of setting an economically justified choice, the MFC – CMP and the hospital pharmacist play a direct role in price negotiation for pharmaceuticals delivered by the hospital pharmacy. As such, in hospital settings, direct negotiations between purchasers (hospital pharmacists) and providers (pharmaceutical companies) may 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. Due to these negotiations, the actual costs for the hospital pharmacy may differ to that charged at invoicing to the third party-payer. Hospitals do not have any obligation to communicate the actual discounted price paid and any surpluses between the third-party payer reimbursement level and the "hospital discounted price"[m] remain as a part of the hospital (pharmacy) budget.

As is the case in Belgium, the Hospital Pharma Report (PHIS) showed that the commercial practice of providing discounts (or other advantages such as rebates) to hospitals occurs in many European countries. Advantages provided to hospitals by pharmaceutical companies are also kept confidential in other European countries. The authors mention that the extent of discounts may vary according pharmaceutical specialties (with limited or no discounts for on-patent pharmaceuticals) and among

[l] In Dutch Medisch-farmaceutisch comité (MFC) and in French comité médico-pharmaceutique (CMP)

[m] Hospital discounted price is understood as the price paid after taking into account any discounts or rebates.

hospitals within the same country (with larger discounts being provided to larger hospitals). At a country level, regulation of discounts depends on the organisation of the health care sector and on the actors involved in the procurement of pharmaceuticals. [72]

Vloger et al. argue that even in the light of large financial gains for purchasers, discounts need to be considered as an obstacle to competition. On an international perspective, policies such as external reference pricing may provide limited results in terms of cost-containment as they are based on list prices and not on the actual lower discounted price. Moreover, the presence of discounts may limit national authorities (public payers) capacity to set cost-containment policies leading to savings that may ultimately increase access to medicines. [73, 74] How much discounts entail competition remains an open question. In the case of Belgium, the introduction of public tenders from 1 July 2013 onwards may provide a big change to the current commercial practice of discounts and may open a way to a more competitive market. Discussion on possible implication of the forthcoming public tenders is presented in section 4.3.3.

4.3.2. Public procurement of pharmaceuticals

4.3.2.1. Europe

Public procurement is the purchasing by public sector bodies and certain utility sector bodies of contracts for goods. On the European level, tendering activities are embedded in a predefined and structured legal framework specifying the a.o. different procedures, award criteria, the obligation of publishing the outcomes etc. (see appendix 3 for details). The tendering procedures required under EU public procurement rules aim at more competition, stronger safeguards against corruption and better service and value for money for taxpayers. Tendering of pharmaceuticals is mainly regulated by the general EU Directive 2004/18 that establishes the framework for the tendering of goods, services and supplies. [75] This Directive was to be implemented in the legation of the member states by 31 January 2006. Directive 2007/66/EC aims at the effectiveness of review procedures and legal protection concerning the award of public contracts. [76] Currently, the respective Directives are under revision aiming at a general simplification of procedures. For health services, a specific regime with a higher threshold of EUR 500 000 (for publication of the tender on the EU level) and imposing only the respect of basic principles of transparency and equal treatment was proposed. The evaluation on the impact and effectiveness of EU public procurement legislation has shown that social, health and education services have specific characteristics which make them inappropriate for the application of the regular procedures for the award of public service contracts. [77]

4.3.2.2. Belgium

Public procurement is basically regulated by the law of 24 December 1993. [78] A law passed in 2006 replaces the law of 1993 and implements the European Directive 2004/18. [79] Since the entering into force of the new law is phased, however[n], parts of the 1993 legislation are currently still applicable.

Until the end of 2012 public hospitals[o] were not submitted to the public procurement regulations defined in the Belgian law if the amount of the services does not exceed the European thresholds of 200.000 euro (art. 115 wet van 14 January 2002 houdende maatregelen inzake gezondheidszorg [81]). University hospitals without legal personality are not submitted to the procurement regulations if the services do not exceed the European thresholds, except if they obtain subsidies (art. 4 § 2; 9° Wet 1993). If the amount of the services exceeds the European thresholds the procurement regulations apply if the university can be labelled as contracting authority according to the criteria specified in the respective Directive (art. 1, 9° Directive 2004/18). [79] Private hospitals with legal personality are submitted to the procurement regulations if they meet the criteria of a contracting authority.

---

n Relevant Belgian legislation: Law 24 December 1993 [78], R.D. 8 Januari 1996 (classical sectors), -R.D. 10 Januari 1996 (special sectors), R.D. 18 June 1996 (special sectors), R.D. 26 September 1996 (general execution modalities), Art. 115 from the Law of 14 January 2002, Law from 23 December 2009, Law of 15 June 2006; RD 15 July 2011 (classical sectors), RD 12 September 2011. For an overview of the regulations regarding public procurement see S. Van Garsse, Artikelsgewijze commentaar op de wetgeving overheidsopdrachten (Loose-leaf) Brussel : Politeia, 2011).

oo Public hospitals are defined for as hospitals managed by a legal body of public law or by a Public Municipal Welfare Centre. [80]

The entering into force of the Belgian legislation making tendering for Pharmaceuticals obligatory for hospitals (Law 15 Juin 2006 and it's executory decrees) is foreseen for 1 juli 2013(reference vers AR 14 janvier 2013). This date has not yet been confirmed by law. All Belgian hospitals (except for private for profit hospitals and hospitals without legal personality if the university to which the hospital is linked is not a contracting authority) will be submitted to procurement procedures for the purchase of the pharmaceuticals used in the hospital setting, regardless of the amount of the assignment[p]. [83]

4.3.3. Possible impact of the public procurement for pharmaceuticals

4.3.3.1. Description of the product in the tender: possibility to exclude a specific pharmaceutical?

The description of the pharmaceutical (award criteria) in the tender can lead to an implicit exclusion of a pharmaceutical, for instance a biosimilar. In principle, the contracting authority is free to define the modalities of the subject of the tender within the limits described in the Directive 2004/18. The Directive foresees some restrictions: "unless justified by the subject-matter of the contract, technical specifications shall not refer to a specific make or source, or a particular process, or to trade marks, patents, types or a specific origin or production with the effect of favouring or eliminating certain undertakings or certain products. Such reference shall be permitted on an exceptional basis, where a sufficiently precise and intelligible description of the subject-matter of the contract; such reference shall be accompanied by the words "or equivalent"(art. 23, 8°)." This provision is not specific enough to frame the description of pharmaceuticals. Pharmaceuticals can be defined according to their International Non-proprietary Name (INN), the therapeutic class, the pharmacological class, the ATC code, the indication, etc. Moreover, other parameters such as the dosage, the bioequivalence, the presentation, the expiry date, the therapeutic indications, etc. can be taken into account to define the specific product. Today there are no specific rules or guidance clarifying the required characteristics for the description of pharmaceuticals in tenders. Current practices vary amongst member states. In a study using data on pharmaceutical expenditures from 2005 to 2009 in Denmark, calls for tender for pharmaceuticals were analyzed. It appeared that overall the description of the pharmaceutical was very specific, stating the exact pharmaceutical substance, anatomical therapeutic chemical (ATC) classification code (WHO Collaborating Centre for Drug Statistics Methodology 2008), strength, dispensing form, potentially package sizes and an estimate of the expected amount of units demanded of each pharmaceutical. Calls for tender were organised on the level of generic substitutability rather than therapeutic classes. Results from a study of tenders for pharmaceuticals in Italy, however, show it was organized on the level of the therapeutic class. [84] Seldom, public procurement is the only procedure used to purchase pharmaceuticals in hospital settings. However tendering is still a major purchasing policy in many European countries. [72] It should be noted however that, although there is no particular framework for the description of pharmaceuticals in tenders, the general rule of non-discrimination and equal treatment of tenders applies.

4.3.3.2. More transparency in prices and other advantages?

Although the application of the procurement procedures obliges pharmaceutical firms to make their prices and adjacent services transparent, details are solely available for the parties concerned (see appendix 3). It is unclear to what extent governmental authorities will be aware of the real prices for pharmaceuticals in the respective hospitals. Today, in principle pharmaceutical firms are obliged to notify the real prices to the "Service des prix" of the Federal Service Economy (art. 10 Ministerial Decree on prices of reimbursable pharmaceuticals [85]). In practice, the notion of real price is to be understood as the list price. The amount of rebates and discounts is thus not notified. Moreover, pharmaceutical firms are obliged to keep a file containing all financial and in natura benefits to hospitals or prescribers (as referred to in art. 10 § 7 Geneesmiddelenwet [86]) linked to the respective pharmaceutical for which they own a market authorization. This allows the Federal Agency for medicines and health products to identify and check these advantages (art. 15 Koninklijk besluit betreffende de voorlichting en de reclame inzake geneesmiddelen voor menselijk gebruik). [87] It is doubtful, however, whether these files are kept in practice, if they are checked and whether information on discounts and rebates is included. Other advantages that

[p] On the discussion applicability public procurement rules to hospitals see also J. Van der Gronden e.a. Health Care and EU law. [82]

are frequently granted to hospitals are chairs, scientific prices, sponsoring. If they are not linked to any promotion of the respective pharmaceutical (as referred to in art. 9 and 10 Geneesmiddelenwet [86]), these advantages are legal. The Deontological Code of Pharma.be specifies that these advantages need to serve health promotion or the promotion of scientific research (art .38 Code pharma.be). [88]

With the introduction of the public procurement procedures all advantages playing a decisive role in the hospital's choice of a firm delivering the pharmaceutical should be included in the tender. This should in principle lead to increased transparency on prices and adjacent services. Several attempts are being made worldwide to enhance transparency in the advantages that are granted by pharmaceutical firms to health care professionals, hospitals or other health care institutions. The American Sunshine Act for instance provides patients with the right to know about potential conflicts of interest between their physician and industry, and intends to help to protect patients from payments or financial relationships that could compromise the quality or cost of their healthcare. The first reports will be due 31 March 2013 for the calendar year 2012. [89] In France similar legislation providing that health products companies must make available to the public the existence of any contract with health care providers and certain entities of the health sector has been adopted. [90] The implementing Decree has not been passed yet.

4.3.3.3. The force of competition versus discounts?

According to the law on pharmaceuticals, it is prohibited for companies to grant financial or in natura benefits to hospitals or prescribers, delivering, administering medical devices (art. 10 § 7 Geneesmiddelenwet van 25 maart 1964). [86] Discounts and rebates however are allowed as far as they are transparent, objective, non-discriminatory and non-excessive (article 101 Wet betreffende marktpraktijken en consumentenbescherming [91], prohibits to sell at a loss and as far as the practice is no unfaithful (in the sense of articles 84 - 87, 91 and 94 - 99 Wet betreffende marktpraktijken en consumentenbescherming [91]). Firms obtaining a monopoly position for instance cannot grant excessive discounts to maintain this position. Tendering may disturb the current common practice of discounts in the negotiations between pharmaceutical firms and hospitals. In the idea of quantity-based discounts, "losses" for one product are compensated by the benefit of another product. The application of the tendering procedures, however, hampers these practices because tenders will be launched for separate product groups. It is unclear if the competition aspect will compensate this effect.

4.3.3.4. Impact on parallel import?

Parallel imports are goods produced under patent placed into circulation in one market, and then imported into a second market without the authorization of the local owner of the intellectual property right. [92] For example, according to the rules of internal market in the European Union, a hospital pharmacy is allowed to purchase quantities of prescription pharmaceuticals in another country and import them without the approval of the local distributor owning licensed patent rights. Parallel imports are identical to legitimate products except that they may be packaged differently and may not carry the original manufacturer warranty. It is conceivable that procurement procedures with publication in the European Union will increase competition between local and foreign distributors.

4.4. Pharmaceutical expenditures and cost-containment policies in Belgium

4.4.1. Recent evolution of pharmaceutical expenditures for the third-party payer

In 2010, 17.23% of total RIZIV – INAMI health care expenditures[q] concerned reimbursed pharmaceuticals. Pharmaceutical expenditures in community pharmacies increased by 6.2% and 12.24% respectively for the periods 2006-2007 and 2007-2008. The large increase between years 2007 and 2008 can in part be attributed to the integration of small risk coverage for self-employed since 1 January 2008. For the years 2008-2009 and 2009-2010 increase of expenditures by the RIZIV – INAMI in community pharmacies was respectively of 3.98% and 1.66%.

Concerning pharmaceuticals delivered by hospital pharmacies, RIZIV – INAMI expenditures for ambulatory patients have exceeded expenditures for hospitalized patients since 2007. Pharmaceutical expenditures for

[q] http://www.inami.fgov.be/information/fr/accounting/budgets/press/budget2010/press2009102102.htm

ambulatory patient have continuously increased while expenditures for hospitalized patients have decreased since 2007. Overall, total expenditures for pharmaceuticals in hospital settings continue to increase.

Table 3 – RIZIV – INAMI Pharmaceutical expenses in community and hospital pharmacies 2005-2010 (in million euros)

	2005	2006	2007	2008	2009	2010
Community pharmacy	2 205.5	2 155.1	2 288.8	2 568.9	2 670.1	2 714.3
Hospital pharmacy						
Ambulatory patients	451.3	477.7	570.0	671.8	736.3	814.1
Hospitalized patients	513.5	503.0	502.3	510.2	497.4	484.4
Total	3 170.3	3 135.8	3 361.2	3 750.8	3 903.8	4 012.7

Source: Monitoring of reimbursement significant expenses (MORSE). Semi-annual Report (semester 1-2011) data 2010 http://www.inami.fgov.be/drug/all/drugs/statistics-scientific-information/report/pdf/morse201001.pdf

The following table includes RIZIV – INAMI expenditures for top 20 pharmaceuticals in community and hospital pharmacies. Within the top 5 of higher reimbursements for RIZIV – INAMI, we find three monoclonal antibodies (infliximab and adalimumab and trastuzumab) and two statines (atorvastatin and rosuvastatin). Within this top 5, one has already lost his patent (artorvastatin) and one (infliximab) will see their patent expire in 2014. Currently, two biosimilars for infliximab are being evaluated by the European Medicines Agency.

Table 4 – Top 20 pharmaceutical expenses (in €) for RIZIV – INAMI

	ATC	International Non-Propietary Name (INN)	RIZIV – INAMI	Setting
1	C10AA05	Atorvastatin	116 688 162	Community
2	L04AB04	Adalimumab	97 673 654	Community
3	L04AA12	Infliximab	90 266 686	Hospital
4	C10AA07	Rosuvastatin	72 394 577	Community
5	L01XC03	Trastuzumab	61 337 274	Hospital
6	L04AB01	Etanercept	60 585 181	Community
7	J06BA02	Immunoglobulins	53 467 686	Hospital
8	B03XA02	Darbepoetin alfa*	53 457 323	Hospital
9	A02BC01	Omeprazol	51 859 963	Community
10	R03AK06	Salmeterol and other drugs	46 220 175	Community
11	A02BC02	Pantoprazol	44 661 079	Community
12	B02BD02	Coagulation factor viii	44 175 266	Community
13	R03AK07	Formoterol and other drugs	42 520 678	Community
14	L03AB07	Interferon beta-1a	36 575 993	Community
15	N05AH04	Quetiapin	34 254 864	Community
16	S01LA04	Ranibizumab	34 166 762	Hospital
17	C10AA01	Simvastatin	33 849 926	Community
18	N06AB10	Escitalopram	33 681 106	Community
19	L01XC02	Rituximab	32 602 143	Hospital
20	L03AA13	Pegfilgrastim*	31 981 299	Hospital

4.4.2. Recent policies aiming at reducing pharmaceutical expenditures

Before presenting thoroughly the biosimilar regulation, a rapid overview of measures undertaken in Belgium to reduce expenditures for pharmaceuticals is provided in this section. Indeed, encouraging use of biosimilars is in line with recent pharmaceutical policies aiming at reducing pharmaceuticals expenditures. Measures undertaken since 2011 include:

- Larger price reduction for pharmaceuticals included in the reference price system. Reductions are set to:
  - 31% for pharmaceuticals included in a reference group for less than two years (41% for pharmaceuticals in category A)
  - 35.14% for pharmaceuticals included in a reference group for over two years (additional decrease of 6%)
  - 38.71% for pharmaceuticals included in a reference group for over four years (additional decrease of 5.5%; additional decrease of 7% for pharmaceuticals in category A)
  - Moreover, the different galenic forms of pharmaceuticals and sisters molecules of an original subject to generic competition who were previously exempt from reduction are now reduced by the halve of the required percentage.
- In 2012, the pay back system for pharmaceutical companies was enlarged setting new modalities on the payment of contributions by the pharmaceuticals companies on the turnover of pharmaceuticals for which a contract has been concluded with the NIHDI. Because these contracts resulted in a refunding of a certain amount to the NIHDI, the contribution will not be due on the part refunded.
- The Hospital budget for pharmaceuticals: Since July 2006, a prospective budget for inpatient pharmaceuticals in acute hospitals was introduced. Most inpatient pharmaceuticals are integrated in this prospective budget for 75% of their value. Each hospital prospective budget is calculated based on its case mix and the national average cost per APR-DRG, taking into account the severity of illness. These average costs are established annually. In 2012, this budget was globally reduced by € 15 million in the idea of recovering rebates granted to hospitals by pharmaceutical companies.
- Regular price reductions have been imposed on “old” pharmaceuticals (i.e. reimbursed for over 12 or 15 years). On 1 April 2012, an overall decline of 1.95% for all pharmaceuticals came into force. Pharmaceutical companies had the choice between two solutions: 1) a linear reduction of 1.95% on all their products; or 2) a flexible reduction of prices on several products (further decrease the prices of certain medicines to keep others unchanged). It is also foreseen to look for the evolution of ex-factory prices in Germany, France, the Netherlands, Finland, Austria and Ireland for pharmaceuticals under patent on the Belgian market for over 5 years and under 12 years.
- Delivery of the pharmaceutical amongst the cheapest for prescriptions under the International Nonproprietary Name (INN): Since April 2012, community pharmacists are obliged to dispense a pharmaceutical among the group of cheapest medicines for every prescription under the INN. The group of cheapest medicine concerns medicines with the same molecule, the same administration form, the same dosage and for which the public price is in a range of 5% around the cheapest (determined by the reimbursement basis of the ex-factory price divided by the number of units). The pharmacist has the choice between at least 3 specialties. As a consequence, if the group of cheapest medicines only include one pharmaceutical, the pharmacist has the choice between this pharmaceutical and the second and third least expensive even if it exceeds the range of 5%.
- Delivery of the pharmaceutical amongst the cheapest for acute treatments with an antibiotic or an antifungal: For acute treatments with an antibiotic or an antifungal, the pharmacist should treat the prescription as a prescription under the INN (see above), even if a specific medicine was mentioned. Exceptions are however foreseen, i.e. the physician can specify that the order should be strictly followed for a therapeutic reason or because of allergy or intolerance to an excipient with known effects. Moreover, this obligation only concerns acute treatment.As in the case of a prescription under the INN, the prescriber keeps his therapeutic freedom because he still decides about the active ingredient, the administration form, the dosage, and other specifications (e.g. effervescent tablet).

- Savings on proton pump inhibitor: Since June 2012, a ceiling-reimbursement basis was calculated for each molecule of the group. This ceiling corresponds to the reimbursement basis of the cheapest medicine in the group (= products with same molecule, administration form, dosage and pack size) increased by 23.7%. Specialties with a higher price than the ceiling are not reimbursed (resulting in a price reduction for some of them).
- Refunding by pharmacists: Between 1 July 2012 and 31 December 2012, community pharmacies must refund an amount of € 17 787 000.
- € 15 million to compensate the public rebates that pharmaceutical companies could grant in the cadre of the substitutive measures for prescriptions under INN coupled with the mandatory provision of the less expensive pharmaceutical for acute treatment with an antibiotic or an antifungal.
- € 2.787 million to compensate the agreement on a full indexation of pharmacist fees from 1 April 2012 instead of the half indexation imposed to the entire sector during the setting of the budgetary objective for 2012. This payment will be made through a contribution per package for each reimbursed pharmaceuticals send between 1st July 2012 and 31 December 2012. The contribution depends on the pharmacy size (i.e. the classification of community pharmacies is done according to the total amount of fees perceived for the delivery of reimbursed pharmaceuticals). This contribution will amount to € 0.20 per package for community pharmacies whose fees are lower than the 21 percentile, € 0.38 for those above the 79 percentile, and € 0.32 for the others.

4.5. Biosimilar pricing and reimbursement procedure

Request for reimbursement for biosimilars follows the same pathway than any other pharmaceutical in Belgium. The current reimbursement framework does neither contain clauses determining the reimbursement basis nor a mandatory price reduction for biosimilars. [67] All reimbursement claims for biosimilars have been filled under class 2 (more precisely in the sub-class 2B) 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. Therefore, current pricing and reimbursement rules for generics are not applied to biosimilars.

Companies producing biosimilars proposed an initial voluntary price reduction with respect to list price of the reference product comprised between 10 and 15% (see Table 5). However, negotiations between pricing authorities and biosimilar firms have lead to further price reductions ranging from 20% to 34%. Until July 2012, 6 reimbursement request files were filled resulting in five positive decisions (Binocrit, Retacrit, Omnitrope, Zarzio, Tevagrastim) and in one negative decision (Nivestim). Pharmaceuticals containing epoetin, filgrastim and somatropin are considered as vital and therefore patient cost-sharing is limited (see appendix 2 for details).

Table 5 – Information on therapeutic class, pricing and market share for available biosimilars in Belgium

Reference product (RP)	Available In Belgium	Information from the request for reimbursement*		Ministerial decision**	
		Class	Initial price difference with RP	Price difference with RP	Patient reimbursement
Eprex (epoetin)	Binocrit (01/2010)	2B	-15%	-30%	A (Fa)
	Retacrit (10/2010)	2B	-20%	-34%	A (Fa)
Genotropin (somatropin)	Omnitrope (04/2008)	2B	-12%	-22%	A/B
Neupogen (filgrastim)	Zarzio (01/2010)	2B	-15%	-20%	A
	Tevagrastim (02/2010)	2B	-10%	-20%	A

*Source: * Evaluation Report from the Drug Reimbursement Committee (CTG – CRM) (http://www.inami.fgov.be/drug/fr/drugs/decisions_report/report_crm_cgt/index.htm). Files not available online were requested to the CTG – CRM. Results in the table correspond to the first file sent by pharmaceutical firms for request for reimbursement. ** Ministerial Decisions (http://www.inami.fgov.be/drug/fr/drugs/decisions_report/decisions_minister/index.htm). N.A: not applicable because low-cost quotas only cover pharmaceuticals delivered in community pharmacies.*

4.6. Biosimilar uptake and expenditures

The tables in this section show the evolution of the market shares of the three groups of pharmaceuticals for which a biosimilar is currently available (see Table 6 to 9). We include both biosimilars and the reference product as well as non-reference product within the same therapeutic class. Data in this chapter aims at providing a descriptive overview. It is not within the scope of the study to interpret changes in prescription for the different molecules (e.g. first in class and second- generation pharmaceuticals). Uptake of biosimilars for erythropoietin has been almost zero, except for some minimum sales in 2011 (62.34 DDD corresponding to € 477 for the RIZIV – INAMI, see Table 6).

Table 6 – DDD and RIZIV – INAMI expenses for all available epoetins in Belgium

	Setting	Product	2007	2008	2009	2010	2011
Volume (DDD)	Hospital pharmacies	Binocrit	0	0	0	0	62
		Eprex	2 338 571	2 334 895	2 213 900	2 133 197	1 963 627
		Neorecormon	2 427 041	1 986 680	1 385 991	1 014 000	719 180
		Recormon	77	1 000	198	0	0
		Aranesp	4 042 261	4 048 273	4 272 566	4 278 633	4 859 673
		Mircera	0	146 263	592 881	745 938	1 000 960
RIZIV – INAMI Expenditures (Euros)	Hospital pharmacies	Binocrit	0	0	0	0	447
		Eprex	23 922 283	24 053 580	22 786 601	21 710 972	19 348 364
		Neorecormon	26 304 956	21 480 058	13 312 252	9 239 702	6 423 067
		Recormon	1 104	12 976	2 656	0	0
		Aranesp	45 572 724	45 702 351	47 538 917	47 173 865	53 457 323
		Mircera	0	1 983 690	8 128 863	10 374 531	13 883 347

Source: RIZIV – INAMI. Provisory data for 2011.

As for erythropoietin, take up of biosimilars for filgrastim has been almost zero, except for some minimum for Zarzio sales in 2011 in hospital pharmacies (277 DDD corresponding to € 18 938 for the RIZIV –INAMI and for Tevagrastim in community pharmacies (77 DDD corresponding to € 5 516 for the RIZIV – INAMI (see Table 7).

Among the three categories of pharmaceuticals for which a biosimilar is available, only the somatropin biosimilar has had a market penetration. Somatropin is mostly dispensed in community pharmacies and current sales (2011) for Omnitrope account for 21 375 DDD, representing a RIZIV – INAMI expenditure of € 318 560. In hospital settings, sales for Omnitrope are null (see Table 8).

Table 7 – DDD and RIZIV – INAMI expenses for filgrastim (biosimilar and reference product) as well as for pegfilgrastim

	Setting	Product	2007	2008	2009	2010	2011
Volume (DDD)	Hospital pharmacies	Neupogen	50 932	50 792	53 409	52 648	56 366
		Granocyte	8 398	11 541	7 984	2 564	2 653
		Neulasta	301 660	341 800	396 500	445 500	510 464
		Zarzio	0	0	0	0	277
		Tevagrastim	0	0	0	0	0
	Community pharmacies	Neupogen	5 875	6 155	5 720	5 005	4 649
		Granocyte	263	421	406	53	68
		Neulasta	4 440	4 060	1 400	1 264	420
		Zarzio	0	0	0	0	0
		Tevagrastim	0	0	0	0	71
RIZIV – INAMI Expenditures (Euros)	Hospital pharmacies	Neupogen	4 660 657	4 531 470	4 797 178	4 682 434	4 884 814
		Granocyte	1 024 046	1 304 186	894 485	280 281	284 960
		Neulasta	19 355 764	21 912 837	25 265 386	28 015 444	31 981 299
		Zarzio	0	0	0	0	18 938
		Tevagrastim	0	0	0	0	0
	Community pharmacies	Neupogen	585 856	600 948	560 444	486 753	442 438
		Granocyte	32 990	50 051	47 743	6 019	7 597
		Neulasta	295 779	270 465	92 320	82 225	27 283
		Zarzio	0	0	0	0	0
		Tevagrastim	0	0	0	0	5 516

Source: RIZIV – INAMI. Provisory data for 2011.

Table 8 – DDD and RIZIV – INAMI expenses for somatropin (biosimilar and reference product)

	Setting	Product	2007	2008	2009	2010	2011
Volume (DDD)	Hospital pharmacies	Omnitrope	0	0	0	0	0
		Genotonorm	2 398	2 552	3 316	2 824	4 814
		Humatrope	216	783	810	504	368
		Norditropin	0	293	968	1 058	1 093
		Nutropin	480	45	45	360	108
		Zomacton	492	774	798	150	68
	Community pharmacies	Omnitrope	0	225	2 025	11 189	21 375
		Genotonorm	470 814	509 828	529 060	531 866	518 444
		Humatrope	92 961	96 813	93 483	81 889	70 335
		Norditropin	237 578	271 125	283 185	296 007	307 350
		Nutropinaq	32 385	41 910	49 980	57 399	66 465
		Zomacton	43 386	52 440	58 794	65 962	75 486
RIZIV – INAMI Expenditures (Euros)	Hospital pharmacies	Omnitrope	0	0	0	0	0
		Genotonorm	44 586	47 489	61 650	52 353	79 350
		Humatrope	3 914	7 211	9 024	8 142	5 504
		Norditropin	0	5 534	18 295	19 815	20 145
		Nutropinaq	605 214	783 968	935 704	1 062 185	1 202 269
		Zomacton	7 468	1 796	1 306	2 934	1 343
	Community pharmacies	Omnitrope	0	3 498	31 428	170 516	318 560
		Genotonorm	8 861 004	9 590 254	9 943 911	9 874 930	9 433 164
		Humatrope	1 737 240	1 723 327	1 663 339	1 438 778	1 124 622
		Norditropin	4 691 718	5 358 282	5 596 490	5 779 453	5 870 335
		Nutropinaq	605 214	783 968	935 704	1 062 185	1 202 269
		Zomacton	918 988	1 110 767	1 245 355	1 385 430	1 555 406

Source: RIZIV – INAMI. Provisory data for 2011.

4.7. Measures for biosimilars

As was previously mentioned, price negotiations are set on a per case basis for each new biosimilar. Initially, it was propose to transfer all biosimilars from Chapter 4 to Chapter 1, therefore no longer needing "a priory" approval by the medical officer of the sickness fund. However, given current market barriers for biosimilars, these measures were not applied. In the summer of 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. Polices were designed to avoid transferring costs to patients and to take into account biosimilars specific characteristics. Measures to stimulate use of biosimilars included [93]: i) inclusion of prescription of any biosimilar in quotas for low-cost prescription[r]; ii) inclusion of epoetin and somatropin in the hospital prospective budget for pharmaceuticals and iii) inclusion of epoetin in the category F. In addition, from 1 February 2013 hospitals will receive the flat rate fixed for the category F even if it exceeds the list price of the epoetin biosimilar. Position concerning intercheangeability and substitution of biosimilars are also explained hereafter.

4.7.1. Policy measures to stimulate biosimilar uptake

4.7.1.1. 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.

[r] In French "Prescription de medicaments bon marché" and in Dutch "voorschrijven van goedkope geneesmiddelen"

4.7.1.2. 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: 1) original pharmaceuticals for which a generic alternative exist and which have reduced the retail price so that patient do not have to pay the reference supplement, (2) generics and copies, (3) prescriptions under the International Nonpropietary Name (INN). [74] 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. Given that the biological reference product is not considered as a "low-cost" alternative, the patient does not pay a reference supplement when using the reference medicine.

4.7.1.3. 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. This flat rate corresponds to an ex-factory price of € 8.1344 per 1000 UI equivalent erythropoetin (based on Eprex). It was also determined that 1 µg darbepoetin corresponds to 200 UI erythropoetin and that 1 µg methoxypolyethylenglycol-epoetin beta corresponds to 222 UI erythropoietin. Consequently, the reimbursement basis for Aranesp and Mircera differ from their list price (see an example in Table 9).

4.7.1.4. Higher reimbursement for hospitals using biosimilars

In general, the payment from the third-party payer to a hospital cannot exceed the reimbursement basis of a pharmaceutical. Indeed, the new provision of article 35 bis, § 2a, second paragraph, of the Act allows SSI to set a fixed repayment basis which may possibly be greater than the cost of the least expensive pharmaceutical, in this case the biosimilar. This exception to the principle that the refund cannot exceed the price cannot

penalize the less expensive medicine in the application of the technique of reimbursement for treatment that will be used for epoetins.

Pharmaceuticals having a price below the flat rate in category F, can (by the initiative of the firm) ask to be reimbursed at the level of the flat rate. This implies that the hospital receives a reimbursement according to the flat rate (e.g. € 1 000) and not according to the reimbursement level of the pharmaceutical (e.g. € 800). Therefore, Article 123 of the Law-Program of 22 June 2012 created an incentive for hospitals to make savings (increasing their pharmaceutical budget) by using biosimilars. While this ruling may lead to fewer savings for the third-party payer, it can be perceived as a way of increasing "competition" between pharmaceuticals within a therapeutic class. Indeed, large discounts and rebates accorded to hospitals by originator companies make their reference product be priced below the "less expensive" biosimilars. From 1 February 2013, hospitals will receive this flat rate that is higher than the list price for the biosimilars Binocrit and Retacrit [94] Whether this policy effectively enhances competition is discussed in chapter 7

Table 9 – Prices and reimbursement basis for different erythropoietin

Brand name	Pharmaceutical dosage	Setting	Unit	Price (€)	Reimbursement basis (€)	Patient co-payment (€)
Eprex (reference product)	1000 IU/0,5 ml 2000 IU/ml epoetin alfa (r-HuEPO alfa 3 ml injection solution)	Ex-factory price	Package of 6 syringes	48.80	48.80	€ 0
		Ambulatory patient	Price per syringe	9.8067	9.80	€ 0
		Hospital	Price per syringe	8.6217	8.62	Flat rate of € 0.62 per day
Binocrit (biosimilar)	1000 IU/0,5 ml 2000 IU/ml epoetin alfa (r-HuEPO alfa 3 ml injection solution)	Ex-factory price	Package of 6 syringes	41.66	48.80***	€ 0
		Ambulatory	Price per syringe	8.54[1]	9.80***	€ 0
		Hospital	Price per syringe	7.36[2]	8.62***	Flat rate of € 0.62 per day
Aranesp (second-generation product)	10 µg	Ex-factory level	Package of 4 syringes	91.54	65.08****	€ 0
		Ambulatory	Price per syringe	26.03*	19.02****	€ 0
		Hospital	Price per syringe	24.25**	17.24****	Flat rate of € 0.62 per day

Source: RIZIV – INAMI (http://www.inami.fgov.be/inami_prd/ssp/cns2/pages/SpecialityCns.asp), For pharmaceuticals delivered in ambulatory care the price is calculated by multiplying the ex-factory level price by the value added tax (VAT) of 6% and by charging a delivery margin of 21.746% (with a maximum of € 7.11 per package per large package).** For pharmaceuticals delivered for hospitalised patients, the price is calculated by multiplying the ex-factory level price by the VAT of 6%. Unit price is calculated by dividing the package content by the number of units.*** Since 1 February 2013, the hospital receives an increased reimbursement for Binocrit and Retacrit.**** Reimbursement basis limited, as according to the category F. For instance, the price for one syringe of Aranesp for a hospitalised patient is equal to 8.1344*2*1.06*4/4=17.24, where 8.13 44 is the flat reimbursement and 2 corresponds to the dosage strength.*

4.7.2. Intercheangeability and substitution

The Belgian Centre for Pharmacological Informations provides guidance rules for INN prescription. Since 2001, INN prescription is possible in Belgium. INN prescriptions are encouraged (but not mandatory) and included in the calculation of low cost prescribing quotas. However, the Federal Agency for Medicines and Health Products (FAMHP)t recommended to exclude biological from INN prescription. As to biosimilars, there is no specific Belgian legislation on the substitution/interchangeability. In general, substitution is prohibited (art. 11 RD 78 [95]), apart from some exceptions defined in law. It is up to the specialist to prescribe the product he/she prefers for the individual patient. The law foresees the possibility to introduce substitution by Royal Decree, if the active substance of the pharmaceutical is the same, if the prescriber did not expressively oppose to substitution and if the price of the pharmaceutical is cheaper for the patient. These conditions are not fulfilled for biosimilars. The active substance of a biosimilar pharmaceutical is similar but not the same as the originator product. Moreover, replacing an originator product by a biosimilar in a hospital setting has no impact on what the patient pays (for currently available biosimilars). Introducing interchangeability or substitution for biosimilars would thus require a modification of art. 11 of the Royal Decree n° 78. [95] Since 1 May 2012, pharmacists' automatic substitution is mandatory in Belgium for antibiotics and antimycotics. The pharmacist needs to deliver the antibiotic or antimycotic of the cheapest pharmaceutical group. For all other pharmaceuticals, pharmacist substitution is not allowed.

5. IMPACT OF BIOSIMILARS ON THE HEALTH CARE SYSTEM

A scale down market authorization for biosimilars was design in order to allow pharmaceutical companies to provide a less expensive alternative to biologicals while ensuring biosimilar quality, safety and efficacy. Based on a structured literature research, the aim of this section is to provide evidence on the impact of biosimilar competition on price reduction, market uptake and savings for the third-party payer.

5.1. Methods

A structured review of the literature was performed in Embase, MedLine OVID, PUBMED and Econlit with the following terms: "biosimilar*" or "biosimilar pharmaceuticals/MeSH"[u]. After discarding duplicates, 735 references remained. Based on titles and abstracts, articles having information on price, uptake, incentives or health expenditures relating to biosimilars were select for a full review. Articles containing empirical data, theoretical models as well as discussions or reviews were included. A complementary search was done in institutional and grey literature databases (DRIVER and OAISTER). After applying inclusion criteria, thirty-five articles and one book remained. Full texts were then searched and inclusion/exclusion criteria were applied on full texts. Abstract were only available for 9 articles [96-104], 3 articles [105-107] could not be accessed. Seven articles did not comply with the inclusion criteria [108-114] and five articles [115-119] were excluded because they covered cost-effectiveness of biosimilars, which was not within the scope of this report[v]. A total of 11 articles and 1 book were considered relevant and were included in our review (details on the structured review of the literature can be found in appendix 4). We also included information provided by the project group Market Access and Uptake of Biosimilars[w]. Most articles related to the potential cost-saving

s In French Centre Belge d'Information Pharmacothérapeutique (CIBP) and in Dutch Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI)

t In French "Agence Fédérale des Médicaments et des Produits de Santé" (AFMPS) and in Dutch "Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten" (FAGG)

u Last update 8 November 2012

v Cost-effectiveness analysis is performed in KCE health technology assessment (HTA) reports

w The KCE was aware of the EU initiative and followed the last steps of the discussion for the Consensus Paper. The KCE was not actively involved in the biosimilars group discussion but attended the meetings as an observer The final consensus paper was not yet published at publication of this report.[17] The EGA kindly provided all information on EGA's survey on good practices and obstacles for the market uptake of biosimilars. http://www.egagenerics.com/images/EGA%20Survey%20to%20MS%20on%20Biosimilars.pdf)..

from biosimilar use were sponsored by industry while others were related to general aspects determining price reductions or potential factors determining uptake. Globally, the literature provided little (no) description or evidence on evaluation of successful policies which influence biosimilar uptake.

5.2. Characteristics of biosimilars market

According to the literature, potential savings are uncertain and are dependent on the price reduction compared to the original, the related market share of biosimilars, delay of introduction of biosimilars after patent expiry and price and reimbursement policies. In addition, rate of biosimilar penetration may vary according to disease: chronic use, indication, patient type and physician specialty. [120] For instance, for somatropin that is used for chronic use, it is a common practice to maintain patients on the same product despite that several originator products are available (and that there is a strong competition among them). Therefore, it is uncertain whether in this case physicians will substitute an already established treatment for a biosimilar. [121] The latter would reflect acceptability of different stakeholders of using and eventually switching patients to the less expensive alternatives.

The introduction of biosimilars is intended to reduce pharmaceutical expenditures due to price reductions from both the biosimilar and the reference product. However, these savings and price reductions are uncertain. Some authors have mentioned that biosimilar price competition may follow a similar pathway to that of generic medicines. [1, 122, 123] However, empirical evidence on price reduction and savings for the third-party payer is still limited and is mostly based on expectations. [1, 124-126] The following section presents theoretical models and current available empirical data on price reductions.

5.2.1. Theoretical models for biosimilar competition

For theoretical analysis of biosimilar market competition we refer to Grabowski et al. (2007) [122] and Chauhan et al (2009) [120]. Both models use different assumptions regarding the type of competition that takes place at market entrance of biosimilars. Grabowski et al. (2007) [122] use a monopolistic competition model to explain how large investment cost relating to biosimilar production lead to fewer competitors and less price erosion than in markets facing generic competition[x]. Chauhan et al. (2009) [120] provide a different theoretical framework where biosimilar competition is set in a segmented market model. In a segmented market model, biosimilar competition depends on a price-sensitive and non-price sensitive portion of the market. The non-price sensitive market can be understood as the "loyal" segment where individuals are willing to pay a higher price for the reference product. In this case, the biosimilar may not gain market shares by reducing its price (even if the price difference is high). On the contrary, competition between the biosimilar and the reference product is possible in the "non-loyal" (price-sensitive) section of the market. This model is useful in that it provides an analysis framework for factors such as physician loyalty (e.g. loyalty to the reference product) and its impact on biosimilar competition. Towse et al. (2009) [127] also point out that in a segmented market, firms producing the reference product (originator) may be reluctant to reduce their price even if they face competition from lowered priced biosimilars. The reference product firm may prefer to maintain a higher price as it does not affect her profit in the loyal market. Given such a high price for the reference product, the biosimilar firm may gain some market shares in the non-loyal market[y]. Yet, biosimilar companies may avoid setting a large discount strategy as it may not allow them to gain additional market shares in loyal markets.

Compared with price reduction created by generic competition in some countries (e.g. in the UK an 80% price discounts between the generic and the brand pharmaceuticals), the two models predict for pharmaceuticals facing biosimilar competition a lower price reduction. In the long-run, Chauhan et al. (2008) expect higher price erosion than that estimated by

---

x A monopolistic competition model assumes that firms face the price-sensitive part of the demand (downward-sloping), firms make no profit and that price changes of one product have a limited impact on the demand of any other product. According to Tirole (1988), this model is a useful framework to study the number of products in a given market. For biosimilars, Grabowski et al. (2007) considered that high investment costs lead to fewer companies to produce biosimilars.

y Towse et al. (2009) present an analysis mostly based on Chauhan et al. (2009) [120]

Grabowski et al. (2007) (according to Grabowski et al. with reduction between 40 and 50%). According to Chauhan's model, larger experience with biosimilars may be a key driver for enhanced competition.

5.2.2. Procurement policies

Biosimilars segmented market may also be influenced by different procurement policies for pharmaceuticals. Procurement policies may be determined by local entities in charge of pharmaceutical policies (e.g. regionalization of policies) [120] as well as by the constitution of Group Purchasing Organizations (GPOs) [128] (e.g. groups of hospitals). Product selection can be negotiated with few suppliers as hospital GPO may have large bargaining power. [128] Depending on the size of the GPOs, reference products may provide large discounts. [120]

Therefore, biosimilars competition takes place in markets where discounted prices for reference products may be set at a low competitive level [128] Beside GPO's market power, the actual tender procedure may have an impact on the choice of a pharmaceutical. Tendering aims at promoting competition but may set entrance barriers for companies not having enough resources to respond to the tenders. [120] Competition between firms is not only determined by the characteristics of their product but also by the firm's ability to appropriately answer the tender. In addition, final choice for a pharmaceutical may depend on negotiations between purchasers (pharmacists) and physicians which will reflect differences in conservative attitudes toward interchanging products.

Circumventing such barriers may prove to be difficult for biosimilar companies. Companies may attempt to implement strategies to counter high discounts within hospital by influencing prescribers. Chauhan et al. mention that in the UK, a possible strategy is to influence primary care providers (GPs) by offering price reduction to Primary Care Trusts (local payers). In return, primary care providers may influence the hospital choice of product. However, this strategy will increase biosimilars use only if GPs and not specialists determine pharmaceutical prescription. [120] In the United States, remuneration of providers on the sales price of pharmaceuticals is calculated in the same way for the biosimilars and reference product, namely 6% of reference product's average sales price (ASP). The 6% on the ASP aims to cover services and expertise needed to provide a given pharmaceutical. Total reimbursement to providers for biosimilars, is the sum of the biosimilar's average sales price (ASP) and six percent of the ASP of the reference product (6% of the ASP). The ASP is based on the net average sales price of a pharmaceutical to all purchasers including all possible volume discounts, rebates, generic substitution and prompt-pay discounts. Thus, the ASP reflects any discount when any purchaser is sold. Before 2005, reimbursement was based on the average wholesale price, which did not take into account discounts or rebates. Yet, it remains an open question to know if setting same financial incentives at the same level is sufficient to overcome loyalty to reference products. [128]

5.2.3. Production cost and marketing strategies

Some authors have argued that compared to generics, large fixed investment costs are needed for biosimilars. [1, 120-124, 128] Limited price reductions for biosimilars compared to generics may therefore also result from those higher costs. Yet, besides higher production cost for biosimilars, need for marketing strategies and other services aiming at improving market entry of biosimilars, [120, 121, 123, 124, 128] could also limit price reduction. For chemical pharmaceuticals were substitution is defined a priory, generic competition was fuelled by the substitution principle and relied less on marketing strategies by the firms. Because, substitution is not granted a priory for biosimilar and the reference product, biosimilar market penetration may depend on marketing strategies leading to enhance trust (create reputation bonds) with prescribers and key opinion leaders. [124, 128]

Grabowsky et al. (2011) mentioned that for some pharmaceuticals (e.g. Omnitrope), investment in costly sophisticated delivery systems determines competition between the biosimilar and the reference product. Conversely if biosimilar companies invest less in devices (in order to cut cost), this may reduce their chance to gain market shares. [124, 128]

5.2.4. Competition and second generation pharmaceuticals

Competition with second generation pharmaceuticals may also influence biosimilar use. Biobetters offer therapeutical advantages to the reference product that makes biosimilars use less relevant in some situation. [120] Yet, biosimilars may also set incentive to firms to improve or innovate available products on the market. [123, 124]

5.3. Available empirical data on price reductions, uptake and savings

5.3.1. Reported price reductions

Available information for Europe on price reduction or biosimilar use (measured in DDDs) is mostly based on IMS data[z]. [1, 125, 128, 129] IMS data provides information on the retail sector, which is base on list prices and not on discounted prices. Yet, tenders as well as buyer groups (hospitals, regions) may receive large discounts from firms. Therefore, discounted list price may differ into a large proportion with respect to the list price set by the authorities. Based on information provided by pharmaceutical firms, Moran reported that price reduction ranges from 10% to 35%. [121] However, the author does not specify for which country. Based on the British National Formulary[aa], Hugues reports price reduction for available biosimilars in the UK varying between 10% and 25%. [130] Liefner (2010) mentions that biosimilars for epoetin were launched in Germany with a discount around 30% below the price of the reference product (see section 0 for more details) and that subsequent price discounts took place for the biosimilar and for the originator[bb]. [131] The author also mentioned that price discounts for Omnitrope (biosimilar of the growth hormone) differed among a selected number of European countries. Discount range varied between 0% in Finland to 25% in Germany. Rovira et al. (2011) provide estimates for price reduction between biosimilars and the reference product based on IMS data as well as on information provided by national authorities. [1] The authors point out that price reduction between biosimilars and references product varies between 2007, 2008 and 2009. Changes in price reduction between the different years may be related to price variation for different products. In 2009, price difference between biosimilars and reference product accounted on average for 14.1%, 17.0% and 30.5% respectively for somatropin, epoetin alfa and filgrastim. According to interviews with stakeholders, Rovira et al. also provide estimates on price reductions. For Spain, the stakeholder reported that the biosilimar price was set with a reduction of 30%. For Italy, price discounts amounted to 20.0%, 15.0% and 22.0% respectively for somatropin, epoetin alfa or epoetin zeta and filgrastim. [1]

5.3.2. Uptake in DDDs per molecule

As previously mentioned, most information on biosimilar uptake comes from IMS data analysis. In this section, we do not discuss data estimation of previous studies. [1, 125, 128, 129] We present the most recent IMS data included in the project of the Group on Market Access and Uptake of Biosimilars. [17] According to the IMS study, biosimilar sales (in DDDs) are still a relatively small segment of the EU pharmaceutical market, but have strong annual growth. Uptake measured as percentage of DDD of total market (including reference and non-reference products in the form of me-too pharmaceuticals) is presented in Figure 1[cc]. Uptake for biosimilars in the three medicine categories (epoetin, somatropin and filgrastim) varied among countries. Uptake for epoetin's biosimilars was highest in Germany (45%), Greece (54%) and Sweden (24%) and lowest (null) in Belgium, Luxembourg and Portugal. Highest uptake for filgrastim biosimilars was found in Austria (64%), Norway (64%) and Sweden (50%). Biosimilars for filgrastim were not used in Belgium, Luxembourg and Portugal.

Data on biosimilar uptake for epotin and for filgrastim did not differ between the two available sources for Belgium (RIZIV – INAMI and IMS). However, biosimilar uptake for somatropin differed between the two sources (4.08% for RIZIV – INAMI and 6% for IMS Health). The difference in uptake may be explained by the fact that RIZIV – INAMI data contains information on reimbursements while IMS data contains information on sales. As such, off-label use and free medicines (sample available to prescribers or pharmacists) may be reflected in sales but not in

z Two articles where only an abstract was available reported using IMS data. [96, 99]

aa The British National Formulary (BNF) provides up-to-date, practical guidance on prescribing, dispensing, and administering medicines. This essential reference reflects current best practice as well as legal and professional guidelines relating to the use of medicines

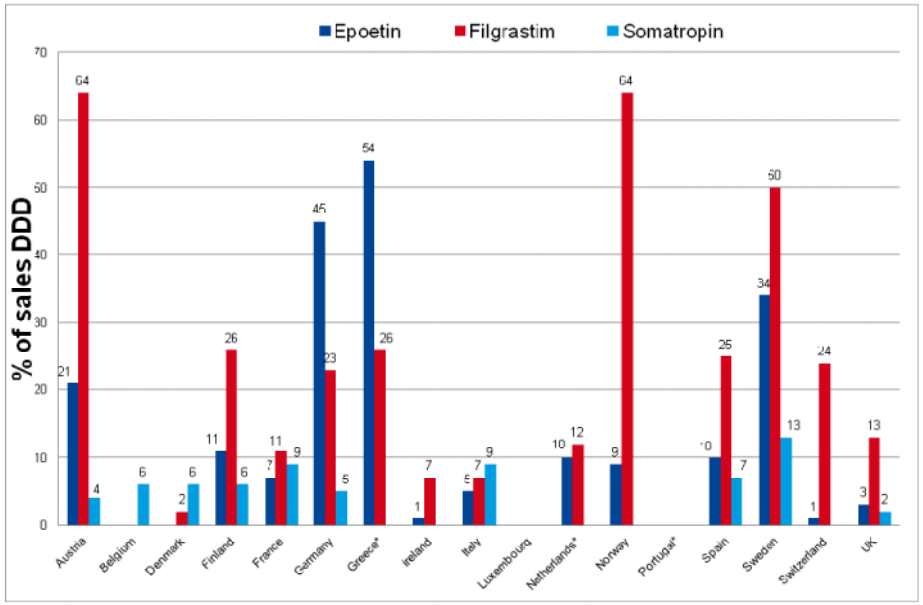
bb The author discussion is based on results from the consultancy firm Simon Kucher and Partners. Cornes (2012) also cited Leifner results in their paper. [129]

cc Only a selection of countries included in the IMS report is presented in the figure. Countries not included: Czech Republic, Estonia, Hungary, Iceland, Latvia, Liechtenstein, Lithuania, Poland, Romania, Slovakia and Slovenia.

reimbursements for the third-party payer. In addition, RIZIV – INAMI data for 2011 is provisory meaning that not all reimbursements may have been taken into account.

Finally, growth hormone's biosimilars had lowest uptake compared with epoetin and filgrastim biosimilars. Highest uptake was found for growth hormone in Sweden (13%), Italy (9%) and France (9%).

Figure 1 – Percentage of sales in DDD of biosimilars on total market (biosimilars, reference product and non reference product)



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

5.3.3. Savings for the third-party payer

Rovira et al. mentioned that estimations of biosimilars savings are based on different modelling strategies and are dependent on hypothesis used by different analysts. [1] In addition, estimates for Europe mostly come from the pharmaceutical sector or in some case from consultancy firms. As such there is a lack independent analysis from current and future savings arisen from biosimilars use. Several authors reported estimation from the European Generic Association where savings could attain up to € 1.6 billion conditioned to a 20% price reduction for five patent expired biologicals. [121, 123, 124, 129] A recent study sponsored by Sandoz from the IGES in Germany used IMS data to provide estimates on savings for Germany, France, the UK, Italy, Spain, Sweden, Poland and Romania. Savings are calculated for epoetins, filgrastim for which biosimilars already exist, as well as monoclonal antibodies (mAbs). Savings are calculated for different scenarios according to Germany's experience: 1) low penetration rate for generics, 2) penetration rate of epoetin between 2007 and 2010, 3) high penetration rate for generics. Price reductions are also estimated according to three scenarios (maximal, average and minimal price reduction in national markets between reference product and biosimilars). Other factors in their analysis include pricing and the time period for market entry of biosimilars after patent expiration. Savings for the eight countries for the period 2007-2020 vary from € 11.8 billions (slow penetration and minimal price reduction) to € 33.4 billion (fast penetration and maximal price reduction). [132]

5.4. Available information on measures aiming at increasing uptake of biosimilars

Description and evaluation of policies leading to biosimilar uptake is lacking. Rovira et al. provide a short description on policies in selected countries. [1] Only a recent EGA survey provides a listing of policies implemented in Member States and EEA countries[dd]. The survey was conducted from December 2011 to June 2012. Because the survey was set during a large period, policies reported hereafter may have evolved. Terms used in this section correspond to those used in the EGA survey.

[dd] 29 countries were surveyed and answers were received from the following 24 National Competent Authorities or Payer Organisations: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom. Information in the table includes only countries for which we included information on biosimilar uptake (see Figure 1)

Definitions of these policies were not included in the survey. None of the countries participating in the survey has set automatic substitution for biosimilars. Three countries (Denmark, Germany and Italy (Tuscany region) set quotas for biosimilars. No details on quotas' level, settings (ambulatory or inpatient) or indications are provided. In the survey, two countries included (Germany and Italy) prescription targets for biosimilars. One country (Austria) includes biosimilars as alternatives to the reference product in the electronic form of products admitted for reimbursement. In the list, products are sorted by price leading prescribers to see less expensive alternatives. Finally, one country (Norway) reported having a specific reimbursement for the filgrastim biosimilar (Tevagastrim). In other countries, were biosimilar's uptake is high (Finland and Sweden) no specific policies for biosimilars were mentioned in the EGA survey.

Table 10 – Measures to stimulate biosimilar uptake in selected Member States and EEA countries

Measures (EGA)	Austria	Belgium	Denmark	Finland	France	Germany	Greece*	Ireland	Italy	Net	Norway	Portugal	Spain	Swed	Swit*	UK
Quotas	No	No	Yes	No	No	Yes	n.a.	No	Yes	No	No	No	No	No	n.a.	No
Prescription targets	_	No	No	No	No	Yes	n.a.	No	Yes	No	No	No	No	No	n.a.	No
Incentive	_	No	No	No	No	No	n.a.	No	No	No	Yes	No	No	No	n.a.	No
Automatic substitution	No	No	No	No	No	No	n.a.	No	No	No	No	No	No	No	n.a.	No
Others	Yes										Yes					

*Source: EGA survey (Source: EGA- http://www.egagenerics.com/images/EGA%20Survey%20to%20MS%20on%20Biosimilars.pdf) and IMS report. * Information on these countries was not available in the EGA survey. "Net" stands for the Netherlands, "Swed" for Sweden, and "Swit" for Switzerland.*

6. INTERNATIONAL COMPARISON OF POLICIES STIMULATING BIOSIMILAR UPTAKE

6.1. Introduction and method

Most articles related to the potential cost-saving from biosimilar use were sponsored by industry while others were related to general aspects determining price reductions or potential factors influencing uptake. Globally, the literature provided little (no) description or evidence on evaluation of successful policies which influence biosimilar uptake. Only Rovira et al. (2011) and a recent EGA survey provide a list of measures aiming to stimulate biosimilar uptake in Europe (see section 5.4). This chapter aimed at identifying detailed information on measures adopted aboard to stimulate biosimilar uptake. We first selected neighbouring countries (France, Germany, and the Netherlands). We also selected Sweden for their strong policy concerning generic and biosimilar uptake.

A classical international comparison was performed using a two step analysis:

- review of scientific literature (described in the previous chapter) and a review of the grey literature including information on biosimilars regulation from national authorities;
- information collected in the first step was validated by national experts. Contacts with national experts were not only used to validate the information found through the first step but also to obtain more precise data. The analisis for Germany was again sent to national experts to ensure interpretation of our results.

Sources and person/organization contacted for each country are available in the appendix 5.

This chapter begins with a snap-shot of marketed biosimilar and relative price reduction in the sampled countries. This snap-shot is then followed by an overview of the main pharmaceutical policies having an impact on biosimilar uptake, i.e. incentives or constraints for physicians, pharmacists, patients, and hospitals.

The objective of this chapter is not to determine if these policies are effective in terms of cost-containment but rather to list measures (incentives or constraints) that could potentially stimulate biosimilar uptake. It should be noted that education and information campaigns on biosimilars is an important aspect to stimulate biosimilar uptake but this point was not covered in this report (information difficult to obtain).

6.2. Results and discussion

6.2.1. Marketed biosimilars

Marketed biosimilars in our sample countries are presented in Table 11. While several biosimilars come from the same manufacturer they are commercialized by different companies. The number of commercialized biosimilars is lowest in Belgium and highest in the Netherlands followed by Germany. Several biosimilars in the same market may lead to more competition and therefore higher price reductions.

Table 11 – Products admitted for reimbursement in a selected number of countries

	Reference product	Biosimilar	Company	Manufacturer	Belgium	France	The Netherlands	Germany	Sweden
Human growth factor	Genotropine	Omnitrope	Sandoz	Sandoz	PH	PH	P	PH	PH
	Humatrope	Valtropin (Withdrawn 4/2006)	Biopartners	LG Life Sciences	not marketed	not marketed	H	not marketed	N/A
Epoetin	Eprex/Erypro	Retacrit	Hospira	Norbitec	H	PH	P	PH	PH
		Silapo	Stada	Norbitec	not marketed	not marketed	H	PH	N/A
		Abseamed	Medice	Rentschler Biotecnologie	not marketed	PH	P	PH	N/A
		Binocrit	Sandoz	Rentschler Biotecnologie	H	PH	P	PH	PH
		Epoetin alfa Hexal	Hexal	Rentschler Biotecnologie	not marketed	not marketed	H	PH	N/A
Filgrastim	Neupogen	Biograstim	CT Arzneimittel	Sicor Biotech	not marketed	not marketed	H	PH	N/A
		Ratiograstim	Ratiopharm	Sicor Biotech	not marketed	PH	P	PH	PH
		Filgrastim Ratiopharm (Withdrawn)	Ratiopharm	Sicor Biotech	not marketed	not marketed	H	not marketed	N/A
		Tevagrastim	Teva	Sicor Biotech	PH	PH	P	PH	PH
		Nivestim	Hospira	Hospira Zagreb	not marketed	PH	P	PH	PH
		Zarzio	Sandoz	Sandoz	PH	PH	P	not marketed	PH
		Filgrastim Hexal	Hexal	Sandoz	not marketed	not marketed	H	PH	N/A
Total number of biosimilars who are commercialized					5	8	14	11	7

Source: Thristrup,S. [133] and forthcoming from the Market Access and uptake of Biosimilars Group. [17] Reimbursement status in: P = primary care, H = hospital, PH = both

6.2.2. Price differences between countries

Data on relative price reduction (% of the price the reference product) were obtained either from Rovira et al. (2011) or from national authorities. [1, 134, 135] The accuracy of these data varies across countries and prices are likely to be list prices which do not take into account discounts or rebates. Relative price reduction with respect to the reference product varied among the selected countries. Reported reductions for somatropin (growth hormone) differed less between countries than for epoetin and filgrastim. Highest relative price reduction for epoetin and for filgrastim was found respectively in Sweden. It should be noted that data from Sweden was estimated based by national authorities and not using the IMS dataset. Because data concern percentage of reduction with respect to the reference product price, it may be possible that larger reduction for biosimilars in some countries may be related to an initial higher price for the reference product.

Table 12 – Price reductions between the reference product and biosimilar prices

	Belgium	France	The Netherlands	Germany	Sweden
Mandatory reduction	No	No	No	No	No
Price reduction					
Epoetin	2012 - 30-34%	2009 - 26%		2009 - 33%	2011 - 40%
Growth Homone	2012 - 22%	2009 - 20%	2009 - 20%	2009 - 19 %	2009 - 22%
Filgrastim	2012 - 20%	2009 - 38%		2009 - 18%	2011 - 50%

Source: Different data sources. [1, 134, 135] The most recent information found was included.

6.2.3. Physician incentives and constraints

Policy measures aiming at improving physician prescription behavior may influence biosimilar uptake, i.e. prescription quotas, budget target, prescription monitoring, financial incentives or penalties, and prescription conditions/guidelines (including prescribing by the international non-proprietary name (INN) and official recommendations on switching and interchangeability policies). The implementation of these measures in our sample of countries is described in Table 13 and Table 14. In Table 13 several measures apply for biologicals[ee] in general. Therefore, the table specifically mentions if the policy only covers biosimilars. Conditional rules for reimbursement as well as INN prescription did not include specific clauses for biosimilars. INN prescribing is not allowed for biologicals. Switching during treatment was in general not recommended for all biologics. Only for France, the health authorities provided additional warning of reducing switching as much as possible between the reference product and the biosimilar. In Germany and Sweden, while switching for biologicals is not recommended, the authorities allow switching (see automatic substitution in chapter 2) for biosimilars coming from the same manufacturer.

[ee] As biosimilars are per definition biologicals, when the table mentions biologicals it includes biosimilars.

Table 13 – Prescription conditions/guidelines

	Belgium	France	The Netherlands	Germany	Sweden
Conditional reimbursement	Yes: Biologicals/ biosimilars are only reimbursed under specific conditions and with the agreement of the advisory physician of sickness funds (chapter IV)	Yes: Biologicals/biosimilars are only reimbursed under specific conditions: • Omnitrope : (1) Pharmaceutical of exception*; (2) Initial annual prescription at the hospital and by a specialist • Retacrit /binocrit: (1) Pharmaceutical of exception*; (2) initial annual prescription at the hospital • Ratiograstim/tevagrastim/ nivestim: (1) initial prescription for each quarter at the hospital	Yes: Biologicals/ biosimilars are only reimbursed under specific circumstances (annex 2)	No	No
INN prescription	Not allowed for biologicals	Not allowed for biologicals	Not allowed for biologicals	Not allowed for biologicals	Not allowed for biologicals
Primary substitution for biosimilars	-	-	Biosimilars can be considered as interchangeable for naïve patients (CVZ).	For specific defined groups (see hereafter)	No
Switching during treatment	Switching for biologicals is not recommended and should be initiated under supervision of the physician (AFMP-FAGG)	Switching for biologicals is not recommended. Switching between the reference product and biosimilar should be performed as little as possible for the same patient (ANSM)	Switching for biologicals is not recommended.	Switching for biologicals is usually not recommended except for specific groups of biosimilars (same producer– see Table15)	Switching for biologicals is not recommended except for products included in the substitution list from Medical Products Agency, i.e. products with same producer (see Table 15). Switching is possible under the responsibility of physicians and collective healthcare centres (including hospitals)

** pharmaceutical of exception: the reimbursement modalities are fixed by an order of the Minister of Social Security and include a sheet on therapeutics information (such as indications, prescription and use modalities, treatment duration, etc.). These pharmaceuticals must be prescribed with a specific prescription format, implying that the prescriber certifies the adequacy to the requirements contained in the information sheet. Naïve patients are patients who are starting a treatment.*

The inclusion of biosimilars in quotas and/or the definition of (individual) target budget stimulating the use of less expensive alternatives are expected to positively influence the prescription of biosimilars by physicians (see Table 14). In our sample of countries, prescription quotas for biosimilars are applied only in Germany (see section 6.3 for details on quotas). In Sweden, France and Germany prescription targets aiming at controlling prescription of expensive alternatives may influence in general prescription of biosimilars. To strengthen these measures, they should be complemented by a monitoring of prescription patterns and by really enforcing financial incentives or penalties. However, although penalties may exist they are rarely enforced. Incentives for prescription of less expensive alternatives were only found in Sweden.

Table 14 – Measures for physicians potentially influencing biosimilar prescription in outpatient settings

	Belgium	France	The Netherlands	Germany	Sweden
Quotas on biosimilars*	No quotas for biosimilars exist. However, prescription of Omnitrope is considered as a prescription of a low-cost medicine	No	No	Local prescription quota on biosimilars varying per local physician associations (quotas on EPO in dialysis centres between 10-50%	No
Target budget**	No	Yes, expenditure targets at the national and regional levels.	No	Yes (regional and physician budgets)	Yes
Monitoring of prescription patterns for biosimilars	Yes	No	No	Yes	Monitoring of budget target
Financial incentives/penalties	Penalties: There may be financial penalties if quotas are not respected (not frequently enforced)	No	No	Penalties: The difference with the budget targeted may be required (not frequently enforced).	Incentives: Rewards given by some county councils if the targets of prescription of less expensive alternatives are reached.

** Percentage of biosimilars to be prescribed by each physician.** A maximum pharmaceutical budget may be defined per period, reg ion, field of specialty and physician*

6.2.4. Pharmacist incentives and constraints

Measures for pharmacists are listed in Table 15. Substitution rights by the pharmacist and preference policies on biosimilars through public tendering system in outpatient settings (implemented in Germany and the Netherlands) are expected to increase biosimilar uptake. However, in the Netherlands, such system is yet in process for biosimilars and will be limited to naïve patients. It should also be noted that preference policies may force a number of companies out of the market and decrease the competition (dominant position for the few remaining companies), what could potentially lead to an increase of prices in the future.

Substitution by the pharmacist is usually not allowed for biologicals or is limited (only for epoetin alfa and zeta with the same manufacturer in Germany or for biologics/biosimilars pharmaceuticals with the same manufacturer in Sweden).

Moreover, substitution policies can only work if they are mandatory or if they are accompanied by measures on the pharmacist remuneration making substitution financially neutral or even attractive for the pharmacist. Specific incentives or penalties for substitution are a first component. France and Belgium have no specific incentives for biological substitution (not allowed) but have specific incentives for generic substitution, i.e. equalisation of the pharmacist margin between the generic and the original product in France or fixed sum for the dispensing of pharmaceuticals prescribed by INN in Belgium.

Secondly, the way of remunerating pharmacists has an influence. A percentage component in the pharmacist remuneration is a disincentive for dispensing biosimilars (lower margin due to the lower price). A regressive mark-up is a first solution compared to a linear mark-up but may not be sufficient. Totally removing the price-dependent part of the remuneration and replace it by a dispensing fee or a fee-per-performance payment is expected to have a higher impact. [136]

Discount or rebates are also part of the pharmacist remuneration and may influence their behavioural. A regulation of these discounts to the benefit of biosimilars (such as in France for generics) could be beneficial for biosimilar use. A regulation of the maximum size of the discounts (such as in France) is expected to decrease the impact of discounts on the pharmacist behaviour but is also surrounded by the usual lack of transparency of these discounts. It should be noted that even if discounts are regulated in France, actual discounts are usually higher than the officially allowed discounts. According to Dylst et al., having analysed pricing policies for generic medicines, an enforced prohibition of discounts coupled with compensation in the pharmacist remuneration could be a solution. [136]

Table 15 – Measures for pharmacists potentially influencing biosimilars dispensing

	Belgium	France	The Netherlands	Germany	Sweden
Substitution right* and preference policies for biologicals/ biosimilars**	Not allowed	Not yet allowed but the law has been adapted in January 2013 to allow the possibility to create groups for substitution (known as group of similar biologicals that will be determined by the ANSM; art. L. 5121-1 and L. 5125-23 of the social security code)	Not yet allowed. Preference policies for biosimilars are in process in some insurers but limited to naïve patients.	Not allowed in general but substitution is possible for specific groups of biosimilars (same producer) Groups for substitution: • Epoetin alfa: Abseamed, Binocrit, Epoetin alfa Hexal • Epoetin zeta: Silapo, Retacrit. • Rebate contracts on biosimilars	Not allowed in general but substitution is possible for specific groups (listed by the Medical Products Agency as substitutable). Groups for substitution: • Epoetin alfa: Abseamed, Binocrit, Epoetin alfa Hexal • Epoetin beta: Only NeoRecormon • Epoetin theta: Biopin and Eporatio • Epoetin zeta: Retacrit and Silapo • Somatropin: Only Omnitrope • Filgrastim: Filgrastim Hexal and Zarzio • Filgrastim: Biograstim, Ratiogastrim and Tevagrastim
Remuneration	Regressive financing + dispensing fee	Regressive financing + dispensing fee	Dispensing fee	Linear financing + dispensing fee	Regressive financing
Discounts	Allowed	Limited by law: capped to 17% for generics and pharmaceuticals under TFR, while capped to 2.5% for brand pharmaceuticals under RPS	Allowed	Allowed and statutory rebate	Allowed
Claw back	No	No	Yes : 6.82% (2009) of the total remuneration***	No	No
Other financial incentives	No	No but margin equalization for generic	In case of contract, the dispensing fee may increase and the percentage of claw back may decrease	Information not found	Extra fee for substitution

** Substitution rights represent the ability of the pharmacist to dispense a cheaper and similar reimbursable pharmaceutical than the one prescribed by the physician.*
*** Preference policies in the Netherlands: through public tendering process, sickness funds may establish one or a limited number of products per category or cluster as preferred for a fixed period. ** Preference policy in Germany: Preferential reimbursement on preferred multi-source (generic) medicines determined by the sickness funds or rebate contracts (direct price arrangements contract between sickness funds and pharmaceutical companies). The pharmacist will automatically give the cheapest alternative for that particular insurer. TFR = tarif forfaitaire de responsabilité (responsibility tariff). *** Total remuneration that pharmacies receive from the sickness funds.*

6.2.5. *Patient incentives and the reference price system*

Preference policies on biosimilars (see Table 15) are also incentives because if the patient choose the preference product, there could have no or limited co-payment. Because current biologicals with biosimilars are therapeutically important, the patient cost-sharing for these pharmaceuticals and therefore their sensitivity to the price is limited (see Table 16). However, the inclusion of biologicals in the reference price system (such as for example in the Netherlands) could make the biosimilars more attractive as the patient pays no reference supplement.

Table 16 – Measures for the patients concerning outpatient pharmaceuticals

	Belgium	France	The Netherlands	Germany	Sweden
Co-payment for biologicals with biosimilars	Category A/B of reimbursement (around 80-100%)	Between 65% and 100%: • Human growth factor : Reimbursed at 100%. • Epoetin: Reimbursed at 65%. • Granulocyte colony stimulating factor: Reimbursed at 100%.	100%. Patients only pay a yearly deductible	100% but through the mandatory co-payment of 10% of the medicines' price (min € 5 – max € 10), the rate could be lower. Lower ceiling and exemption of co-payments for vulnerable groups.	Annual capped co-payment for pharmaceuticals (2 200SEK). This amount is usually reached for biologicals (high costs). After attaining the capped co-payment, patients receive full reimbursement (100%).
Is there a Reference price system?	Yes	Yes	Yes	Yes	No
Are biosimilars included in the RPS?	No	No	Yes	Yes	No
Cluster level for biosimilars?	-	-	• Erythropoietin: (ATC-4 level) Epoetin alfa (Abseamed, Binocrit, Eprex), Epoetin beta: (NeoRecormon), Epotin zeta (Retacrit), Darbepoetin, Methoxy (Aranesp), Polyethylene glycol-epoetin beta (Mircera). • Filgrastim (ATC-4 level): Neupogen, Ratiograstim, Tevagrastim, Zarzio, Granocyte, Granulokine, Neulasta. • Growth hormone (ATC-5 level): Genotropin, Humatrope, Norditropin, Nutropinaq, Omnitrope, Zomacton	Erythropoietin (ATC-4 level): Epoetin alfa (Abseamed, Binocrit, Eprex), Epoetin beta: (NeoRecormon), Epoetin theta (Eporatio), Epotin zeta (Retacrit), Darbepoetin, Methoxy (Aranesp), Polyethylene glycol-epoetin beta (Mircera)	-
How is the Reference price calculated	-	-	Equal to the average price of pharmaceuticals or below	Econometric formula that includes the molecule strength	/

6.2.6. Hospital incentives and constraints

The level of pharmaceutical financing in hospitals may also influence biosimilar uptake. Table 17 gives an overview of financing mechanisms for biologicals having a biosimilar. Inclusion in a DRG system of payment or in a lump sum system is expected to stimulate the use of less expensive alternatives. Fixed sum per treatment are also potential incentives, e.g. inclusion of epoetin in the list of expensive pharmaceuticals paid at the top of DRG according to a responsibility tariff in France, inclusion of epoetins in the category F in Belgium, ZE amount (fixed price per cumulative dosage groups) paid at the top of the DRG for filgrastim in Germany. However, these measures may be hampered by discounts. A policy aiming at limiting the impact of discounts (such as in France) could positively influence behaviours. Public procurement at the regional or national level (such as in Sweden at the county level or Germany) could also allow to have more control on uptake for biosimilars. Other policies such as quota, budget target and related financial incentives in hospitals are limited (see Table 18).

Table 17 – Hospital financing for inpatient pharmaceuticals (for biological products having a biosimilar)

Belgium	France	The Netherlands	Germany	Sweden
• Pharmaceuticals excluded from the lump sum: o Filgrastim: Neupogen, Tevagrastim, Zarzio (100%), o Pegfilgrastim: Neulasta (100%) o Lenograstim: Granocyte (100%) Pharmaceuticals included in the lump sum (reimbursement = a flat rate per admission + 25% of the RB): o Erythropoietin: Eprex, Neorecormon, Retacrit, Binocrit o Darbepoetin: Aranesp o Methoxy polyethylene glycol-epoetin beta: Mircera o Somatropin: Genotonorm, Omnitrope, Humatrope, Norditropin, Zomacton, Nutropinaq • Category F reimbursement for epoetins (RB = lump sum): Eprex, Neorecormon, Retacrit, Binocrit, Aranesp, Mircera	• Included in the G-DRG system of payment. • Except biologic/biosimilar products included in the list of expensive pharmaceuticals: all epoetins (Abseamed, Binocrit, Eprex, Dinepo, NeoRecormon, Mircera, Retacrit) with the same responsibility price. If hospitals buy one of these products at a higher price, they have to pay the difference.	• Biosimilars are financed through add-on: High-cost medicines are not covered by DBCs: o Previously: 80% (100% for orphan pharmaceuticals) was directly reimbursed while 20% was financed by the hospital's budget. o Since 2012: Add-on system, i.e. full reimbursement on the top of the DBC tariff: based on negotiation with insurers. • Some outpatient care under the responsibility of a specialist (e.g. epoetin, filgrastim) are (will be) transferred to the hospital financing system (possibility to ask for add-on reimbursement): o Since 2012: TNF alfa inibitors o In the future: orphan pharmaceuticals, pharmaceuticals for the treatment of cancer, growth hormones, fertility hormones, some pharmaceuticals for anemia, HIV inhibitors and immunoglobulins.	• Included in the G-DRG system of payment • ZE amount for Filgrastim (short acting) (ZE40): fixed price per cumulative dosage groups	• Inpatient pharmaceuticals are negotiated by the County Council (list of preferred products)

RB = reimbursement basis; DBC= diagnosebehandelingcombinatie; G-DRG = german diagnosis related groups; ZE = zusatzentgelte.

Table 18 – Other measures in hospitals possibly influencing biosimilar prescription

	Belgium	France	The Netherlands	Germany	Sweden
Quotas / target budget (+)	No	No	No	No	County councils set targets and quotas within therapeutic classes
Other financial incentives/penalties (+)	No	50% of rebates and discounts obtained during negotiations return to sickness funds	No	No	• Rewards by some county councils if targets are reached. • Rebates and discounts obtained during negotiations usually return to hospitals.
Procurement of pharmaceuticals and public tendering	Until January 2013, direct negotiations were the main procedure for procurement of pharmaceuticals in hospital settings	Individual or collective (groups of hospitals). Criteria can be the clinical need, the ASMR, the price, practice consideration such as the use by nurse or their handling at the pharmacy, the level of risks related to the supply chain, etc. These specifications must be published on a transparent way before initiating the call for tender.	Most pharmaceuticals are purchased by tendering in regional purchasing groups (preferred medicines) but some of them are bought on an individual basis through negotiation with the wholesaler or the manufacturer.	Hospital purchasing groups exist but the objective is often to get higher quality deliveries and to save time, not necessary to lower prices. There is an informal exchange of price information between hospitals.	Done at the level of the counties (some small counties come together) with the pharmaceutical therapeutic committee. These procurement procedures lead to lower prices than in community pharmacies. Weighting criteria in tenders are similar between counties. Once the county accepts a tender offer, inpatient pharmaceuticals are put on a list of preferred medicines.

ASMR = amelioration du Service Medical Rendu

6.3. Case study: policies for epoetin biosimilar in Germany

Germany is currently the "best-in-class" for the use of epoetin biosimilars with 45% of total DDDs. [17] However some argue that the success is still only anecdotal. Moreover, as showed in the structured literature review (see chapter 1.1.1), there is still little evidence on what factors actually leaded to Germany's success story with Biosimilars. Some authors have argued that biosimilars have been successful thanks to the diverse payer environment and widely accepted policies relying in generics. [128] In addition, the third party payer (Gemeinsamer Budesausschuss der Selbstverwaltung) and the sickness funds (Krankenkassen) have widely accepted biosimilars and have a large influence on dispensing and prescribing. [1] In order to have more information on Germany, three national experts were interviewed for the project. Biosimilar uptake was initially slow. [111] However, physician association (Kassenärztliche Vereinigung) performed studies to evaluated cost (savings) of biosimilars and provided non-mandatory guidelines. According to interviewed experts, high biosimilar uptake for EPOs is highly related to biosimilar use in the biggest group of dialysis centres[ff] in Germany (KfH), accounting for about 30% of all dialysis patients. Biosimilars are used in KfH for all types of dialysis and pre-dialysis patients.

Each individual centre affiliated with KfH may differ in the use of biosimilars[gg] but all epoetins are procured centrally (usually 5 to 6 products including biosimilars), limiting fringe benefits (directly or indirectly) provided to centres or physicians. As different epoetins are purchased, physician still keeps his/her freedom of prescription. Information on cost differences between original and biosimilars are communicated together with the suggestion to use biosimilars. Some centres also participated in phase III trials. [137] The success factors for the implementation of biosimilars in the dialysis centres were identified by an insider as follows:

- Firstly, early introduction of biosimilars in clinical guidelines by physicians associationshh and the GBA (Gemeinsame Bundesausschuss, which groups the physicians together with the hospitals and sickness funds) boosted clinical acceptability of biosimilars.
- Secondly, physicians from the field were involved in the decision making process in the group;
- Thirdly, all physicians are informed on use of specific biosimilars in specific indications and on costs differences for biosimilars (transparency in prices).
- Fourtly, there was a high acceptability by physicians. Within the scientific committee of doctors, more than 50 % had no problem with using biosimilars and they helped to convince the rest. In addition, physicians in Germany are sensitized for cost of pharmaceuticals, because of the prescription budget target for each physician. Still, they are partially held financially responsible. The average cost of prescriptions for each individual physician is compared to the group (e.g. dermatology, nephrology etc.). If the physician exceeds the average he has to explain why.
- Finally, it must be noted that these centres are not linked to hospitals. Kidney transplant are performed in hospitals, but preparation phase and follow-up is done by these dialysis centres and the reference price system is applied (All epoetins are included in the reference price system at the atc-4 level).

Moreover, the states' physicians associations make every year contracts with the regional sickness funds containing minimal prescription quotas on biosimilars within the context of cost-saving on pharmaceuticals expenses. The quotas agreements do not apply to hospital environment, but only in outpatient setting ("Vertragsärzte" physicians' contracts). One expert was of the opinion that biosimilar uptake was less related to prescription quotas, as they were not enforced (although theoretically sickness funds can ask for it, penalties are not really used in reality).

ff KfH: Kuratorium für Dialyse und Nierentransplantation (Curatorium for Dialysis and Renal Transplantation): largest provider of renal care in Germany currently treating over 18.500 patients. KfH operates a network of over 220 medically managed kidney centres offering all forms of renal replacement therapies

gg Some centres use 100% biosimilars, while others have mixtures

hh http://www.akdae.de/Stellungnahmen/Weitere/20081209.pdf
http://www.g-ba.de

In 2010, level of minimum prescription quotas varied from 3% in Saarland to 53% in Bremen. For 2013, minimum prescription quotas were set higher for all local authorities and vary from 17.7% in Baden Württemberg to 59.8% in Bremen. Prescribing of biosimilars (measured as percentage of total DDD) is also highly state dependent: according to the report of Barmer GEK the prescription varied in 2010 from 16.2 % (Saarland) to 69.2 %. [138] BARMER GEK is the single largest sickness fund in Germany (the whole AOK would be bigger, but consists of 11 legally autonomous parts, with currently 9.1 mill members and a turnover of € 22.7 billion of which € 3.93 billion in medicines.The authors assume that such large variations depend on the minimal prescription quotas as well as on communication around the quotas. Some states have specific working groups to analyse spending, monitor and stimulate the implementation of the quotas on a regional level (http://www.kvsaarland.de/wivo).

Box 7 – Success factor biosimilar market penetration in Germany

Mostly outpatient prescription.

Central procurement, disconnecting procurement with individual centres or prescribers (no kick-backs or link to clinical research).

Local outpatient prescription quota on biosimilars agreed upon by sickness funds and physicians.

Budget target responsibility for physician, supported by local physician associations.

Involvement of physicians in decision making for quality of care and savings for the health system.

Inclusion of epoetins in the reference price system.

Adoption of biosimilars by the biggest dialyse centre network in Germany.

Positive communication in clear and unambiguous wording by several stakeholders and peer associations to physicians: medical and physician associations, sickness funds, minister.., etc.

High acceptance of generics (also in hospitals).

Table 19 – Erythropoiesis-stimulating active substances: minimal prescription quotas and actual DDD in 2010 (for Barmer GEK)

	Minimal prescription in DDD (%)	DDD (Thousand)	Biosimilars sold on total DDD (%)	Difference between minimal quotas and prescription (%)
Baden Württemberg	10	136.8	30.1	20.1
Bayern	29	114.2	67.2	38.2
Berlin	22	88.2	53	31
Brandenburg	13	67.6	40.8	27.8
Bremen	53	8.4	69.2	16.2
Hamburg	21	51	47.5	26.5
Hessen	13	67.5	36.7	23.7
Mecklenburg-Vorpommern	24	49.5	41.2	17.2
Niedersachsen	37	179.9	64.8	27.8
Nordrhein	25	249.6	56.9	31.9
Rheinland-Pfalz	20	84.1	59.9	39.9
Saarland	3	23.5	16.2	13.2
Sachsen	17	75.7	47.6	30.6
Sachsen-Anhalt	16	66.4	46.8	30.8
Schleswig-Holstein	29	69.4	51.2	22.2
Thüringen	30	53.4	56.8	26.8
Westfalen-Lippe	23	129.3	64.1	41.1
K A		71.3	42.6	
Total		1585.70	52.1	

Source: Glaeske 2011 [138]

7. USE OF BIOSIMILARS, ADVANTAGES AND BARRIERS: A STAKEHOLDER PERSPECTIVE

The analysis of the literature on the impact of biosimilars on the health system provided limited evidence on pricing and reimbursement policies and their impact on biosimilar use. Moreover, it is unclear how uptake of biosimilars is influenced by distinctive characteristics of pharmaceutical financing in Belgium (e.g. discounts and impact of public tendering, see chapter 4). Therefore, the purpose of this chapter is to build on-the-ground evidence on which factors determine biosimilar uptake in Belgium.

7.1. Methods

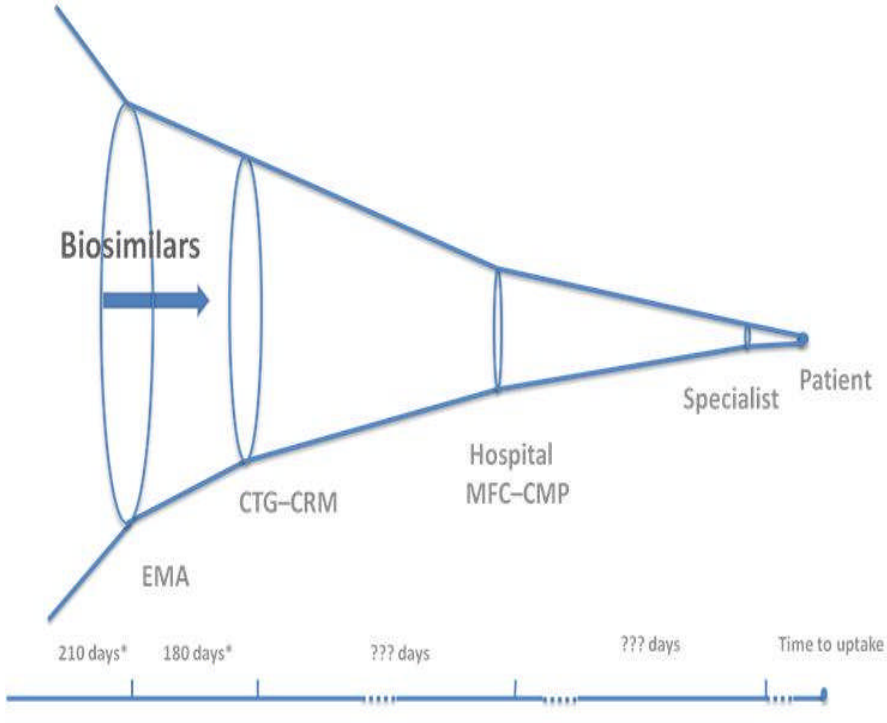
A combination of qualitative and quantitative research methods was used to enhance the understanding of barriers and policies measures determining biosimilars uptake. First, face-to-face interviews with key players were performed in order to understand knowledge, attitude and external factors linked to biosimilar use. Second, in order to quantify findings from face-to-face interviews a web survey was sent to chief hospital pharmacists and to specialists with the help of professional and scientific societies. Methods used followed the KCE process notes on Qualitative Research Methods (QRM). [139]

7.1.1. Face-to-face interviews

7.1.1.1. Identification of key informants and sampling

The sampling of key players for the face-to-face interviews aimed at including at least one representative of interest groups involved market access, dispensing or prescription of a biosimilar. The biosimilar uptake was conceived as a sequential process starting from the production of biosimilars and ending with patient use (Figure 2) and at each step barriers for uptake were introduced.

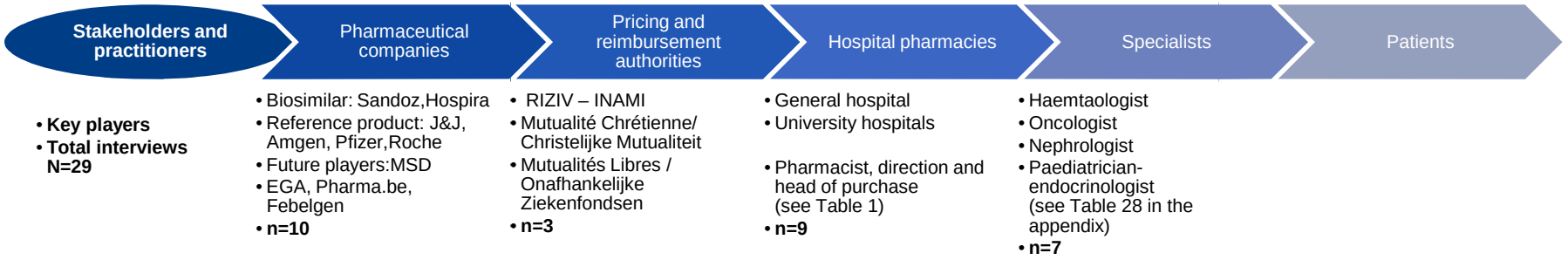
Figure 2 – Biosimilar uptake process and decision makers involved



Theoretical sampling was performed to get respondents at every step of the biosimilar uptake process (see Figure 3). The number of interviews and the timing was a result of this theoretical sampling. Patient views were not accessed through face-to-face interviews but instead at the stakeholder meeting. Interviews with representatives of pharmaceutical companies were performed between 1 June 2012 and 6 November 2012 including 1) companies currently marketing a biosimilar in Belgium (Sandoz and Hospira); 2) companies holding a patent for a pharmaceutical for which a biosimilar is available (J&J, Amgen, Pfizer and Roche); 3) one company who will face competition from biosimilars in the near future (MSD).

Interviews with representatives of pricing and reimbursement institutions were performed between 5 July 2012 and 4 September 2012 including: 1) RIZIV – INAMI and 2) two sickness funds. A key issue for the study was to understand purchasers (hospitals) and physician views. Interviews with representatives of purchasers included hospitals pharmacists, direction members and head of purchase from both general and university hospitals. As mentioned in chapter 4, biosimilars are most often dispensed by hospital pharmacies (see chapter 4). However, somatropin is mostly dispensed by community pharmacies...

Figure 3 – Biosimilar uptake process and key players included in face-to-face interviews



Interviews with prescribers included specialists whom may prescribe on their daily practice one of currently available biosimilars: a) Epoetin which can be used by oncologists and haematologists (supportive care during chemotherapy) as well as by nephrologists (pre-dialysis and dialysis); b) filgrastim which is mostly prescribed by haematologists (bone marrow transplant patients and donors) and oncologists; and c) growth hormone which is prescribed by paediatricians-endocrinologist[ii] to treat growth hormone deficit in children. Paediatricians-endocrinologists usually work in hospital settings. The choice of specialty was validated during preliminary discussions about the content of the semi-structured questionnaire. French and Dutch-speaking purchasers and prescribers were interviewed. All interviews were carried between 1 June 2012 and 7 December 2012. A variety of channels were used to recruit participants: 1) by inviting hospital pharmacists, directors, head of purchase or specialists participating in previous validations or expert meetings at KCE *(convenience sampling)*; 2) by asking during the interviews whether other field experts should be contacted (*snowball sampling*). Table 29 in the appendix 6 presents a detailed description of the number of purchasers' and prescriber interviews.

All interviews were carried as follows: 1) contacting participants; 2) making appointments with those who agreed to participate; 3) at the start of the interview, providing them with prior information on the project aims and

[ii] Not all paediatricians will prescribe a treatment for growth hormone deficits. In Belgium, the treatment of this pathology is covered by paediatricians-endocrinologists.

structure; 4) interviews were not recorded and computer notes were taken; 5) a memorandum containing the interviews notes was sent for validation to each participant; 5) Comments and corrections were included in a final document to be used for the analysis. Interviews were carried out by KCE team members.

7.1.1.2. Construction of the semi-structured questionnaire

The semi-structured interviews were based on findings from the face-to-face interviews and were completed by on one opinion survey on biosimilars carried by the Dutch Medical Evaluation Board.[140] The preliminary version was adapted following exploratory meetings with different stakeholders or practitioners to correctly target the Belgian situation (one pharmaceutical firm, one minister representative and one hospital pharmacist). The final version was reviewed by all KCE team members and by an external expert. Five different questionnaires were designed to target the different key players (see appendix 6). Questionnaires included common as well as specific issues. Information included in Table 30 in the appendix regroups the content of the different questionnaires. Data extraction followed a two-step procedure:

- Using an inductive approach, a KCE researcher abstracted the following information from half of the interviews (n=15): barriers, advantages and policies' implications. The expert did not participate in the interviews. This allowed having an external view on actor perceptions and views. Based on this inductive analysis, the KCE team (including team members who participated in the interviews) focused on how repetitive barriers or problems fitted different parts of the biosimilar uptake process.
- All barriers inductively abstracted from the interviews were organized into three groups based on whether they were related to knowledge (cognitive factors), attitude (affective factors) or environment factors influencing purchasing or prescribing of biosimilars. This coding organization is inspired by Cabana's model on physician adherence to practice guidelines[jj]. [141] Cabana's model was useful to understand how different factors interfere in changing acquired practices (i.e. biosimilar uptake). A deductive data extraction in all interviews was then performed for all barriers included in this classification using the Nvivo© sofware.

7.1.2. Web survey

7.1.2.1. Sampling

A web-based survey was conducted with the collaboration of 8 scientific societies or associations, from 14 September 2012 until 8 of October 2012. The web survey and its analysis used Modalisa© software. The scientific societies or associations sent the link to the web survey to 1126 physicians and chief hospital pharmacist. A response rate of 11.2% was obtained (see Table 20) However, response rates varied for the different scientific societies or associations (see appendix 7 for details).

7.1.2.2. Construction of the questionnaire

The questionnaire was based on experiences from previous surveys.[140, 142], pre-tested with four KCE experts, and then submitted to four external experts. Adaptations were made following their remarks.

Table 20 – Response rate to the web survey on biosimilars

	N members	N members who were sent the link	N responses	Response rate (%)
Total specialist	1066	945	98	10.4
Total chief hospital pharmacist	183	181	28	15.5
Total specialist and chief hospital pharmacist	1 249	1126	126	11.2

[jj] Cabana's model was adapted for the project as we do not only analyze knowledge, attitude or practice ("behavior" in Cabana's article) of physicians but also of other practitioners and stakeholders.

7.2. Barriers for biosimilar uptake

Table 21 presents specific barriers (issues of concern mentioned during the interviews) at the diverse levels within the uptake process. For example, during the "purchase and inscription on formulary" step, the pharmaceutical and therapeutic committee (MFC – CMP) may not include biosimilars in the pharmaceutical formulary given that the price it is too high compared to that of the originator. Yet, including the biosimilar in the formulary does not guarantee its prescription as other barriers exist during the prescription step (e.g. physicians have to deal with dosage and devices difficulties).

Table 21 – Barriers for biosimilar uptake at the different levels of the uptake process

			Reimbursement	Hospital	Specialist	Patient
Knowledge	Lack of information	safety, efficacy and pharmacovigilance	X	x	x	x
		cost-containment data	X	x	x	
	Lack of appropriate information dissemination channels	insufficient marketing strategies by biosimilar firms		x	x	
		insufficient information provided by authorities		x	x	
Attitude	Lack of good faith towards biosimilars	information provided to the CTG – CRM is not trusted	X			
		protection of innovation and R&D	X	x	x	
		favour free market competition	X	x	x	
	Lack of confidence	concerns on safety, efficacy and pharmacovigilance	X	x	x	
		lack of confidence in biosimilar companies.		x	x	
		lack of confidence in the need for biosimilars		x	x	
	Lack of motivation/inertia of previous practice	prescription habits and loyalty to firms			x	
		patient's habits, education and compliance				x
Environmental factors	Price concerns	biosimilars are not the least expensive alternative in hospitals		x		
	Logistic concerns	dosage and devices differences			x	x
		logistics difficulties (storage, delivery)		x		
	Lack of fringe benefits with biosimilars	concerns for research budgets			x	
		concern for services to health care professionals		x	x	
		concerns for services to patients			x	x

7.2.1. Knowledge and perceptions

Factors hindering the biosimilar uptake process through a cognitive component were considered as barriers affecting knowledge. Informed decision-making requires to have access to and to fully understand the correct information. The knowledge one has about biosimilar can affect one's perception towards biosimilars (the expectancy or assumptions someone makes around biosimilars). For example, if one believes a biosimilar to be a generic and to be assessed like a generic, then one might not trust (to use) the biosimilar, given the particularities of biologics in general. In accordance, when one does not understand or accept the concept of comparability exercise, but expects a real efficacy proof (instead of proof of no clinical significant differences), the clinical data of the biosimilar process will never be enough. This does not exclude that experts who fully understand the comparability exercise may still not be convinced of the clinical safety and efficacy of a specific biosimilar in specific indications (attitude). From the information we gathered during the interviews, it is not always possible to distinguish between knowledge and perception on one side and attitudes on the other, because we did not test the exact knowledge of each of the interviewees on biosimilars. In general however, it can be expected that clear, unbiased information and communication is a absolute prerequisite for building positive attitudes (e.g. confidence) towards biosimilars.

7.2.1.1. Lack of information

Several interviewed physicians or representatives of physician's associations were not aware of the presence of biosimilar products on the Belgian market, within his/her specialization or on the hospital pharmaceutical formulary. According to the survey, 23% of the physicians did not know whether there were biosimilars on the formulary.

Information on safety, efficacy and pharmacovigilance

Some physicians may not have enough information to understand the approval of biosimilar products and this has contributed to a perception that biosimilars are inferior to the reference product despite the assessment and approval by the European Medicines Agency scientific bodies. In general, the procedures for market approval (MA) for biosimilars by EMA were not known or the interviewees did not understand the principles of the comparability exercise for the assessment of the biosimilars for MA. As a consequence, some of the interviewees assumed that the procedures were (close to) that of a generic. Some physicians mentioned that there were not (enough) patients tested, not long enough safety data or no appropriate clinical endpoints. Few others did apprehend the comparability exercise and procedure, but questioned the appropriateness of the procedure exercise[kk] (see section 7.2.2).

From the interviews, it became clear that there was a lack of knowledge about biosimilars, misaligning expectations, beliefs and data. Indeed, several stakeholders did not know what a biosimilar is or misunderstood the concept of biosimilarity. In the survey, 8.7% of the respondents correctly defined a biosimilar to be comparable in quality, safety and efficacy to the reference biological while 32.5% defined biosimilars as generic medicines[ll].

However, interviewees, specifically physicians, expressed their concerns either on safety or on efficacy consequences of the biosimilars or a combination thereof. Their arguments explaining the reluctance towards biosimilars in many cases, but not always, reflect insufficient or incorrect knowledge and information about biosimilars on several levels. Arguments presented by different interviewees are mentioned hereafter:

- The market approval requirement and procedures and concept of biosimilarity: doubts that the EMA procedures for biosimilars will lead to qualitative bio-equivalent products, no clarity about the level of similarity that is acceptable, obscurity about exact criteria used to compare the originator and the biosimilar (a non-inferiority test or a bio-equivalence test), assumed insufficient number of patients tested.

---

kk As mentioned before, during the interviews it was not possible to differentiate actual accurate knowledge from lack of knowledge on biosimilars and how it affects their attitudes towards biosimilars (e.g. missing knowledge or no trust on the biosimilar pathway)

ll This was a multiple choice question. Percentage was calculated as the number of respondents who defined biosimilar as a generic as minimum one of the answers, divided by the total number of respondents. See appendix 7 for all answers.

- Safety and efficacy: Physicians in particular mentioned that they had no information of how efficacy and side effects seems to be tested. Both physicians and some hospital pharmacist mentioned that they had no information on immunogenicity (any change in a biological product can alter the immunogenicity profile (often referred to Eprex PRCA case), lacked detailed unbiased information and the absence of (reported) experience with the product, lack of knowledge about the interaction between biosimilars and others pharmaceuticals in combination (might give unpredictable side effects), insufficient follow up period of safety studies.
- Pharmacovigilance: In general, interviewees mentioned that biosimilars are not followed-up sufficiently after market approval, and that there is no diffusion or appropriate communication of possible problems.
- Naming and traceability: Naming was mentioned by some physicians as being confusing and error inducing. The term "Biosimilar" is badly chosen, if they get the same INN name (which implies identical), but using different INN means completely different biologicals (although possibly with the same mechanism of action); INN systems should be adopted for biologicals.
- Interchangeability: for the interviewees it is often not clear if products are interchangeable for specific indications and for which patient groups.
- Also, there were significant doubts about the (reasoning beyond) extrapolation of indications. Some physicians suggest that a clear list of minimum set of indications to be investigated should be set a priori before a biosimilar is developed/evaluated and what extrapolations are judged acceptable. However, when and how extrapolation is judged and which arguments are used is not always known. Physicians do not always have access to all the relevant data (for example pharmacovigilance data) or the data is not easy accessible or readable (physicians will rarely read EPAR).

Cost-containment data

Some physicians and pharmacists were hesitant to believe that biosimilar would mean "significant savings". The level of savings considered significant varied. Although most interviewees agreed that a price difference of 20-30% with respect to reference product would be acceptable, minimum yearly potential justifying public measures in favour of biosimilars varied. Credible data or analysis on the cost containment potential of biosimilars place in the Belgian context (or the communication thereof) is lacking. These views were confirmed by the survey as 53% of the respondent requested more information on the cost-containment potential of biosimilars.

7.2.1.2. Lack of appropriate information dissemination channels

Insufficient marketing strategies by biosimilar firms

During the interviews, a majority of physicians and hospital pharmacists declared not having had a direct contact or information from firms producing biosimilars. Hospital pharmacist as well as physicians mentioned that biosimilar/generic companies do not offer this level of support and the lack of such competent contact person is big problem, especially for biologicals. During the interviews, biosimilars companies acknowledged that the level of marketing activities was linked to expected gains. Given the difficulty to introduce biosimilars in the hospital pharmacy (due to discounts and rebates), companies expressed having a passive attitude regarding marketing strategies in hospital settings. Therefore, biosimilar companies expressed that even after contacting physicians, biosimilars were not included in the hospital formulary. On the other hand, paediatricians-endocrinologists had more contacts and information from biosimilar companies probably given to the fact that human growth factor is the only product which is sold in public pharmacies. Paediatricians-endocrinologists in Belgium make treatment decisions on a common basis by monthly consultation meetings on individual patients.

During the interviews, "traditional companies" acknowledge their future investment in the biosimilar market. However, they were less clear on whether the same strategies for reference products (e.g. strong marketing strategies) will be use for marketing their forthcoming biosimilars.

Insufficient information provided by the authorities

The biosimilar companies, in addition to some pharmacists, found that the information given on public websites (i.e. FAGG – FAMHP) was ambiguous or insufficient. The biosimilar firms argue that there is a lot of misinformation at the regulatory and reimbursement agencies. Although explicitly left at the responsibility of the national agencies, no official

position on interchangeability and switching per product–class has been published, although switching is discouraged in general. Unbiased, unambiguous information regarding biosimilars is lacking according to these interviewees. However, The FAGG – FAMHP has not developed national guidelines for biosimilars, since the EMA guidelines for biosimilars developed by the BMWP are recommended to be applied. References to these guideline documents as well as the EMA "Question and answer document on biosimilar medicines" and European Public Assessment reports (EPAR) are included on the FAMHP website

According to the survey, for physician the main source of information on biosimilars was medical scientific literature (60.2%) followed by medical conferences (42.9%), biosimilar companies (38.8%), professional medical associations (29.6%), and innovator companies (12.2%). Only 4.2% of physicians cited having received information from the hospital pharmacist. For hospital pharmacist, the main source of information was biosimilar companies (64.3%), followed by medical scientific literature (57.1%), medical conferences (46.4%), innovator companies (32.1%) and professional medical associations (17.9%). The FAMHP was cited as a source of information by 25.0% of the hospital pharmacist and by 9.2% of the physicians. The RIZIV – INAMI was cited as a source of information by 17.9% of hospital pharmacist and by 15.3% of the physicians.

Key Points

Issues concerning knowledge

- **Low awareness of biosimilars, particularly with physicians.**
- **Limited knowledge about the approval procedure for biosimilars, in particularly the principle of the comparability exercise, possibly leading to a misalignment about expectations, beliefs and the available data.**
- **Information gap on the realistic saving potential of biosimilars in the Belgian context, now and in the future.**
- **Non-effective (or appropriate) information dissemination channels.**

7.2.2. Attitude

Factors hindering the biosimilar uptake process through an affective component were considered as barriers affecting attitude. Attitudes can be influenced by perception, culture, prejudices and lack of knowledge. As such, it not always possible to analyse attitude separately from the knowledge.

7.2.2.1. Lack of good faith towards biosimilars

Information provided to the CTG – CRM is not trusted

Interviewees among biosimilar companies as well as some companies not producing biosimilars, expressed their concerns about the attitude of the CTG – CRM or certain of its members towards the EMA procedure (in general). One innovator noted that in general regulatory agencies are more and more risk averse. For biosimilars, companies expressed that the CTG – CRM is not always willing to accept the EMA ruling on sufficiency of clinical evidence between products and focus primarily on budgetary impacts. A biosimilar company and other representatives mentioned that a filgrastim biosimilar (Nivestim) was refused for reimbursement based on the quality of the clinical trials, although this was deemed sufficient for the EMA for MA. Also, pharmaceutical firms mentioned that for biologicals, more phase III data is asked and often specific Belgian data is required for (continued) reimbursement. However, in practice the clinical evidence is then re-assessed at the hospital level as expressed by some hospital pharmacists.

Protection of innovation and R&D

Most physicians share the perception that biosimilars do not contribute to innovation. In the survey, a part of the respondents identified "the implementation of biosimilars removes R&D capital from innovating companies" as a reason not to prescribe biosimilars (pharmacists 17.8% and physicians 37.7%). Also from the survey, only a minority considers biosimilars important to stimulate innovation of biologicals (pharmacists 32.0% and physicians 10.0%). Some physicians also mentioned that to participate in clinical studies for biosimilars, one exposes patients to uncertain risks with no expected (clinical) benefit or innovation. Moreover, they argue that the scientific interest to participate in such studies is low as publication possibilities are uncertain.

In line with this, biosimilars companies mentioned that it is hard to find specialist willing to participate in clinical trials (even if they are phase IV studies) or willing to commit to test the products.

Both authorities and physicians expressed the need to protect the innovator companies, in particular, the research and development industry to ensure the important economic interests and the scientific pole position that exist in the Belgian context. In relation to this, several interviewees noticed that current measures around biosimilars and epoetins in particular, favour a product of a specific innovator company with strong Belgian roots, while punishing other innovator products, without having any impact on biosimilar uptake. In contrast with these results, some pharmaceutical companies mentioned the production of biosimilars will contribute to innovation in biologicals, specifically in the manufacturing processes and analytical testing procedures.

Favour free market competition

Some firms, pharmacists and physicians are in favour to let market mechanisms regulate the competition between products and are against interference of the government with measures favouring biosimilars uptake. However, most of them convey that the entry of biosimilars into the hospital market is highly unlikely without additional measures dealing with the hospital financing system. Therefore, they acknowledge that short term measures to stimulate the uptake of biosimilar and to gain clinical experiences might be necessary during a certain transition period.

7.2.2.2. *Lack of Confidence*

Concerns on safety, efficacy and pharmacovigilance

Most interviewees did not question the quality of manufacturing and the product per se (quality controls etc.) of biosimilar companies. An often heard argument was that in contrast to generics, biosimilars could not be made in “your own backyard”: the development and production of EU biosimilars is trusted to be done by competent people and companies. However, in general physicians are not convinced by the existing clinical evidence on safety and efficacy. The scepticism is fuelled by the limited number of patients involved in clinical trials, the use of clinically unsatisfying endpoints, limited patient populations, inconsistency around the acceptable variability range or the lack of any data in specific patient groups due to the extrapolation of the data. Extrapolation of data of the originator to the biosimilar based on pharmacokinetics/pharmacodynamics alone is not good enough according to several physicians. Moreover, the use of biosimilars in extrapolated indications is for several physicians (groups) unacceptable: they argue that with the clinical trials that were conducted, it is not always possible to judge efficacy and safety in all indications the originator products has. The scientific arguments deducted from *in vitro* tests and previous clinical experiences (a.o. mechanism of action, binding assays, detected side effects with reference product) are often irrelevant for physicians: they want to see more clinical arguments and data. The uncertainties due to the low number of treated patients, especially on the level of immunogenicity (which may vary in different patient populations) makes the risk/ benefit consideration by physicians, particularly for individual patients, often unfavourable. For physicians, the well being of the patient precedes all budgetary implications. Even though from a scientific point some physicians acknowledge that all data requirements set by the EMA are met, at this point in time, the field experience showed that these do not fulfil the expectations of many physicians in Belgium. Among physicians filling the survey, 57.2% reported that biosimilars could be used no or minor safety and efficacy concern when initiating treatment. Yet, in the survey uncertainty about the efficacy and the safety are the most often cited reasons not to prescribe biosimilars for physicians in the web survey (59.2%). Concerning treatment for naïve patients, 82.1% of pharmacists answering the survey were of the opinion that biosimilars could be used without any major safety or efficacy concern for first use. For switching a treatment, 42.9% of all respondents reported that biosimilars could be used no or minor safety and efficacy concerns. Significant differences in opinions concerning switching during treatment were not found between pharmacists and physicians. Finally, seventy two percent of the respondents singled out well-monitored post-marketing efficacy and safety studies as the best intervention to promote biosimilar uptake.

Lack of confidence in biosimilar companies

Although the manufacturing capacity and quality aspects of the biosimilar producers are not put in question, there is a sense that product knowledge and competence of the people is insufficient at biosimilar companies. This can include information about interaction with other medication, experience with the pharmaceutical itself, but also inferior access to competent people

and delays in information given, etc. However, the innovator companies which are embarking on biosimilars, will have an advantage over pure biosimilar/ generic producers, because of their image of providing correct and full information. It remains to be seen if those companies indeed will provide the same services from that perspective or will adapt their strategy and investments towards a more biosimilar approach. In accordance with the interviews, the survey identifies the trust physicians have in innovator firms as the single most cited important reason not to prescribe biosimilars according to pharmacist (75%), and third most cited with physicians (42%).

Lack of confidence in the need for biosimilars

Although physicians and pharmacists do not see a need for biosimilars from a medical perspective, they recognize that biosimilars are important to contain cost for the health system, either by putting price pressure on existing originator or by providing cheaper products. From a government perspective, the decision to use biosimilars is linked to budgetary policies. During the interviews, authorities mentioned that introduction of biosimilars is needed to stimulate competition, innovation (e.g. development of second generation pharmaceuticals to counter competition), supply alternatives in case of pharmaceutical shortages and to obtain cost-savings for the third-party payer in order to ensure sustainability of the system. Yet, not all actors agree that biosimilars will lead to long-term savings. First, all interviewees mentioned that reference products may be more expensive for RIZIV – INAMI but not for hospitals for which reference products are available at a low discounted price (list price minus discounts). Secondly, some physicians argue that when correctly used, the most expensive (often second generation on-patent) product will be even less expensive than the biosimilar. Thirdly, pharmaceutical firms pointed out that other strategies (not relating to biosimilar market penetration) are possibly more effective to contain cost in medications (e.g. diminishing the price after patent expiry, promote and control good use of medication etc).

However, companies mentioned that diminishing the price of medication after patent expiry too much will discourage innovation, although some innovator firms expressed their willingness to discuss further price discounts as long as in–patent products are spared. In the survey, the majority of the respondents identified cost-containment as the most important reason for biosimilars (68.2%).

7.2.2.3. *Lack of motivation/inertia of previous practice*

Prescription habits and loyalty to firms

Physicians and hospital pharmacist acknowledged that existing kick-backs (fringe benefits[mm]) to the physicians, for example in the form of training financing, clinical research grants, exchange of scientific knowledge, creates a dependency which make individual physicians loyal to the traditional pharmaceutical firms. Physicians will only use something new when they have an advantage (possible clinical benefit for patient of personal advantage in form of clinical grants). As such, loyalty can be influenced by marketing tools and services such as compassionate care, off-label use programs or good corporate policy/ governance practices. Moreover, for most physicians there is no reason for change if something you are used to work with performs well.

The survey showed that 59.5% of the respondent has never prescribed a biosimilar. Unexpectedly, the survey did not confirm fringe benefits as a major reason not to prescribe biosimilars. “Physicians have a better relationship with the innovator pharmaceutical firms” was cited as the second reason not to prescribe a biosimilar by pharmacist (57%), although for physicians this was a less cited reason (27%).

Patient's habits, education and compliance

While neither patients nor patients associations were interviewed, physicians expressed their concern on respecting patient habits as they may influence compliance. For chronic treatments patients are used to specific routines (e.g. one hospital visit per month) or to a specific device (e.g. for human growth factor).

Changing of treatment, especially an efficacious treatment can lead to unnecessary mental stress or medical errors when dosage and appearance are different or names sound like other co-medication. However, especially when a special device is used for application, a change of devices requires extensive training and control. In this sense, when the use of biosimilars leads to changes in patient habits or worsens the ease of use, they will be less successful to gain market share.

[mm] An incidental or additional advantage or incentives given to physicians or hospitals

Key Points

Issues concerning attitudes towards biosimilars

- **Limited trust in the biosimilar pathway procedure (e.g. extrapolation of indication or concerns on safety, efficacy and pharmacovigilance).**
- **Physician and pharmacist loyalty and habits towards reference product companies.**
- **Insufficient quality and quantity of scientific and clinical services to physicians from biosimilar companies.**
- **Doubts on the economic need for biosimilars.**
- **Risks for compliance of changing patients already established treatments.**

7.2.3. Environmental factors

Factors affecting stakeholder or practitioner ability to produce, register, purchase or prescribe biosimilars despite their good knowledge or positive attitude towards biosimilars, were considered as barriers affecting practice. In general, there is a lack of stimulus for prescribers/ pharmacists to use biosimilars other then possible spontaneous personal concern for health system budget impact.

7.2.3.1. Price concerns

Biosimilars are not the least expensive alternative in hospital settings

Compared with the discounted price for reference products, hospital pharmacists as well as some physicians mentioned that biosimilars are not the least expensive alternative in the hospital settings. Discounts on the list price at the hospital pharmacy are high on products such as epoetin and filgrastim, possibly because there are several me-too pharmaceuticals already on the market. Some pharmaceutical companies as well as some hospital pharmacists mentioned that reference product companies provide large discounts, ranging for epoetins from 30 to 75%. For products without competition (first in class) no discounts are provided. Overall discounts and other advantages for hospitals can account according to interviewees for 5% to 20% of the total hospital budget for pharmaceuticals. In addition, hospitals pharmacists as well as pharmaceutical firms mentioned that current rebates on list price from reference products combined with current reimbursement from the RIZIV – INAMI based on the list price constitute a considerable part of the hospital overall budget. All stakeholders agreed that such a system leads to non-transparency and difficult negotiations. Pharmacy benefits are said by hospital managers to be used to cover deficits within the hospital. The survey results were not in line with the discussion on discounts and rebates as hospital fringe benefits was almost not cited as reasons not to prescribe/ use biosimilars for both pharmacist and physicians (only 5 persons).

Whether the discounts for future classes of biosimilars is/will be as substantial remains to be seen and the time of entry of the biosimilars after patent expiry might play a role. However, for TNF inhibitors for example a range of alternatives are available leading to competition often resulting in considerable discounts already. While this was mentioned by pharmaceutical companies and some hospitals, the issue of competition from future biosimilars was only shortly discussed during the interviews.

7.2.3.2. Logistic concerns

Dosage and devices differences

Hospital pharmacists as well as physicians mentioned that differences in dosage or devices could be considered when choosing a biosimilar instead of the reference product. It was mentioned, that as with generics, different packaging methods (no unidose available) or no pre-filled syringes may impair practicality considerately or decrease safety or traceability the biosimilars. It was also mentioned that compared to generics, reference products have more galenic forms and “non-profitable” dosage (for example no paediatric dosages). If only the intravenous route of administration is approved for biosimilars, the reference product or another should anyways still be procured for subcutaneous use. Finally, change of devices might cause reluctance with prescribers and patients. It was mentioned for instance that uptake of Omnitrope was only realised after the adaptation to a pen injection device very similar to the original.

Logistics difficulties (storage, delivery)

Pharmacists expressed that a secured and trusted supply and distribution channel is gaining importance as a criteria for procurement of pharmaceuticals in the hospitals, mainly because of experiences of stock breaks and pharmaceutical shortages. Moreover, there are additional costs and efforts to change supplier. Since physicians in general do not want to

switch patients, the introduction of biosimilars would imply the need of additional storage capacity for cold-chain medicines in the hospital (both originator and biosimilar) in an often already stretched infrastructure, according to pharmacists. As claimed by some firms, storage cost can play a big role in deciding the number of pharmaceuticals included in the formulary. Therefore, some pharmacists suggested to shift biosimilars to public pharmacies. Biosimilar companies recognized this problem and one suggested that alternative delivery programs could be negotiated. Storage goes through wholesalers in the Netherlands, where several medicines can be delivered at once in a timely manner, decreasing storage and handling cost for the hospital.

7.2.3.3. Lack of fringe benefits with biosimilars

Concerns for research budgets

According to a biosimilar firm, physicians are very reluctant to prescribe biosimilars, not because they doubt quality or effectiveness, but because they are afraid to loose funding for clinical trials from pharmaceutical companies. Indeed, several pharmacists and clinicians, especially in university hospitals, acknowledge that they depend considerately on companies for the financing of the clinical research. In addition, fees for services for (clinical) research from biosimilar/generic companies are not competitive with those of originator companies. Some pharmacists and physicians expressed concerns that by (only) purchasing “low cost”, companies will not invest in research. In addition, physicians share the opinion that policies should consider the importance of the originator pharmaceutical industry in Belgium and their contribution to investment in academic research and clinical trials. All actors agree more funding for research from the government could reduce the ties with the industry. Moreover, one company expressed the need for a more central administration of clinical trials, possibly as a private-public partnership for the negotiation of clinical trials and to share data. In the survey, none of the questions explicitly referred to grants. 35% of the respondents believed that “the implementation of biosimilars removes R&D capital from innovating companies” as a barrier for the prescription of biosimilars. Authorities pointed out discounts (or other fringe benefits) from pharmaceutical firms combined with full reimbursement for pharmaceuticals from the third party payer lead to non-transparent management of public resources. In addition, this “financing system” does not allow to have an objective image of budgetary needs of the hospitals sector.

Concerns for services for health care professionals

Besides grants and discounts, pharmaceutical companies provide also other forms of fringe benefits including paying financial support for employees (e.g. support for personnel caring for cancer patients, in trials or not), honoraria for scientific consulting and funding for scientific congresses. Although this emerged in the face-to-face interviews as an important barrier for biosimilar uptake, in the survey, only a minority of respondents (11.1%) suggested fact that fringe benefits from innovator pharmaceutical firms was a barrier in the prescription of biosimilar. Originator firms organize educational sessions for physicians and nurses to educate about the pharmaceuticals (including correct use of the device, pharmaceutical interaction, pharmacovigilance, etc). Also physicians and pharmacists value greatly the representative (or the medical information department of the originator company) as the main source of information and support for scientific updates, correct use, monitoring, quality, pharmacovigilance data around its products and the competitors.

Concerns for services to patients

Physicians mentioned that services to patients such as education of patients on disease, pharmaceutical and device use, home visits by nurses for injection services, etc can have an impact on compliance. As such, larger provision of these services from reference product companies is a factor determining the choice of treatment. In addition, this services free resources from hospitals and time for physicians.

Key Points

Issues concerning environmental barriers towards biosimilars

- **Currently, biosimilars are not the least expensive alternatives for the hospitals, because they are unable/unwilling to give the type of discounts or other advantages as the reference product. Advantages include financing of clinical research and funding for training for physicians.**
- **Reference product companies provide more services that can enhance patient compliance and free hospital's resources and physician's time.**
- **Differences in packaging, dosages and devices make use of biosimilars less attractive for physicians and patients.**
- **Additional cost relating to storage and delivery need to be taken into account when including biosimilars in hospital pharmacies.**

7.3. SWOT analysis for main policy interventions

This chapter summarises the opinions of the interviewees on several policy options targeting the increase of uptake of biosimilars and savings for the third party payer. Measures presented and discussed included:

Policies introduced by the Minister of Social Affairs during the summer of 2012 aiming to save cost for the third-party payer and possibly to increase biosimilar uptake such as:

- Inclusion of erythropoietin and growth hormones in hospital prospective budget and inclusion of erythropoietin in the category Fa
- Inclusion of prescription of any biosimilar in the existing quotas for low-cost prescription in ambulatory care
- Increase reimbursement price for biosimilar
- Planned measures such a the impact of public tender on biosimilar uptake
- New incentives for biosimilar prescription such as quotas for biosimilars in hospital settings

At the moment of the interviews, not all interviewees were equally informed of measures introduced by the minister. Some measures came into force after the interviews. The results of the analysis of the interviews are presented in a SWOT analysis, structuring the strengths, weaknesses, opportunities and threats of each policy. Since the SWOT analysis is solely based on the input of the interviewed experts, statements are always perceptions which may not necessarily reflect correct or exhaustive information. As for other policies, it may be desirable to evaluate their impact on biosimilar uptake, savings for the third party payer as well as on physician prescription habits. The latter may also imply to acknowledge their impact on patient outcomes.

7.3.1. Recently introduced measures

7.3.1.1. Introduction of epoetins in the hospital prospective budget and in the category Fa

- **Strenghts**

Pharmaceutical firms producing biosimilars as well as authorities mentioned that all policy measures taken for biosimilars by the minister are a first step towards inclusion (recognition) of biosimilars in hospital pharmacies. Authorities pointed out that policies are expected to provide savings in the middle-long term and to incentive hospital pharmacies to set cost-effective practices (e.g. using the most expensive alternative for indications where it is the more cost-effective). The policy design aimed at setting the reimbursement level between most expensive and least expensive alternatives and the flat rate of category Fa would still allow hospitals to cover costs when using the most expensive alternative in a subgroup of patients. Pharmaceutical firms mentioned that the measures led to direct short-time savings.

- **Weaknesses**

Hospitals mentioned that including epoetin in the hospital prospective would be only relevant for a very small proportion of patients who were treated with epoetins during a hospitalisation[nn]. In addition, financial responsibility relies only on the hospital (no shared responsibilities with the prescriber). An appropriate communication about the measure and transition period for implementation from the authorities was lacking. Hospitals pointed out that policies' impact on running contracts with

[nn] This policy was set early during the 2012 summer while the category Fa was set at the end of the summer.

pharmaceutical firms was neglected and that such measures ignored the PCT decisions.

The policy was perceived by companies and hospitals as a tool to transfer discounts received by the hospital to the third-party payer. All pharmaceutical companies mentioned that current savings for the third party payer were not related to biosimilar uptake but to a reduction of the reimbursement basis for on-patent pharmaceuticals. Moreover, pharmaceutical firms believed that the policy would be ineffective in increasing biosimilar uptake, yet decrease on-patent second generation long-acting epoetins. For some pharmaceutical firms, the policy did not respect patent protection and only benefited the reference product since the policy was price neutral for Eprex. In line with this, some hospitals and pharmaceutical firms mentioned that the reference product would still be chosen because the flat rate was set above the price of the biosimilar.

- **Opportunities**

Some physicians mentioned that the policy (and in general reimbursement policies based on a flat rate) should be linked to performance indicators (e.g. quality indicators for dialysis)[oo]. This could lead to rational use of expensive pharmaceuticals while freeing budget for other necessary and life saving treatments.

Some physicians and hospital pharmacists mentioned that finding the appropriate percentage in charge of the hospital and in charge of the RIZIV – INAMI (or appropriate flat rate) could improve cost-containment policies.

- **Threats**

Some hospitals mentioned that these policies could lead in the long-run to under-treatment of patients (i.e. not treated when hospitalised), to decide not to provide a certain service or not to treat a specific disease (e.g. sending patient to other hospitals). In addition to this, risk of switching was also mentioned by some hospitals pharmacist and pharmaceutical firms. Moreover, hospital pharmacists mentioned that they were unprepared to estimate the financial impact of the policy. Pharmaceutical firms not currently producing biosimilars pointed out that large reimbursement categories ("Jumbo category") should be dealt with caution (e.g. anti-TNF). Moreover, appropriate and effective policies need good communication and trust between the parties, which according to hospitals and pharmaceutical companies is currently lacking.

Key Points

Introducing epoetins in the prospective budget and in the category Fa

- **Introducing epoetins in the prospective budget and in the category Fa seems successful as a means to set short-term cost-savings for the third-party payer.**
- **The policies seem to fail to provide incentives to promote biosimilar use in hospital settings.**
- **Six months after policy implementation, the use of biosimilars has hardly changed.**
- **Lack of communication and trust between parties is a barrier for implementation of effective cost-containment policies.**

7.3.1.2. Inclusion of biosimilars in low-cost prescription quotas in ambulatory care

- **Strengths**

As for other measures, pharmaceutical firms producing biosimilars mentioned that this policy is a first step towards recognition of biosimilars. In ambulatory settings, biosimilars are less expensive than the reference product (as opposed to hospital settings).

- **Weaknesses**

Physicians mentioned that this policy fails to recognize inherent differences between biologicals and small chemical molecules. Substitution between products is not recommended for biologicals, whereas it is for small chemical molecules. Therefore, quotas should be set only for naïve patients (primary substitution). Quotas obliging physicians to choose a given treatment may interfere with patient compliance (e.g. devices, dosages, frequency of treatment).

[oo] According to a nephrologist, examples of quality indicators could be: haemoglobulin values (which should be in 80% of the cases within the pre-defined norms) and Number of blood transfusions should be the same and not increase (blood transfusions still used in cases of acute blood loss, big infections, …)

Pharmaceutical companies not currently producing biosimilars mentioned that this policy is discriminatory as a reference product reducing the price to the level of the biosimilar will not be considered “a low-cost prescription”. In this case, no incentives for price competition are set. Sickness funds are concerned that this policy can lead to higher patient’s out-of-pocket expenses. However, as expressed by some pharmaceutical companies, the reference supplement (and therefore patients additional out-of-pocket expenditure) is limited to 10.8€

- **Opportunities**

No opportunities were indentified.

- **Threats**

Physicians mentioned that differences in devices (this is not unique for biosimilar, also generics (e.g. for asthma) or type of treatment (chronic vs. non-chronic treatment) may determine their choice regarding the biosimilar or the reference product. Therefore, differences on these two aspects will affect the extent into which physicians may respect their prescription quotas. Enforcement of quotas is not applied in Belgium. Therefore, there are little incentives for physicians to respect the quotas.

Key Points

Biosimilars in low-cost prescription quotas in ambulatory care

- **Quotas in ambulatory settings may increase biosimilar take-up. However, higher uptake will be linked to the number of new patients.**
- **Savings for the third-party payer may be obtained through biosimilar uptake in ambulatory settings.**
- **Conditions determining acceptability of the policy include: i) Quotas cover only new patients; ii) Ease of use needs to be considered when setting the quota level (devices, dosages).**
- **Not including a reference product that reduced the price to the level of the biosimilar, diminishes price competition, therefore leading to lower savings for the third-party payer.**
- **Policy interventions such as quotas may reduce market competition. Justification of quotas for biosimilars are related to the savings for the third-party payer. However, if the reference product lowers its price to the level of the biosimilar, the objective justification is no longer valid.**

7.3.1.3. *Increase reimbursement for hospitals when using a biosimilar*

- **Strengths**

Pharmaceutical companies producing biosimilars mentioned that this policy sets reimbursement from the RIZIV – INAMI at the same level for all firms. This direct subsidy from RIZIV – INAMI to hospitals, enables all pharmaceuticals to provide similar discount levels (see section **Error! Reference source not found.** for an example).

- **Weaknesses**

Physicians point out that if the originator has the same price as the biosimilar, use of the originator will be privileged[pp]. It is not intuitive and undermines the main reason for a shortened for a biosimilar pathway: namely having a lower price for payers.

- **Opportunities**

No opportunities were indentified.

- **Threats**

Pharmaceutical companies not producing biosimilars pointed out that the policy is a direct subsidy from the third-party payer to biosimilar producers. They argued this subsidy is discriminatory and interferes with competition. The policy leads to no savings for the third-party payer as the reimbursement basis is the same for the biosimilar and the reference medicine. Moreover, the measure adds more complexity to the financing system of hospitals. It provides a "solution" to discounts by indirectly letting some companies to provide higher discounts.

[pp] This opinion was not expressed particularly concerning this policy but in a general basis.

Key Points

Reimbursement of biosimilars at the level of the flat rate of category F

- **Costs for the third-party payer are the same for biosimilars and reference products. Therefore, the policy does not lead to cost-savings. However, the measure adds complexity to the hospital financial system as it creates an indirect incentive to provide more rebates and discounts.**
- **When hospitals use a biosimilar with the reference product having the same price as the biosimilar, the use of the originator will be privileged. Therefore, we may expect that this policy will have a very limited impact on biosimilar take-up.**

7.3.2. *Planned measures*

As tendering affects the purchase of pharmaceuticals in general, and not only impacts biosimilars, the discussion focussed at the general part as well as biosimilars.

7.3.2.1. *Impact of public tender impact on the purchase of pharmaceuticals*

- **Strenghts**

Overall, all interviewees agreed that tendering can lead to greater transparency in purchasing of pharmaceuticals given that tender applicants will need to answer to same selection criteria. Authorities interviewed as well as pharmaceutical firms also mentioned that tender can lead to better structured and motivated procurement decisions of the awarding party[qq].

- **Weaknesses**

Hospitals[rr] as well as pharmaceutical companies mentioned that tendering procedures are time and resources consuming and no clear guidelines have been provided by the authorities. Hospitals as well as pharmaceutical

[qq] Authorities refer in this section to the RIZIV – INAMI as well as sickness funds.

[rr] Unless otherwise mentioned, we use the term " hospitals " to describe opinions from pharmacist, direction and head of purchase.

companies mentioned that not all actors are prepared to face additional work relating to the tender process. Moreover, most hospitals mentioned that, when possible, direct negotiations will be preferred to tenders (in particular given the work load). For hospitals as well pharmaceutical companies, there is uncertainty on the content of public tenders, in particular which services can be set as part of the offer, whether prices will be publicly disclosed and whether RIZIV – INAMI will reimburse the list price or the tender price. As explained by several interviewed experts, contracts between hospitals and pharmaceutical companies are mostly set as a "gentleman agreement". Therefore, new negotiations (e.g. following a new pricing measure) can be set at any moment. However, hospital pharmacist expressed their concern on how to deal with a negotiated contracts (binding after the tender) after a change in a reimbursement policy. Another area of concern for hospitals as well as for physicians is the extent to which tenders can change (reduce) fringe benefits (e.g. research grants) or even lead to higher prices. Pharmaceutical companies mentioned that with tenders services offered must be directly related to the pharmaceutical and that fringe benefits for physician are excluded (e.g. congress).

Physicians as well as some pharmaceutical companies expressed that tender should not interfere with physicians' prescriptions freedom or lead to automatic substitution of pharmaceuticals (except when a generic alternative is available). Moreover, for products with no alternatives tenders will probably not apply as negotiations can go through a direct negotiated procedure without prior advert. In this case, the negotiation process starts always discussing the product quality. Finally, avoiding a monopoly and guaranteeing continued security of supply of the medicine should be taking into account when setting a tender.

- **Opportunities**

A majority of authorities, hospitals as well as specialists mentioned that tendering can lead to better prices when negotiations are set by large hospitals or hospital groups (if such groups have appropriate coordination). Some hospital pharmacists also mentioned that tenders can lead to less stock rupture through competition from parallel imports (e.g. foreign firms applying for a tender). Some pharmaceutical companies also mentioned that competition is enhanced by being able to take legal steps to unfair tender criteria.

- **Threats**

According to the pharmacists, there will be creativity in the specifications of the tender (setting selection criteria, adjusting lot sizes or combining products in one tender, etc.) to purposely or not purposely exclude manufacturers. The biggest concern for payers is whether tenders will be effective in setting more price transparency. Indeed, without full price disclosure transparency is unlikely.

7.3.2.2. Impact of public tender and biosimilars

- **Strenghts**

Some pharmacists mentioned that biosimilars as well as other pharmaceuticals in the same therapeutic class may enter the same tender if the selection criteria for the tender are set at a therapeutic level for a group of pharmaceuticals. This may lead to an increased uptake of biosimilars if they offer the most advantageous conditions.

- **Weaknesses**

Pharmaceutical companies mentioned that tenders could be set with narrow selection criteria that automatically exclude biosimilars.

- **Opportunities**

Some pharmaceutical companies mentioned that public tender sets a first opportunity to gain market shares in hospitals. In this case, the same competition rules may apply to the biosimilar and the reference medicine. Indeed, portfolio contract and matched discounts are excluded from the tenders.

- **Threats**

Some pharmaceutical companies and pharmacist mentioned that the introduction of tenders for products that have biosimilars could be delayed over several years (therefore not opening an opportunity for biosimilars) because: currently some hospitals are setting long-period contracts to avoid entering in the short-term the tender procedures. Secondly, the tender procedure will only stepwise be introduced per hospital. The hospital can decide on its own which molecule to do first, possibly delaying those molecules with the biggest discounts.

Key Points

Tender and biosimilar uptake

- **From discussion with different interviewees, it was unclear whether tenders will lead to an increased take-up of biosimilars. This will depend on the tender selection criteria and on companies' ability to provide a competitive offer.**
- **Therefore, savings for the third-party payer linked to biosimilar take-up are not ensured by a public tender.**

7.3.3. Measures to be considered

7.3.3.1. Quotas on biosimilar prescription for hospital settings?

Quota can be set at different levels. According to some hospital pharmacists and physicians quotas at prescriber level (as in ambulatory settings cfr. supra) were considered not feasible at the hospital because traceability of the prescriber is difficult. This measure has not been applied in Belgium.

- **Strengths**

Therefore a quota at level of the hospital seems the best tool to increase biosimilar uptake. Although the measure does not seem acceptable to most interviewees, actors from all stakeholder groups agreed that quotas at hospital level may be the best tool to incentive biosimilar uptake. Acceptability of the policy was assessed during the interviews and a minimal set of conditions need to be covered. Some physicians and hospital pharmacist mentioned that quotas should be calculated: 1) only considering naïve and 2) not leading to exclude other companies (never 100% of all naive patients, otherwise in the long-run competitors will be excluded from the market). In this way, freedom of prescription for specialist is respected (as mentioned by specialists and pharmacist).

- **Weaknesses**

Physicians and hospitals mentioned that such a measure is not easy monitored and imposes using pharmaceutical which is not the least expensive alternative for the hospital. Moreover, it will need complex patient monitoring to follow which patients started on a given treatment. Pharmaceutical firms not currently producing biosimilars mentioned that this policy does not incentive competition (does not incentive biosimilar companies to be more competitive). Some hospitals also mentioned that a measure setting more competition would be to set a quota on low-cost prescription (e.g. including the biosimilar and the reference medicine). However, for hospital, a low-cost prescription cannot be defined as for community pharmacist: lower ex-factory price. For hospital, a low-cost alternative needs to be calculated based on the ex-factory price minus discounts. This is unlikely as discounts are not known and can vary from hospital to another. Hospitals mentioned that mandatory quotas imply to force inclusion of 2 products for specific indication in the hospital formulary. As a consequence, new costs must be taking into account: administration, storage, etc. In addition, quotas for small population (few treatments in a given hospital) may be unfeasible.

- **Opportunities**

Some pharmaceutical companies mentioned that quotas combined with financial incentives (instead of penalties) can be an effective policy measure to open the market for biosimilars. An incentive can be set as positive premium (i.e. doctors managing a general medical record receive a payment). Premiums (and to a lesser extent penalties) may induce a shared financial responsibility between specialist, hospitals and the third-party payer. Some hospitals mentioned that discussion on how to implement quotas (e.g. for which indications) should be left to each hospital. In this way, decisions will reflect each hospital characteristics and will involve all concerned parties (involved in the PCT)[ss]. Some physicians mentioned that more clinical data (e.g. extrapolation of indication or switching studies) are the best tool to make this policy acceptable. Otherwise, quotas should only be imposed for appropriate indications (for which clinical data is available)

- **Threats**

Some pharmaceutical companies as well as physicians pointed out that patients will not have a choice concerning the use of a biosimilar.

[ss] Advantages for quotas on hospital level without specific treatment group (e.g. hospital choice only for supportive oncology treatment to use a biosimilar epoetin and only originator pharmaceuticals for dialysis) In contrast, prescription quota's per treatment group (e.g. 10% of new patient for both for supportive oncology treatment and for dialysis).

Enforcement of quotas is unlikely as financial rewards (or penalties) can be outpaced by gains given through discounts and rebates. In addition, this policy is perceived as discriminatory and a threat to competition. Moreover, in the light of future tender procedures, some hospitals mentioned that quotas deemed as "uncompetitive" are against the main reason for the tenders: to improve competition.

Key Points

Quotas on biosimilar prescription for hospital settings

- **Given current financing of hospitals, quotas at hospital level seem the best tool to guarantee increased market access for biosimilars.**
- **This can in exchange lead to savings for the third-party payer. However, if biosimilars and the reference product have the same reimbursement basis, savings can be null because the use of the reference medicine will be privileged.**
- **Policy short-comings include: i) difficulty to enforce quota because benefits from discounts may outpace any financial incentive (or penalty) provided to hospitals; ii) close patient monitoring to avoid switching, iii) biosimilars are not necessarily the least expensive alternative in hospital settings ; iv) policies at a hospital level need to take into account each hospital characteristics (e.g. number of patients, indications).**
- **Quotas should be set only for naive patients.**
- **A low-cost prescription for prescribers is unfeasible in hospital settings because of difficult prescriber traceability. Moreover, there is incoherence between the definition of low-cost according to the concerned party and settings (for who? RIZIV – INAMI vs. hospital, and where? community pharmacy vs. hospital).**

7.3.3.2. Alternative financing for hospitals?

Concerning prices and reimbursement policies on pharmaceuticals, national authorities should therefore ensure to eliminate barriers that limit the use of the least expensive alternative among equally high quality treatment options. Moreover, rules should guarantee as much as possible transparent and fair competition. However, all interviewees mentioned that current financing system of hospitals leads to difficult implementation and monitoring of policy interventions. For biosimilars, price competition seems more difficult in part because of lack of transparency on price. Moreover, pharmaceutical companies agreed that prices paid between hospitals may differ.

- **Strengths**

Lead to transparency, better policy implementation and monitoring. Of course depending on the system

- **Weaknesses**

Currently no sufficient communication and trust between parties exist. Therefore, discussion on financing will certainly not be an easy step.

- **Opportunities**

Transparency for better quality outcomes. Definition of a long-term financing system less focused on short-term policies

- **Threats**

Changing the current financing system is not a simple task and will certainly be a long-term process. Therefore, this will not provide a solution for biosimilar uptake in the short-term.

7.4. Stakeholders meeting: opposing and common positions

Results from the research were presented to stakeholders. Invited stakeholders included representatives of national authorities, pharmaceutical firms (including generic and biosimilar as well as originator pharmaceutical industry), sickness fund, professional and scientific societies as well as representatives from hospitals' association. Opinions during the meeting turned around four main subjects: i) need for policy intervention for biosimilars, ii) financing of pharmaceuticals in hospital settings, iii) questions on data and information on biosimilars (and other biologicals) and iv) limits of the KCE study. From the discussion, opposing positions as well as common views are described hereafter.

7.4.1. Is there a need for policy interventions for biosimilars? Free market versus intervention for biosimilars

Originator companies as well as their representatives expressed that uptake of biosimilars should depend on a free market mechanisms without government interventions. It was mentioned that most if not all innovator companies are developing biosimilars. They conveyed their opinion that any interventions specifically favouring biosimilars would discriminate innovating companies unfairly. Moreover, it was mentioned that originator companies should not put at a disadvantage especially in review of their important contribution to the Belgian economy (providing significant employment in Belgium, the most important private investment in R&D in Belgium and the significant contribution to the balance of trade of Belgium). On the opposite position, biosimilar industry and their representatives argued that there is a need for governmental intervention to give biosimilars a chance to gain market share in Belgium. They argue that biosimilars are entering an uneven competition field in hospital settings, due to significant, but non-transparent discounts and other advantages (e.g. R&D funding) granted by originator companies. According to them, it is essential to warrant market share for biosimilars in order to keep biosimilars in the Belgian market and to realize (now and in the future) their real savings potential. These two opposing views were clearly expressed during the face-to-face interviews. As such, policies introduced by the Minister during the 2012 summer are far from being accepted by all involved parties.

7.4.2. Financing of pharmaceuticals in hospital settings

It was discussed during the stakeholder meeting that cost are not transparent in the current financing of pharmaceuticals in hospitals settings. This point was mentioned during the face-to-face interviews. According to some stakeholders, if rebates on pharmaceuticals in hospitals are abolished, an alternative funding for the hospital and for clinical research needs to be found. Yet, while this financing system may limit cost transparency, it was mentioned that discounts and rebates are generally used to finance under-supported or-performing activities in the hospitals and are not by any means illegal. It was also mentioned that prescription guidelines for appropriate use of pharmaceuticals can lead to savings for the third-party payer.

7.4.3. Questions on data and information on biosimilars (and other biologicals)

Need for more information on biosimilars was a point openly discussed in the stakeholder meeting. How and who should provide this information was more a matter of debate. Biosimilar companies and their representatives agreed that more information needs to be provided. Yet, they expressed that investment may only come when the market is accessible (less financial barriers) for biosimilars. On the other hand, representative of originator companies argue that information provided by the authorities should not replace efforts from biosimilar companies. All taken into account, more neutral information from the authorities is welcomed by all stakeholders.

Issues regarding use of biosimilars (and biologicals) and the level of available safety and efficacy data were also raised by physicians during the stakeholder meeting. Clinicians were also sceptical about the communication of the safety issues. Doubts and concerns relating to available information on biosimilars safety and efficacy data were clearly expressed during the face-to-face interviews.

Four points not mentioned during the interviews were raised during the stakeholder meeting. First, physicians as well as a representative of the BCFI – CBIP mentioned that policies to promote biosimilars should not have the effect of promoting inappropriate use of biologicals. Second, changing prescription habits (e.g. leading to use more biosimilars) may not be easy as physicians may not even have enough information on the

product that they are currently using. Third, there is a need of independent national patient registries which could provide more information on clinical data. This in return could help improve knowledge on safety and efficacy for different pharmaceuticals and as such improve physician's prescription habits. Finally, information to specialists may not be sufficiently provided by independent information channels (e.g. EBM guidelines are currently targeting more general physicians).

7.4.4. Limits of the KCE study

Originator companies as well as some physicians' scientific societies pointed out that the scope of the report did not include an overall view of the biosimilar context. Originator companies as well as their representatives argued that the scope of this study could have been enlarged to an analysis of how to improve savings for the third-party payer for all biologicals or by setting cost-effectiveness analysis for product classes where biosimilars are available. For physicians, stimulating use of biosimilars should be set hand in hand with appropriate prescription guidelines for each indication.

8. SUMMARY, CONCLUSION AND DISCUSSION

8.1. Background

Before discussing the results of this study, a rapid overview of the context in which biosimilar competition takes place in Belgium is needed. 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 in order to ensure savings for patients and the third party payer. Second, in hospital settings, direct negotiations between purchasers (hospital pharmacists) and providers (firms) lead in some cases to large discounts and rebates 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, clinical research in hospitals and continued education of hospital pharmacists and physicians are also financed to a large extent via the pharmaceutical sector. Whether this context strengthens pharmacists, physicians and hospitals' loyalty to reference products is an open question. We may hypothesize that biosimilar enters a difficult highly competitive arena. From the perspective of the pricing and reimbursement authorities, it is necessary to determine the extent to which this context limits the use of the least expensive alternative among equally high quality treatment options.

This study is envisaged as a first step to clarify which barriers limit the use of pharmaceuticals, namely biosimilars, which may reduce pharmaceutical expenditures for the third-party payer. Indeed, whereas biosimilars seem to be increasingly adopted in many European countries, Belgium has one of the lowest uptake rates of biosimilars in Europe. Sales concern only one active substance somatropin. Biosimilars for epoetin and filgrastim have not been able to penetrate the market.

Requests for reimbursement for biosimilars follow the same pathway as any other pharmaceuticals in Belgium.

The price negotiations are set on a per case basis for each new biosimilar, in contrast to generics where a mandatory price reduction is fixed to 31%.

All reimbursement claims for biosimilars were filed under Class 2B and included a voluntary price reduction. All products included in Class 2 (which is divided in 2A, 2B and 2C) are considered to have an analogous therapeutic value with respected to another product (comparator) and their prices cannot exceed that of the comparator The initial price reductions proposed by the firms were between 10 and 15% below the reference product. However, negotiations between authorities and biosimilar firms have led to a further price reduction ranging from 20% to 34%. Until July 2012, 7 reimbursement request files were filed resulting in 6 positive decisions (Binocrit, Retacrit, Omnitrope, Zarzio, Tevagrastim) and in one negative decision (Nivestim). In 2011, uptake of biosimilars for epoetin and filgrastim has been almost zero (less than 0.01% of total DDDs in 2011 for these products). Only for somatropin, mostly prescribed in community pharmacies, has a little more market penetration from the biosimilar. Current sales in community pharmacies for omnitrope (biosimilar) account for 3.45% of total DDDs.

During the summer of 2012, three measures to stimulate the use of biosimilars were taken by the Minister of Social Affairs and Public Health: i) inclusion of prescription of any biosimilar in the quotas for low-cost prescription; ii) inclusion of erythropoietin and somatropin in the hospital prospective budget for pharmaceuticals and iii) flat rate reimbursement for all epoetins. In addition, from 1 February 2013 hospitals will receive this flat rate which exceeds the treatment price based on the list price of the epoetin biosimilar (reimbursement basis is higher than the list price).

8.2. Factors determining biosimilar uptake: a literature review

Literature on biosimilars is increasing. However, the structured literature review showed that evidence on pricing and reimbursement policies and their impact on biosimilar uptake is only at the first stage. Biosimilars are expected to offer a less expensive alternative to existing biologicals and by doing so, to reduce expenses for the third-party payer. However, evidence on price reductions and savings is scarce and varies according to different modelling strategies and hypothesis used by analysts.

Some authors have argued that biosimilar uptake may follow a similar pathway to that of generic medicines. Yet, most evidence seems to point out that competition will lead to smaller price reductions between the reference product and the biosimilar than is the case between generics and the reference products. This may particular be true in countries such as the UK or Germany where prices may differ of up to 80% between the brand name pharmaceutical and the generic. Lower price reduction between the reference product and the biosimilar has been attributed to a higher production cost (not well documented) as well as to the stronger need for marketing strategies for biosimilars than for generics. Moreover, high production cost may also lead to fewer competitors producing biosimilars which in return may lead to lower price competition.

Gains in market shares for biosimilars may be linked to procurement policies in hospital settings, which are different from the ambulatory sector. In hospital settings, purchasers may have larger bargaining power and product selection may be negotiated with fewer suppliers. As a consequence, firms producing reference products may provide large discounts. Therefore, biosimilar competition takes place in markets where discounted prices from reference products may be set at a low and very competitive level. In these settings, biosimilars need to be the least expensive alternative for hospitals with respect to the discounted price and not the list price. In addition, in hospitals, the final choice for a pharmaceutical may also depend on negotiations between purchasers (pharmacists) and physicians, which will reflect more or less conservative attitudes toward interchanging products. Conservative attitudes will reflect health care professionals' prescription habits as well as to loyalty to a product.

As for all pharmaceuticals, physician prescription habits and loyalty to a product (i.e. brand loyalty) may determine the choice between a biosimilar and the reference product. For biologicals, in general, substitution during treatment is only recommended under the supervision of a health care professional, while for generics, substitution during treatment is accepted and in several countries is set at the level of the pharmacy (automatic substitution). Therefore, when using a biological, physician loyalty to the reference product cannot be circumvented by policies such as automatic substitution or INN prescribing. In this context, biosimilar market penetration may depend on physician acceptability of the product. Therefore, to the extent into which marketing strategies from biosimilar companies may enhance trust (and knowledge) with health care professionals and key opinion leaders.

In the light of results of the literature review, Belgium seems to be a case study to confront theoretical views on barriers limiting biosimilar uptake. Indeed, direct negotiations between purchasers (hospitals) and providers (firms) lead to set prices for reference products at a low and very competitive level. Prices are low from the point of view of the hospital and not of third-party payer. As such, national authorities claim that they are losing an opportunity leading to reduce pharmaceutical expenditure. In addition, health care professional loyalty to reference products may also be an important barrier for market penetration of biosimilars. Services and other advantages provided by reference product companies may reinforce current physician prescription habits. In addition, given that pharmaceutical financing depends on firms' discounts, hospital pharmacist purchasing habits are also influence by advantages provided by reference product companies. In addition, insufficient information or concerns relating to biosimilars characteristics have not been addressed by biosimilar companies through the provision of information and eventually more access to clinical data.

8.3. Evidence on uptake and policy for biosimilars in Europe

According to IMS data, biosimilar uptake for available biosimilars varies among European countries. Uptake for epoetin biosimilars was highest in Germany (45%), Greece (54%) and Sweden (24%) and lowest (null) in Belgium, Luxembourg and Portugal. Highest uptake for filgrastim biosimilars was found in Austria (64%), Norway (64%) and Sweden (50%). Biosimilars for filgrastim were not used in Belgium, Luxembourg and Portugal. Finally, somatropin biosimilars had lowest uptake compared with epoetin and filgrastim biosimilars. Highest uptake was found for somatropin in Sweden (13%), Italy (9%) and France (9%).

A recent EGA survey provides a first listing of biosimilar related policies set by national authorities. Details or exact definition of policies are not included in the EGA survey. Some countries have set policies to promote biosimilar uptake, while others have refrained from doing so. Three countries (Denmark, Germany and Italy (Tuscany region) have set quotas for biosimilars and two countries included (Germany and Italy) prescription targets for biosimilars. One country (Austria) includes biosimilars as alternatives to the reference product in the electronic form of list for products admitted for reimbursement. In the list, products are sorted by price leading prescribers to see the less expensive alternatives. Finally, one country (Norway) reported having a specific reimbursement for the filgrastim biosimilar (Tevagastrim). In other countries, were biosimilar uptake is high (Finland and Sweden) no specific policies for biosimilars were mentioned in the EGA survey.

8.4. Results from the international comparison: Germany, France, The Netherlands and Sweden

Discussion and evaluation of policies leading to biosimilar uptake is lacking in the literature. Yet, in the light of large differences in biosimilar uptake, it is necessary to question how price and reimbursement policies at a national level may influence market penetration of biosimilars. We gather information from the literature, national authorities' websites and national experts to gain insight on influence of some policy measures on biosimilar uptake in France, the Netherlands, Germany, and Sweden helped. Available information is limited and therefore we could not formally measure how these policies influence biosimilar uptake. A first result from the study is that general policies in a given country encompassing pharmaceutical expenditure or aiming at improving physician prescription behavior may influence biosimilar uptake. For instance, Sweden uptake for biosimilar in the three product groups is amongst the highest in Europe, despite not implementing any specific policy to incentive their uptake. A possible explanation is that in countries (such as Sweden or Germany) where there is a history of large generic uptake, prescribers as well as other actors determining choice of treatment may be more open to adopt biosimilars as they are already more "familiar" with using less expensive alternatives. Of course, this could also reflect active involvement from the authorities as well as from prescriber groups or associations in decisions concerning cost-containment policies and their subsequent enforcement. Germany as well as Sweden have also implemented target budgets which may make physicians more sensitive to use of less expensive alternatives.

Public procurement at the regional or national level (such as in Sweden) could also allow to have more control on uptake for biosimilars. Yet, as for any procurement procedure this will depend on how the tender is defined. If the tender is set at the level of the therapeutic class (e.g. epoetin) it may be possible for biosimilars and reference products to enter the same tender. Concerning impact of tendering on biosimilar uptake, there was

little information provided by national experts. However, tenders at a regional or national level will limit the direct link between individual prescribers or individual hospitals and the supplier/manufacturer. It can be expected that discounts and rebates, or other advantages, may be less determinant on the choice of a product. In tenders at a national/regional level, the main advantage for biosimilar companies might be that discussion on the products characteristics (quality, safety and efficacy) would be set with fewer actors. Yet, this does not undermine the fact that for national authorities it would be the ability of firms (biosimilar companies and reference product companies alike) to provide the most competitive offer that determines their final choice. Whether firms producing biosimilars are more competitive in a national/regional/hospital level of tenders remains an open question.

Fixed price or reimbursement level for specific pharmaceutical categories include molecules where biosimilars are available (e.g. in Germany and the Netherlands via the reference price system and in France all epoetins have the same responsibility tariff). Once again, these policies are not set specifically for biosimilars but in an overall context aiming at reducing pharmaceutical expenditures. As such their overall impact on biosimilar uptake will depend on the acceptability of the policy among prescribers. Finally, because biologicals and biosimilars are therapeutically important, patient's cost-sharing is usually limited. Inclusion of biosimilars in the reference price system, such as in the Netherlands for all biologics with a biosimilars or in Germany for epoetins, could stimulate biosimilar uptake. Yet, uptake in the Netherlands is not particularly high for biosimilars for epoetins or for filgrastim and is null for somatropin biosimilars.

From the four foreign countries analyzed, only Germany has established quotas (for epoetins) to promote biosimilar uptake. Germany high uptake for epoetin's biosimilars may be in part due to these quotas but also to the adoption of biosimilars by the biggest group of dialysis centres in Germany (KfH). Dialysis centres are covered by pricing rules for ambulatory care and as such, prices for epoetins correspond to those fixed within the reference price system (RPS). Policies for epoetins in Germany were implemented hand in hand with information campaigns and prescription guidelines. Physicians in the KfH were informed on biosimilars use in specific indications and on their impact on costs. Thereof, we cannot but credit the combination of measures (instead of a single policy such as quotas) of the Germany's success with biosimilar uptake of epoetin.

8.5. Actors, roles, and positions in the implementation of federal policies aimed at improving biosimilar uptake in Belgium

Qualitative research methods were used to get a thick description of the context in which biosimilars enter the market in Belgium. Based on a web survey and confidential interviews with a large number of physicians, hospital pharmacists and managers we tried to identify reasons leading to the very low market penetration of approved biosimilars (epoetin, filgrastim and somatropin) in Belgium (situation until November 2012). In addition to this, a stakeholder meeting was organised to present results and possible recommendations arisen from this report. As such, crystallization of opposing position was final appraised and describe to have a full view of the current situation.

For the analysis, biosimilar uptake was conceived as a sequential process starting from the production of biosimilars and ending with patient use. At each step of the process, barriers can influence uptake of biosimilars. The biosimilar decision process begins with the introduction of the request for reimbursement to the CTG – CRM. Once a biosimilar is accepted for reimbursement and obtains a list price, biosimilars are available to physicians and patients either in hospital or in community pharmacies. Physicians make the final decision concerning the choice between the reference product and the biosimilar. In this report, biosimilar knowledge was not formally tested and therefore it was not always possible to determine if barriers mentioned during the interviews were related to insufficient or incorrect knowledge (e.g. understanding that requirements for market approval for biosimilars are more stringent than for generics). In some cases, barriers mentioned from well informed interviewees (e.g. not lacking knowledge) may still arise. As we did not perform a scientific appraisal of the biosimilar pathway nor clinical research questions on effectiveness, safety, and interchangeability of currently available biosimilars, we cannot make reject or justify points of view of well-informed actors. As such, results from this report are the first exploratory analysis of perceived barriers.

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

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

8.5.1. Clinical barriers

During the interviews, in particular with physicians, concerns either on safety or on efficacy of the biosimilars or a combination thereof were mentioned as reason not to prescribe them. Their arguments explaining the reluctance towards biosimilars in many cases, but not always, reflect insufficient or incorrect knowledge of the "biosimilar pathway". For instance, only 8.7% of the web survey correctly defined a biosimilar. In other cases, interviewees holding broad knowledge on the biosimilar pathway still claim that more evidence is needed when considering efficacy and safety of current available biosimilars. Even though from a scientific point some physicians acknowledge that all data requirements set by the EMA are met, at this point in time, the field experience showed that these do not fulfil the expectations of many physicians in Belgium. Among physicians filling the survey, 57.2% reported that biosimilars could be used with no or minor safety and efficacy concern when initiating treatment. Yet, in the survey uncertainty about the efficacy and the safety are the most often cited reasons not to prescribe biosimilars for physicians in the web survey (59.2%). Concerning treatment for naïve patients, 82.1% of pharmacists answering the survey were of the opinion that biosimilars could be used without any major safety or efficacy concern for first use. For switching a treatment, 42.9% of all respondents reported that biosimilars could be used with no or minor safety and efficacy concerns. Important differences in opinions concerning switching during treatment were not found between pharmacists and physicians. All points taken into account, i.e. lack of information (i) on market approval requirement and procedures, (ii) on concept of biosimilarity, (iii) on how efficacy and side effects are tested, and (iv) on requirements for pharmacovigilance seems to be key issues that determine physicians' and to a lesser extent hospital pharmacists' reluctance to choose a biosimilar. In line with this, 85.7% of all respondents mentioned to need for more information on efficacy and safety in the survey.

A point that may in part explain the limited knowledge concerning biosimilars is the lack of appropriate information on dissemination channels. On the one hand, hospital pharmacists as well as physicians mentioned that biosimilar/generic companies do not offer this level of support and the lack of such competent contact person is a big problem, especially for biologicals. This was acknowledged by biosimilar companies as the level of marketing activities is linked to expected gains (which are currently limited). During the interviews "traditional companies" acknowledge their future investment in the biosimilar market. However, whether information will be provided at the same level for reference products and for their forthcoming biosimilars remains an open question. Biosimilar companies, in addition to some pharmacists, found that the information given on public websites (i.e. FAGG – FAMHP) was deemed as ambiguous or insufficient.

A medical barrier of routine use by physicians is the reported lack of clinical data supporting safe and effective use in specific indications or situations. Biosimilars tend to prove clinical equivalence versus the reference product in one indication and extrapolate safety and efficacy to the additional indications of the reference product without performing clinical trials, and supported only by the similarity exercise. For generics this is not a discussion item but it is for biosimilars. Guidance from the regulatory authorities (EMA) on the appropriateness of such extrapolations is lacking at the time biosimilar companies embark on the clinical development. Some of the extrapolations of indications for biosimilars are later not accepted by expert physicians in the field (e.g. use of filgrastim for stem cell mobilization in healthy individuals). However, the impact of these extrapolations i.e. group of patients in these extrapolation groups versus tested groups is not known and might not be of direct significant importance for the introduction of biosimilars. However, the reluctance towards the extrapolations damages the credibility/reputation of the biosimilar and makes the use of biosimilars more impractical.

This could mean that for different indications different products need to be stored in hospital settings. Such extrapolations of indications are expected to become even more of an issue with the introduction of biosimilars of monoclonal antibodies. Switching from the originator to a biosimilar molecule is another area of discussion. Also here, the availability of reassuring clinical trial data could greatly reduce the barrier to switch

molecules in a routine clinical use setting. It can be expected that the clinical barriers discussed also limit a larger market penetration of biosimilars abroad, where financial barriers are less an issue. In line with this, seventy two percent of the respondents singled out well-monitored post-marketing efficacy and safety studies as the best intervention to promote biosimilar uptake.

Whether it is based on perception or on scientific arguments –just or unjust-, the fact is that most specialists in Belgium are not satisfied with the current availability of clinical data. As such, concerns on safety, efficacy and pharmacovigilance will be greatly reduced with more data on clinical efficacy and safety in all relevant clinical indications and/or with appropriate dissemination channels on these data. Post-marketing open label studies could fill the gap in many cases. In principle, everybody favours additional data, but the discussion is who should provide this data at which cost and under which budget. 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 be available, lack of appropriate information dissemination channels may limit biosimilar acceptability among different stakeholders. During the interviews, a majority of physicians and hospital pharmacists declared not having had a direct contact or information from firms producing biosimilars. This was further confirmed by biosimilars companies who acknowledged that the level of marketing activities was linked to expected gains. As such, physicians as well as hospital pharmacists pointed out that although manufacturing capacity and quality aspects of the biosimilar producers are not put in question, they lack confidence in services and information provided by biosimilar companies (e.g. information about interaction with other medication). Future biosimilar manufactures include traditional firms. It is an open question whether they will apply the same marketing and service strategies used for their reference products to their forthcoming biosimilars.

Early attempts from biosimilar companies to conduct post-marketing trials in the Belgian context where hampered at several levels including prescriber and patient refusal. Arguments were often financial (for example biosimilar manufacturers were not willing to cover all the cost or provide product for free; some companies even indicate that originator firms put pressure on hospitals not to use the biosimilar in order not to lose their discounts, however this was not confirmed), but also concerned lack of information, doubts about safety and efficacy, refusal to use patients in trials if there was no innovation involved. However, certain manufacturers indicate that for the next generation of biosimilars clinical trials are running also in Belgium and Belgian data will be included.

8.5.2. Lack of financial incentives and other services for the hospital and physicians

The market for pharmaceuticals in hospital settings has several entrance barriers: physician prescription habits, inherent complex managing settings (safety, storage) and current financing structure. The latter are very specific to the Belgian context and efforts to change the system have not been successful so far. How much this latter entails competition is difficult to measure with our data. However, it is certainly a significant part of the discussion on the limited entrance of biosimilars in Belgium. Once again, we should avoid guessing that this is the only and main reason. The qualitative research methods used in this project do not aim at quantifying this phenomenon but more at setting an open discussion on the implications of this system. Off course, negotiations based on discounts and rebates create a problem of asymmetric information. In addition to this, research and continued education services offered by the originator companies are currently part of the negotiation package, mainly in larger hospitals. In the current system, pharmaceutical prices are fixed by the government. While all players have perfect information on the list price, the discounted price paid by the hospital pharmacy is unknown and fixed during direct negotiations. This information is shared neither among hospitals nor with the authorities. From face-to-face interviews, some elements determining the discount level were mentioned: pharmaceutical basket purchased from one firm and volume used for a given pharmaceutical and presence of competitors (me-too alternatives). Also steering prescription habits of opinion leaders in larger hospitals may justify large discounts as part of a marketing effort.

Based on the interviews, hospital pharmacies in Belgium obtain on average 10 to 20% discount on the pharmaceutical products, including volume discounts. The reported discounts can amount to 75% for reference product of the currently marketed biosimilars, making the biosimilars lower list price (between 20%-34%) unattractive from a hospital finance point of view. Biosimilars could also compete for market shares by

granting large discounts. Yet, this is currently not done. In contrast to the situation in France where the discount is to be split 50/50 between the health insurance and the hospital, in Belgium the hospital fully benefits from the discount as the list price remains the basis for reimbursement by RIZIV – INAMI. Larger hospitals argue that the prospective budget does not fully cover medication costs for severe pathology patients and that these discounts compensate for this loss. Moreover, interviewees also argued that benefits at the level of the pharmacy were reinvested within the hospital either to cover underfinanced expenditures within the pharmacy (e.g. cost of preparation of expensive medicines, continuing education of hospital pharmacists) or used to finance other services within the hospital. In smaller hospitals with few severe pathology patients the prospective budget may better cover the costs, but discounts in such hospitals also tend to be lower.

In addition to the discounts, hospitals may receive funding for personnel (pharmacists, study nurses in oncology, material) or educational services such as unrestricted educational grants for chairs, conference organization or participation. 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.

Hospital pharmacists as well as physicians also reported that biosimilar companies tend to visit potential prescribers in the hospital less frequently and do not provide all the services physicians receive from reference product companies, including in some cases medical information service and compassionate use programs. Biosimilars are more complex than generics, therefore more information and services for a product including similarities and differences with the reference product may need to be addressed. For instance, in some cases device differences may need to be explained more fully. Although not all marketing approaches or services have (measurable) added values, some tools, which can be product specific, are relevant for the wellbeing of both physician/pharmacist and/or patients. Physician quoted that an easy reachable, competent person who can provide accurate product information relevant to their patient (for example data on pharmaceutical-pharmaceutical interaction) is a prerequisite for complex medicines such as biosimilars. These factors have important financial consequences for physicians, hospitals and patients and certainly determine current “actors” loyalty towards reference products.

During the interviews all actors acknowledge the role for biosimilars as a cost-containment tool. However, views were opposed when considering which mechanism lead to reduce pharmaceutical expenses. Two different views were expressed: 1) biosimilars only play a role in reducing the price of the reference product or 2) biosimilars should gain market shares through competition and therefore lead to price competition. While all actors agree that currently in Belgium only the first case leads to some savings, the second case leads to more debate among different stakeholders. Firms currently producing biosimilars argue in favour of more policies to counter existing barriers to enter the market (i.e. low-prescription quotas). Other actors on the contrary argued that setting more policies without letting market forces play leads to unfair competition in favour of biosimilars companies. Yet, at least for the inpatient setting, all stakeholders agreed on one point: current financing of “expensive pharmaceuticals” in hospital settings interferes with an open and transparent competition. According to pharmaceutical executives, the extent of discounts and other incentives to hospitals is larger in Belgium compared with the situation abroad. This transfer of RIZIV – INAMI money through pharmaceuticals may thus account for about 2 to 5% of the overall hospital income. The situation is not transparent and not wanted by pharmaceutical companies and other involved parties. Yet, the discounts are generally regarded as an acquired right and hospitals claim to depend on these discounts for their financing.

As a consequence, they argue that taking away this budget from the hospitals will need to be compensated, otherwise –they argue- most hospitals will lead losses. Also government funding for the continuing education of hospital physicians and pharmacists will be insufficient when discounts are being taken away.

8.5.3. Policy analysis based on interviews: why recent biosimilar policies do not increase their uptake

We cannot rule out that biosimilar’s uptake has not been influenced by measures introduced by the Minister because they were only recently enforced. The analysis performed in this report gathers current views of policies which should formally be evaluated in the future. During the

interviews it was clearly pointed out that these measures may fail to increase market shares for biosimilars in Belgium.

Introducing epoetins in the prospective budget and in the category Fa seems successful as a means to set short-term cost-savings for the third-party payer. However savings arise from reducing the reimbursement basis of on-patent epoetins and not from biosimilar uptake. These policies seem to fail to provide incentives to promote biosimilar use in hospital settings. Moreover, allowing hospitals to receive higher reimbursement for biosimilars (not based on the list price but the flat rate for the category F) may not lead to increase their uptake. Because biosimilars and the reference product eprex will be reimbursed at the same level, biosimilars will not lead to savings for the third-party payer.. In addition, discounts received at the hospital pharmacy for the reference product may outpace gains from the increased reimbursement for biosimilars.

The category F seems a step closer to setting a “therapeutic reference pricing”. A therapeutic reference price system can be considered as an option. However an appropriate price reduction needs to be discussed. Whether the choice is kept as today as “per case basis” or as a fixed mandatory reduction is an important issue. Given the differences between current and future biosimilars it is unlikely that a single policy model can be set. In addition, looking at the experience in the Netherlands it seems that reference pricing per se does not guarantee market shares for biosimilars. A “therapeutic reference system” must be set with appropriate guidelines on use of different pharmaceuticals in a class (as was done in Germany for epoetins) and issues surrounding interchangeability should be openly communicate to health care professionals and patients alike. This information must be provided by national authorities.

Introducing somatropin in the hospital prospective budget will have a limited impact on their uptake as these pharmaceuticals are mostly sold by community pharmacies. Limited savings can arise from quotas in ambulatory care for somatropin. However, higher biosimilar uptake will be linked to the number of new patients. Indeed, for chronic illnesses, physicians will be reluctant to switch patients during treatment given differences in dosage and devices. In addition, including only biosimilars and not the reference product in low-cost prescription will not trigger price competition which in return will lead to fewer savings. Yet, this protects patients using the reference product from paying the reference supplement.

Other measures might also have an impact on biosimilar uptake. The forthcoming public tenders may lead to more transparency in prices. 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.

Finally, prescription quotas at the level of the hospital may open the market for biosimilars. Yet, quotas do not trigger competition per se and could enhance the passive marketing strategy of companies producing biosimilars. Quotas for Belgium in the inpatient sector need to be design at the level of the hospital (or larger entity if multiple hospitals make a hospital group tender). This implies taking into account differences between hospitals (e.g. dialysis centre, mostly oncology treatment) and also the size of the population treated (or the most common indications). Effective quotas need to be accompanied by monitoring and appropriate financial incentives (or penalties). With the current financing of pharmaceuticals in hospitals, it may be possible that financial incentives (or penalties) can be outpaced by gains given through discounts and rebates. In addition, quotas may add more of complexity to hospital financing and the selection of pharmaceuticals in the public tendering procedures (e.g. should the quotas be part of the tender?). As it was done in Germany, if quotas are chosen to stimulate biosimilar uptake, a key success factor would be to actively involve all partners in the discussion and fine tuning of the policy.

For example, when introducing quota, the government implicitly states that substitution in some way (presumably primary substitution) is safe, therefore a clear communication plan explaining the rational is needed. Involvement of stakeholders (pharmacist and specialist) preceding such measures would engage the community, could create ambassadors for the cause and increase adaptation.

In addition, reluctance among the 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. Information spreading certainly should come from the authorities. However, firms producing

biosimilars must create reputation bonds with physicians and hospital pharmacist by making information on their product more accessible.

These measures tackle only financial barriers relating to current financing system of the hospital and do not address the lack of appropriate information (dissemination of current data or collection of new data), nor concerns for research funds or lack of services (delivery). The government or medical associations needs to take decisions, possibly on a product-to-product basis, whether to stand by the decisions of the EMA considering the extrapolation of indications and as such follow way by communicating and explaining these decision appropriately and in an unbiased way (or EMA, as they are best placed) need to take stand on. Moreover, even tough the importance of discounts and their impact was discussed with respect to product classes where biosimilars are available; discounts and other advantages cover purchasing of medical products including all pharmaceuticals and probably medical devices. The forthcoming mandatory public tenders in hospital settings may shed some lights on this issue, however transparency on cost still needs to be maintained in situation when tenders will not apply (e.g. under the tender threshold). Policy measures forcing use of less expensive alternatives for the third-party payer may provide a short-term solution to the discount relating financing barrier in hospital setting. However, these measures will only build a weak bridge over a problem that lays down in deep and turbulent waters.

8.6. 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 biosimilars could improve general acceptability of biosimilars.

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.

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 also add innovation in how marketing strategies will target health professionals. Whether innovator companies will use same strategies for innovator products and for biosimilars remains an open question. Yet, we cannot but hypothesize that current 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.

APPENDIX

APPENDIX 1. ADDITIONAL INFORMATION FROM A REGULATORY PERSPECTIVE

Table 22 – EMEA Guidelines for biosimilars

Biosimilar specific guidelines	File	Published date	Effective date	
Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues	EMEA/CHMP/BMWP/42832/2005	February 2006	June 2006	Concept paper on revision of the guidelines, consultation finished in December 2011
Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues	EMEA/CHMP/BWP/49348/2005	February 2006	June 2006	Draft of Revision of the guidelines revised for consultation may 2012
Similar biological medicinal products	CHMP/437/04	September 2005	October 2005	Concept paper on revision of the guidelines, consultation finished Feb 2012
Product-specific biosimilar guidelines	File	Published date	Effective date	
Similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues	EMA/CHMP/BMWP/403543/2010	June 2012	1 December 2012	
Similar biological medicinal products containing recombinant erythropoietins	EMEA/CHMP/BMWP/301636/08	April 2010	30 September 2010	
Similar biological medicinal products containing low-molecular-weight heparins	EMEA/CHMP/BMWP/118264/2007	April 2009	October 2009	
Non-clinical and clinical development of similar medicinal products containing recombinant interferon alfa	EMEA/CHMP/BMWP/102046/2006	June 2009	April 2009	
Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and	EMEA/CHMP/BMWP/31329/2005	February 2006	June 2006	

Biosimilar specific guidelines	File	Published date	Effective date	
clinical Issues - Guidance on biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor				
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	EMEA/CHMP/BMWP/94528/2005	February 2006	June 2006	
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	EMEA/CHMP/BMWP/32775/2005	February 2006	June 2006	
Other guidelines relevant for biosimilars	File	Published date	Effective date	
Immunogenicity assessment of monoclonal antibodies intended for in- vivo clinical use	EMA/CHMP/BMWP/86289/2010	June 2012	1 December 2012	
Comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical Issues	EMEA/CHMP/BMWP/101695/2006	July 2007	November 2007	
Immunogenicity assessment of biotechnology-derived therapeutic proteins	EMEA/CHMP/BMWP/14327/2006	January 2008	April 2008	
Comparability of medicinal products containing biotechnology-derived proteins as active substance - Quality issues	CPMP/ICH/5721/03	December 2003	December 2003	Superseded by ICH Q5E CPMP/ICH/5721/03
Comparability of medicinal products containing biotechnology-derived proteins as pharmaceutical substance: non-clinical and clinical issues	EMEA/CPMP/3097/02	December 2003	June 2004	Superseded by CHMP/BMWP/101695/06

Source: EMA http://www.ema.europa.eu/ema/

APPENDIX 2. REIMBURSEMENT OF PHARMACEUTICALS

Appendix 2.1. Remuneration of wholesalers and pharmacists

A new system of remuneration for pharmacists came into force in April 2010. The remuneration is now composed of:

- an economic margin based on the ex-factory price (see Table 24). This was calculated so that the share of the economic margin amounts to approximately 15% of the total remuneration. This economic margin is included in the retail price of the pharmaceutical;
- a basic fee of € 4.05 per reimbursed product (per packaging), which is expected to make up 75% of the pharmacists' total remuneration. This basic fee is also included in the retail price of the pharmaceutical;
- Specific flat rate (paid by the sickness funds and not included in the retail price);
- an annual lump sum of € 500 per pharmacy to encourage the pharmacist to give detailed information to patients under chronic treatment when giving them their first prescription (or after a delay of six months between prescriptions) of antibiotics, antiplatelet, anti-inflammatory pharmaceuticals, inhaled corticosteroids, or oral antidiabetics;
- a specific flat rate of € 1.24 for the delivery of a pharmaceutical included in the reference price system and prescribed under the INN of the active ingredient;
- a specific flat rate of € 1.24 for the delivery of a pharmaceutical in the chapter IV.

To ensure budget neutrality of the reform, the wholesaler's margin was also modified (see Table 23). The retail price of the pharmaceutical is therefore calculated as follow: (Ex-factory price + wholesaler margin + pharmacist margin) increased by value added taxes of 6%.

Table 23 – Community pharmacy and wholesaler margins

Price $_{ex\text{-}factory}$	Margin
Pharmacist margin	
≤ € 60	6.04% of Price $_{ex\text{-}factory}$
> € 60	€ 3.62 + 2% of (Price $_{ex\text{-}factory}$ - € 60)
Whole saler margin	
< € 2.33	€ 0.35
€ 2.33 - € 15.33	15% of Price $_{ex\text{-}factory}$
> € 15.33	€ 2.30 + 0.9% of (Price $_{ex\text{-}factory}$ - € 15.33)

Appendix 2.2. Reimbursement basis and cost-sharing for pharmaceuticals delivered in community pharmacies

Because of the new remuneration of the pharmacists, patient participation in the cost of pharmaceuticals is now equal to a percentage of the reimbursement basis at the ex-factory level (before the inclusion of pharmacist and wholesaler margins and value added taxes) increased by a fixed amount. Patient coinsurance varies according to the pharmaceutical category. Moreover, patient coinsurance is capped and depends on eligibility to preferential reimbursement.

The reimbursement basis usually corresponds to the retail price of the pharmaceutical and in the same way, reimbursement basis at the ex-factory level usually equals to the ex-factory price. Exception mainly concerns reference medicinal products included in the reference price system, for which the retail price may be higher than the reimbursement basis. In this cases, the "reference supplement" (the difference between the retail price and the basis for reimbursement) is charged to the patient. [74] Since April 2010, a legal upper limit on this reference supplement is applied and the maximum supplement is equal to the reimbursement basis increased by a "security margin" of 25% (with a maximum increase of € 10.80).

Table 24 – Cost-sharing mechanisms in community pharmacies

	A & Fa – vital pharma-ceuticals	B & Fb – therapeutically significant pharmaceuticals for non-life-threatening diseases		B & Fb large package size*		C–therapeutically less significant drugs for systematic treatment		Cs–pharmaceuticals used in certain chronic illnesses		Cx–contraceptives and antispasmodics	
		RBex-fact < € 14.38	RBex-fact > € 14.38	RBex-fact < € 14.38	RBex-fact > € 14.38	RBex-fact < € 14.38	RBex-fact > € 14.38	RBex-fact < € 14.38	RBex-fact > € 14.38	RBex-fact < € 14.38	RBex-fact > € 14.38
RIZIV – INAMI	100% RB	RB – Patient co-insurance	RB – Patient co-insurance	RB – Patient co-insurance	RB – Patient co-insurance	RB – Patient co-insurance	RB – Patient co-insurance	RB – Patient co-insurance	RB – Patient co-insurance	RB – Patient co-insurance	RB – Patient co-insurance

Patient without PR											
Coinsurance	0%	44.2% RBex-fact	27% RBex-fact + € 2.50	44.20% RBex-fact	27% RBex-fact + € 2.50	88.39% RBex-fact	54% RBex-fact + € 5.00	106.07% RBex-fact	65% RBex-fact + € 6.0 0	141.43% RBex-fact	86% RBex-fact + € 8.00
Limited to		11.30		€ 9.30		€ 9.30		Not limited		Not limited	
Patient with PR											
Coinsurance	0%	26.52% * RBex-fact	16% * RBex-fact + € 1.50	26.52% * RBex-fact	16% RBex-fact + € 1.50	88.39% RBex-fact	54% RBex-fact + € 5.00	106.07% RBex-fact	65% RBex-fact + € 6.00	141.43% RBex-fact	86% RBex-fact + € 8.00
Limited to		€ 7.50		€ 14.10		€ 14.10		Not limited		Not limited	

*RB = reimbursement basis (usually equal to the retail price); $RB_{ex\text{-}fact}$ = reimbursement basis at the ex-factory level (usually equal to the ex-factory price); PR = preferential reimbursement. *Large package size corresponds to at least 60 units*

Appendix 2.3. Reimbursement basis and cost-sharing for pharmaceuticals dispensed by the hospital pharmacy

For pharmaceuticals dispensed by the hospital pharmacy, invoicing is done according to the number of units delivered. Unit list prices and reimbursement basis are available on the RIZIV – INAMI website (http://www.inami.fgov.be/inami_prd/ssp/cns2/pages/SpecialityCns.asp) . The reimbursement basis usually corresponds to pharmaceutical unit list price.

Exceptions mainly concern reference medicinal products included in the reference price system and pharmaceuticals of category F. In these cases, the difference between the reimbursement basis and the list price is charged to the hospital. Cost sharing mechanisms differ for ambulatory and for hospitalised patients. Cost-sharing mechanisms for ambulatory patients are summarized in Table 25.

Table 25 – Cost-sharing mechanisms for outpatient pharmaceuticals dispensed by the hospital pharmacy

	A & Fa viral pharmaceuticals	B & Fb – therapeutically significant pharmaceuticals for non-life-threatening diseases	B & Fb large package size*	C–therapeutically less significant pharmaceuticals for systematic treatment	Cs–pharmaceuticals used in certain chronic illnesses	Cx–contraceptives and antispasmodics
Patient no PR						
Co-insurance	0% of the RB	25% of the RB	25% of the RB	50% of the RB	60% of the RB	80% of the RB
Limited to	/	€ 11.30	€ 14.10	Not limited	Not limited	Not limited
Patient with PR						
Co-insurance	0% of the RB	15% of the RB	25% of the RB	50% of the RB	60% of the RB	80% of the RB
Limited to	/	€ 7.50	€ 9.30	Not limited	Not limited	Not limited

** Large package size corresponds to at least 60 units. RB = Reimbursement basis. PR = preferential reimbursement.*

For inpatient pharmaceuticals, cost-sharing mechanisms as well as total reimbursement (third-party payer and patients) received by hospitals are summarized in Table 26. Hospitalized patients pay a fixed sum € 0.62 per day independently of their pharmaceutical consumption. Invoicing to third payer depends on whether pharmaceuticals are included in the hospital prospective budget.

For pharmaceuticals integrated in the hospital prospective budget, hospital invoicing to the third-party payer (sickness funds) is set as follows:

- the hospital retrospectively charges 25% of the reimbursement basis of each delivered pharmaceutical and
- the hospital receives prospective lump sum allocations per inpatient admission.

For pharmaceuticals excluded of the prospective budget, the hospital invoicing is set according to the pharmaceutical category (using the full reimbursement basis).

Table 26 – Cost-sharing mechanisms for inpatient pharmaceuticals

Included in the prospective budget for pharmaceuticals	Pharmaceutical category	Sickness Fund	Patient
Yes	Category A & Fa, B & Fb, C, Cs, Cx	A flat rate per admission[1] + 25% of the RB	€ 0.62 per day*
No	Category A & Fa	100% of the RB	
	Category B & Fb	100% of the RB - € 0.37 per portion**	
	Category C	50% of the RB	
	Category Cs	40% of the RB	
	Category Cx	20% of the RB	

*Notes: [1] http://www.inami.fgov.be/care/fr/hospitals/specific-information/forfaitarisation/index.htm. *€ 0.80 per day in psychiatric hospitals (include also not reimbursed pharmaceuticals of category D); ** defined either by the number of units of the largest individual package of this prescribed specialty or, in the absence of such a reference, by a fixed amount defined in the appendix of the Royal Decree of 21 December 2001 determining the procedures, time and conditions for the intervention of the compulsory health insurance in the cost of pharmaceutical specialties. When the patient is transferred to another service in the hospital, it is necessary to consider a new portion is started.*

APPENDIX 3. PUBLIC PROCUREMENT

Appendix 3.1. Different procedures for public procurement

The rules for applying the standard procurement procedures are divided between those for services (e.g., technical assistance, studies, provision of know-how and training), supplies (i.e., equipment and materials) and works (i.e. infrastructure and other engineering works). The purchase of pharmaceuticals can be considered as supplies. Sometimes the contract will be a mixed contract (e.g. for the supply and supportive services). Where it is, a contracting authority must determine, in accordance with the rules, the predominant element of the contract and, therefore, which set of rules will apply. This is important to get right as the rules vary slightly depending on the type of contract (e.g. lower financial thresholds apply to services and supplies contracts than to works contracts). Where contracts are subdivided in lots, the value of each lot shall be taken into account when calculating the overall threshold. The estimated value of the contract (net of VAT) equals or exceeds the relevant financial threshold. The rules expressly prohibit deliberately splitting contracts to bring them below the thresholds. The next section describes the generalities of the most common procedures.[tt]

Open versus restricted procedure

Under the **open procedure** all interested parties can submit a tender in response to the notice in the Official Journal (S-series) of the European Union (or the "Bulletin for Tendering"[uu] for Belgium). Under the open procedure, any natural or legal person wishing to tender receives upon request the tender dossier , in accordance with the procedures laid down in the procurement notice. When the tenders received are examined, the contract is awarded by conducting the selection procedure (i.e., verification of the eligibility and of the financial, economic, technical and professional capacity of tenderers) and the procurement procedure (i.e., comparison of tenders). No negotiation is allowed.

Under the **restricted procedure** all interested parties may express an interest in tendering for the contract but only those meeting the contracting authority's selection criteria will actually be invited to do so. No negotiation with the tenderers is permitted but there are no restrictions under the Regulations as to when the procedure can be used.

Tender

The contract is awarded to the party with the lowest price (no other element of the tender may be taken into account). The procedure can be open or restricted.

Offer

The contract is awarded to the most economically advantageous tender: Factors (award criteria) other than or in addition to price, like quality, technical merit, support, delivery conditions, running costs, etc. can be taken into account. If this procedure is being used the contract award criteria and any sub-criteria must be set out either in the OJEU notice or the tender documents, they need to be related to the subject for tender and the weighting of each criterion (and sub-criterion, if weighted) must also normally be given, either as an exact number or as a meaningful range (e.g. "price: 30%-40%".). The procedure can be open or restricted.

Negotiation procedure (with/without advert)

There are two types of negotiated procedures. Under the negotiated procedure **without prior** advert, the contracting authority is not required to issue a notice and may negotiate directly with the supplier of its choice. Under the negotiated procedure **with prior advert**, however, an OJEU notice (or Belgian Bulletin der Aanbestedingen) must be published. All interested parties may express an interest in tendering for the contract but only those meeting the contracting authority's selection criteria will actually be invited to do so. Tenderers are invited to negotiate the terms of the advertised contract with the contracting authority. The Regulations do not set out any rules to govern the conduct of negotiations, which means that the contracting authority can, within certain parameters, establish its own procedures for the negotiation and tender stage. This procedure can only be used in the very limited circumstances described in the Regulations.

[tt] For an extensive and detailed overview, see http://ec.europa.eu/europeaid/prag/document.do?chapterId=2.4.6.&id=141

[uu] In French Bulletin des Adjudications and in Dutch Bulletin der Aanbestedingen (https://enot.publicprocurement.be)

Competitive dialogue

This procedure allows the input of those participating in the tender process. All interested parties may express an interest in tendering for the contract but only those meeting the contracting authority's selection criteria will actually be invited to do so.

During the dialogue tenderers are able individually to discuss all aspects of the contract with the contracting authority. Solutions are worked up with each tenderer on the basis of the ideas and proposals put forward by that tenderer. There can be no “cherry-picking” by the authority of the best bits of various individual solutions, except with the consent of those concerned. Once the dialogue has generated potential solutions to the authority's requirements, the remaining tenderers are invited to submit a final tender based on their individual solutions. The best tender can then be selected, but there is very limited room for any further changes to be made once submitted. This procedure can only be used in the limited circumstances described in the Regulations.

Framework agreements

A framework contract is an agreement between one or more contracting authorities and one or more economic operators the purpose of which is to establish the terms governing specific contracts which may be awarded during a given period, particularly as regards the duration, subject, price, implementation rules and the quantities envisaged.

The duration of such contracts may not exceed four years, save in exceptional cases justified in particular by the subject of the framework contract. Contracting Authorities may not make undue use of framework contracts or use them in such a way that the purpose or effect is to prevent, restrict or distort competition.

Dynamic purchasing systems

In order to set up a dynamic purchasing system, contracting authorities shall follow the rules of the open procedure in all its phases up to the award of the contracts to be concluded under this system. All the tenderers satisfying the selection criteria and having submitted an indicative tender which complies with the specification and any possible additional documents shall be admitted to the system; indicative tenders may be improved at any time provided that they continue to comply with the specification. With a view to setting up the system and to the award of contracts under that system, contracting authorities shall use solely electronic means. Contracting authorities shall give any economic operator, throughout the entire period of the dynamic purchasing system, the possibility of submitting an indicative tender and of being admitted to the system. A dynamic purchasing system may not last for more than four years, except in duly justified exceptional cases

Electronic auction

An “electronic auction” is a repetitive process involving an electronic device for the presentation of new prices, revised downwards, and/or new values concerning certain elements of tenders, which occurs after an initial full evaluation of the tenders, enabling them to be ranked using automatic evaluation methods.

Appendix 3.2. Selection criteria and award criteria

Key issues determining participants as well as the content of tenders include selection criteria and as well as award criteria. Selection criteria are used to pre-select appropriate candidates. A contracting authority may automatically exclude a supplier from the tender process, without any assessment of their qualifications having to take place, where certain grounds concerning the supplier's personal position are met (e.g. bankruptcy or professional misconduct). In addition, it is now mandatory to exclude suppliers convicted of involvement in organized crime, corruption, fraud or money laundering. Suppliers can also be assessed and excluded on the basis of their economic and financial capacity (e.g. annual turnover for past three years) and technical capacity (e.g. experience of similar contracts in the past five years).

A tender needs to include clearly defined award criteria on which the tender will be granted. In addition to price, quality, technical merit, support, delivery conditions, running costs, etc. can be taken into account. Award criteria must be known a priory by all tenderers and weight attributed to each criterion must be clearly defined (e.g. 40% on price and 30% on support services).

Appendix 3.3. Publication in Belgium or in Europe

Estimate of the amount of assignment

An estimate of the total amount of the assignment serves amongst others to determine the procedure that should be followed (Belgian or European). Different procedures apply according to certain financial thresholds (cfr. infra). The estimate of the assignment's amount needs to be calculated for the entire period of the contract. If the assignment concerns an indefinite period, the estimate needs to be performed for a 4 year period. Moreover the total value of the assignment needs to be taken into account. It can be questioned whether for pharmaceuticals this implies that not only the invoice price but also the discounts and rebates should be taken into account.

Thresholds

The European procurement procedures apply only to contracts whose value (VAT excluded) exceeds certain thresholds. Other contracts, whose value is considered to be minimal, are not required to be awarded under the Directives' procedures, although the basic rules of the European Treaties, such as non-discrimination, still apply (cfr. supra).

On 30 November 2011, the new European thresholds for public procurement procedures during the period 2012-2013 were announced. [143] These thresholds vary depending on the type of contract (works, supplies, services), as well as the awarding authority. Although Belgian procurement legislation still needs to be modified accordingly, these thresholds are already fully applicable on all procedures that have started as of 1 January 2012. The threshold for supplies for decentralized authorities (like pharmaceuticals in hospital settings) is € 200 000 for 2012-2013. Until today, the other Belgian thresholds remain unchanged. Some of these thresholds will change once the Royal Decree of 15 July 2011 enters into force; this date remains yet to be determined. [144]

Table 27 – Thresholds for procedures for the purchase of pharmaceuticals

Procedures	RD 8 January 1996	RD 15 July 2011 (not yet entered into force)
No procedure	≤5 500	≤8 500
Call for offer to at least 3 supplies	5 500<X≤67 000	8 500<X≤85 000
Publication in Belgium	67 000<X≤193 000	85 000<X≤200 000
Publication in Europe (and in Belgium)	>193 000	>200 000

RD = royal decree

Publication of tenders

In Belgium tenders are published in the Bulletin for Tendering [vv]. On the European level, tenders are published in a Supplement of the Official Journal, the Tenders Electronic Daily (http://ted.europa.eu/TED/main/HomePage.do). Details on the content of the tenders and the timing are included in legislation.

Publication of awarded contracts

Public information

Contracting authorities publish certain information on contracts awarded (or framework agreements concluded) within 48 days of the award in the OJEU. Particulars, including the type of contract, the procedure and award criteria used, the number of tenders received, the name of the successful tenderer, the value of the contract or the range of tender prices, justification for the negotiated procedure, if used, are published. The

[vv] In French Bulletin des Adjudications and in Dutch Bulletin der Aanbestedingen (https://enot.publicprocurement.be)

necessary information can be submitted online to the OJEU on the standard “Contract Award Notice”

(http://simap.europa.eu/docs/simap/pdf_jol/en/sf_003_en.pdf). The notification of the awarded contract in Belgium are published in the Bulletin der Aanbestedingen.

Information for candidates and tenderers

Candidates and tenderers must be informed of decisions for awarding the contract, including the grounds for any decision not to conclude.

On request from the party concerned, the contracting authority shall as quickly as possible inform:

- any unsuccessful candidate of the reasons for the rejection of his application,
- any unsuccessful tenderer of the reasons for the rejection of his tender, including, the reasons for its decision of non-equivalence or its decision that the works, supplies or services do not meet the performance or functional requirements,
- any tenderer who has made an admissible tender of the characteristics and relative advantages of the tender selected as well as the name of the successful tenderer or the parties to the framework agreement.

The time taken may in no circumstances exceed 15 days from receipt of the written request.

However, contracting authorities may decide to withhold certain information, regarding the contract award, the conclusion of framework agreements or admittance to a dynamic purchasing system. Information withholding is possible where the release of such information would impede law enforcement, be contrary to the public interest, prejudice the legitimate commercial interests of economic operators, or might prejudice fair competition between them.

For more information on this topic on the Belgian level, see www.publicprocurement.be.

Information to the EU Commission

The contracting authorities are also required to prepare a written report containing:

(a) the name and address of the contracting authority, the subject-matter and value of the contract, framework agreement or dynamic purchasing system;

(b) the names of the successful candidates or tenderers and the reasons for their selection;

(c) the names of the candidates or tenderers rejected and the reasons for their rejection;

(d) the reasons for the rejection of tenders found to be abnormally low;

(e) the name of the successful tenderer and the reasons why his tender was selected and, if known, the share of the contract or framework agreement which the successful tenderer intends to subcontract to third parties;

(f) for negotiated procedures, the circumstances which justify the use of these procedures;

(g) as far as the competitive dialogue is concerned, the circumstances justifying the use of this procedure;

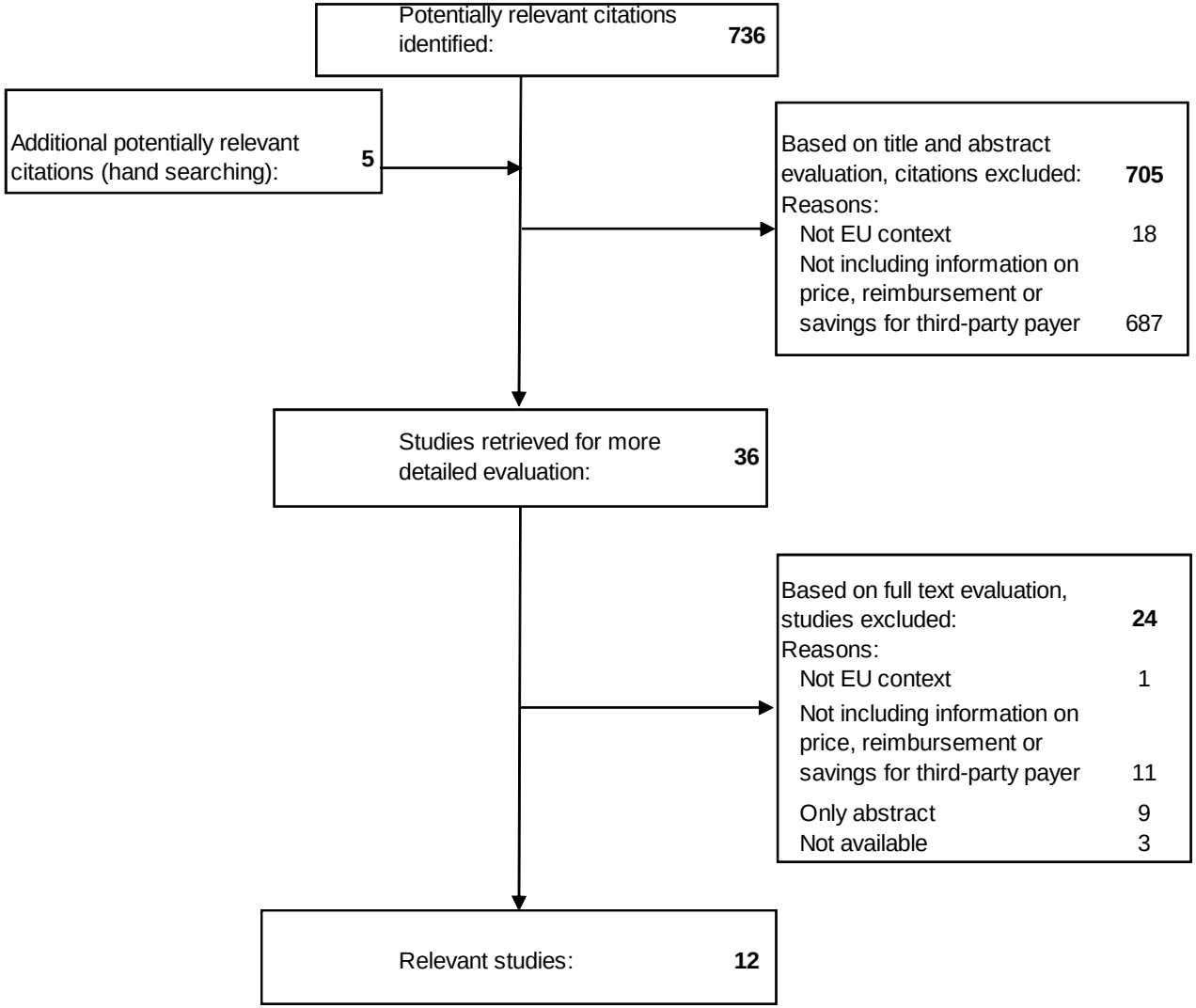
(h) if necessary, the reasons why the contracting authority has decided not to award a contract or framework agreement or to establish a dynamic purchasing system. (Art. 43 of the public sector procurement Directive 2004/18/EC). This report, or he main features of it, may be requested by the EU Commission at any time.

APPENDIX 4. INFORMATION ON THE STRUCTUED LITERATURE REVIEW

Table 28 – Search strategy

Database (name + access ; e.g. Medline OVID)	Date covered	Search Strategy (results)
Embase	1968 up to 8 November 2012	#1. biosimilar* (607)
Ovid MEDLINE	1946 up to 8 November 2012	#1. biosimilar.mp. (330) #2. biosimilar (Including Related Terms) (334)
Pubmed	1946 up to 8 November 2012	#1. biosimilar* (427) #2. biosimilar pharmaceuticals (67) #1 or #2 (427)
Cochrane Database of systematic reviews - Cochrane Library	2000 up to 8 November 2012	#1. biosimilar (16)
Driver	2000 up to 8 November 2012	#1. biosimilar (24)
OAIster	2000 up to 8 November 2012	#1. biosimilar* (48)
Econlit	2000 up to 8 November 2012	#1. biosimilar* (1)

Figure 4 – Flow chart for studies used in the structured literature review



APPENDIX 5. INTERNATIONAL COMPARISON

Appendix 5.1. References per country

Country	References
Belgium	(See chapter 4)
France	Literature and official websites : • Code de la santé publique 1953 [145] • Améli 2012 [146] • ANSM 2011 [147] • Chevreul 2010 [148] • Cubaynes 2011 [149] • Dylst 2012 [136] • GPEM/SL 2002 [150] • Guéniot 2012 [151] • Kavanos 2007 [152] • Le Polain 2010 [65] • Lopes 2009 [153] • MEDISPAR 2012 [154] • Ministère des affaires sociales et de la santé 2009 [155] • Safon 2012 [156] • Vrijens 2010 [74]
The Netherlands **Contact person: Pr. Arnold Vulto** **Institution: Erasmus Medical Centre, Rotterdam**	• CVZ 2011 [157] • CVZ 2012 [158] • Dylst 2012 [136] • Kanavos 2009 [159] • Le Polain 2010 [65] • Nederlandse Vereniging voor Hematologie [160]

Country	References
	• NVZ 2012 [161] • Schaffer 2010 [162] • Storms 2009 [163] • Vrijens 2010 [74] • Zuidberg 2010 [164]
Germany **Contact person: Irene Kraemer** **Institution: Universitätsmedizin der Johannes Gutenberg-Universität Mainz** **Contact person: Claudia Barth Institution: KfH Kuratorium für Dialyse und Nierentransplantation** **Contact person: Roland Windt Institution: Universität Bremen**	• DIMDI 2012 [165] • Dylst 2012 [136] • GKV-spitzenverband 2012 [166] • Hoffmann 2009 [167] • InEK 2012 [168] • Kanavos 2009 [159] • Van de Sande 2010 [66] • Vrijens 2010 [74] • Zuidberg 2010 [164]
Sweden **Contact person: Gustaf Befrits** **Institution: The Dental and Pharmaceutical Benefits Agency, TLV**	• Anell 2005 [169] • Anell 2012 [169] • Chu 2012 [170] • Dylst 2012 [136] • Läkemedelsverket (Medical Products Agency) 2011 [171] • Pharmaceuticals benefit board (LFN) 2007 [172] • OECD 2009 [173] • Sierakowiak 2009 [174] • Svensson 2009 [175] • Vrijens 2010 [74] • Zuidberg 2010 [164]

APPENDIX 6. FACE-TO-FACE INTERVIEWS

Appendix 6.1. Information on methodology used for the semi-structured questionnaires

Table 29 – Sample of face-to-face interviews among health care providers

Health care provider	French community	Flemish community	Sampling channel	
			Convenience	Snowball
University Hospital				
Hospital pharmacist	1	3	2	2
Direction or head of purchase		2	0	2
General hospital				
Hospital pharmacist	2		0	2
Direction or head of purchase	1	1	2	0
Total Hospital	4	6	4	6
Clinicians				
Haematologists	1	1	1	1
Oncologists	1	2	2	1
Nephrologists		1		1
Paediatrician - endocrinologists	1		0	1
Total Clinicians	3	4	3	4
Total number of interviews	7	10	7	10

[1] *First number corresponds to the first channel of recruitment (known experts by KCE workers) and the second number to recruitm ent via the snowball method*

Table 30 – Main issues covered during the face-to face interviews

	Pharmaceutical companies	Belgian institutions	Hospital directors	Hospital pharmacists	Physicians
Functioning and financing of the hospital pharmacy					
Functioning of the hospital pharmacy				X (Pharmacist role)	X (Physicians role)
Decision process in the MFC–CMP				X (Pharmacist role)	X (Physicians role)
Level and type of fringe benefit for pharmaceuticals in hospital settings*	X	X	X	X	X
Alternative modes for hospital financing	X	X	X	X	X
Possible impact of public tender on prices, fringe benefits and work load	X	X	X	X	X
Prior experience with public tenders					
Biosimilars					
Point of view on the need for biosimilars	X	X		X	X
Discussion on quality, efficacy and safety	X	X		X	X
Discussion on primary and secondary substitution	X	X		X	X
Availability of biosimilars (uptake, use)	X	X		X (In the formulary)	X (Prescription)
Biosimilars and biologics in the these same tender	X	X	X	X	X
Acceptability of recent policies for biosimilars (low-cost quotas, category F and introduction Erythropoietin in the lump sum)	X	X	X	X	X
Pricing strategies	X	X	X	X	X
Future policy measures (quotas, information campaigns)	X	X	X	X	X

* *Fringe benefit can include discounts, rebates, grants and research chairs or services (i.e. delivery in case of stock rupture); MFC = Medisch-farmaceutisch comité; CMP = Comité médico-pharmaceutique*

Appendix 6.2. Questionnaire for hospital pharmacist

The interviews aimed at gaining in-depth insights on:1) functioning of the hospital pharmacy, 2) tendering procedures for pharmaceuticals and

3) biosimilars in the hospital setting

Functioning and financing of the hospital pharmacy: How does it work in daily practice?

1. Pharmaceutical provision in hospitals: what is the role of hospital pharmacist?
2. Purchasing of medicines in the hospital sector: how are pharmaceuticals included in the pharmaceutical formulary? (i.e..how often does the medico pharmaceutical committee meet)
3. Are there discounts, rebates or any advantages provided by pharmaceuticals firms (and what is their range)?

Tendering procedures: (about its implementation)

1. Is there prior experience with tendering in your service?
2. Is there an ongoing discussion on the future tendering policies for pharmaceuticals in your hospital?

General issues regarding biosimilars

1. Is there an ongoing discussion on biosimilars?
2. In your opinion, do we need to have biosimilars?
3. In your opinion, are there concerns about the quality of biosimilars?
4. What is your point of view on primary substitution? What is your point of view on switching during the course of treatment?
5. Are there biosimilars on the formulary?
6. In your opinion, what is the expected impact of the new tendering procedure on biosimilar penetration in your hospital? (i.e. Will biosimilars and biologics entering same tender?)
7. In your opinion, what will be the impact of including EPO on the hospital lump sum and of the category F on biosimilars uptake?
8. Is a good communication between the hospital pharmacist and the clinician a good tool to incentive the use of biosimilars?
9. Are there specific intentions/initiatives/pilot experiments in your hospital to stimulate/promote the uptake of biosimilars (i.e. Phase IV studies)?
10. What would be a good tool to stimulate prescribing of biosimilars? What is your point of view on setting quotas at the hospital to incentive biosimilar use?

Next interviews ?

Specific specialist (oncology, nephrologist, hospital pharmacists, policy maker) in your hospital who could elaborate on the issue?

Appendix 6.3. Questionnaire for interviews for sickness funds

The interviews aimed at gaining in-depth insights on: 1) functioning and financing of the hospital pharmacy; 2) identifying barriers or incentives for biosimilar use 3) identifying acceptable and effective policies to give biosimilars easier access to the market .

Functioning and financing of the hospital pharmacy

1. Is there an ongoing discussion on the functioning of the hospital pharmacy (i.e. how is the hospital formulary set)?
2. Do you have information on the level of discounts, rebates or any advantages provided by pharmaceutical companies to hospital pharmacies?
3. Do you have information on the advantages received by doctors?
4. Is there an ongoing discussion on the impact of public tendering for hospital pharmacies?
5. In your opinion, what will be the impact of the new tendering procedure for pharmaceuticals on price negotiation (i.e. discounts and rebates) in hospitals settings?

General issues regarding biosimilars

1. Is there an ongoing discussion on biosimilars?
2. In your opinion, do we need to have biosimilars?
3. In your opinion, are there concerns about the quality of biosimilars?

4. What is your point of view on primary substitution? What is your point of view on switching during the course of treatment?

Biosimilars in the context of the hospital pharmacy

1. In your opinion, what is the expected impact of the new tendering procedure on biosimilar penetration in hospitals? (i.e. Will biosimilars and biologics entering same tender?)
2. In your opinion, what will be the impact of including EPO on the hospital lump sum and of the category F on biosimilars uptake?
3. In your opinion, how should we manage the conflict between hospital financing and cost-containment policies?
4. In your opinion, should the current Reference Price System be extended at the therapeutic level to encourage the use of biosimilars?
5. In your opinion, what is the role of the sickness funds regarding the use of biosimilars?

Appendix 6.4. Questionnaire for interviews for physicians

The interviews aimed at gaining in-depth insights on: 1) biosimilars penetration in the hospital settings 2) identifying acceptable and effective policies to give biosimilars easier access to the market 3) possible barriers for market penetration of biosimilars

Biosimilars penetration in the hospital settings

1. Pharmaceutical provision in hospitals: what is the role of the specialist in the choice of pharmaceuticals in the hospital formulary?
2. Is prescribing electronically arranged?
3. Are there biosimilars on the formulary?
4. In your opinion, do we need biosimilars?
5. Do you prescribe biosimilars?
6. Would you consider prescribing biosimilars (EPO, growth hormone, filgrastim, mAb)? Why or why not?
7. In your opinion, what will be the impact of including EPO on the hospital lump sum and of the category F on biosimilars uptake?
8. Is there prior experience with tendering of pharmaceuticals in your hospital?
9. In your opinion, what is the expected impact of the new tendering procedure on biosimilar penetration in your hospital? (i.e. Will biosimilars and biologics entering same tender?)
10. In your opinion, what will be the impact of the new tendering procedure on your hospital (in general)?

Acceptable and effective policies to give biosimilars easier access to market

1. Is a good communication between the hospital pharmacist and the clinician a good tool to incentive the use of biosimilars?
2. What is your point of view on setting quotas at the hospital to incentive biosimilar use?
3. Are there specific intentions/initiatives/pilot experiments in your hospital to stimulate/promote the uptake of biosimilars (i.e. Phase IV studies)?
4. What would be a good tool to stimulate prescribing of biosimilars?

Barriers or incentives for biosimilar use

1. What are the barriers for Phase IV studies for biosimilars in your hospital?
2. Are there specific barriers for uptake of biosimilars and how is this addressed in your hospital?
3. Is the quality of the biosimilar a discussion issue?
4. What is your point of view on primary substitution? What is your point of view on switching during the course of treatment?
5. Is the current financing of medical products in hospitals a barrier for market penetration of biosimilars? (i.e. discounts, rebates or any advantages on reference products)

Next interviews:

Specific specialist (oncology, nephrologist, hospital pharmacists, policy maker) who could elaborate on the issue?

Appendix 6.5. Questionnaire for interviews for pharmaceutical companies

The interviews aimed at gaining in-depth insights on:1) Impact of future tendering procedure on use of pharmaceuticals in inpatient settings 2) Use of biosimilars in the Belgian context.

Tendering procedures

1. Is there an ongoing discussion on the future tendering policies for pharmaceuticals in hospitals?
2. Is there prior experience with tendering in Belgium? In other countries?
3. In your opinion, what is the expected impact of the new tendering procedure on negotiation in prices, rebates and other contact with hospital?
4. In your opinion, what is the expected impact of the new tendering procedure on biosimilar penetration in your hospital? (i.e. Will biosimilars and biologics entering same tender?)

Barriers or incentives for biosimilar use

1. In your opinion, why is the market share of biosimilars so low in Belgium.?
2. In your opinion, are there concerns about the quality of the biosimilar?
3. In your opinion, is “similar” precisely defined? (i.e. range, definition of similar)
4. What is your point of view on primary substitution? What is your point of view on switching during the course of treatment?
5. In your opinion, what will be the impact of including EPO on the hospital lump sum and of the category F on biosimilars uptake?
6. Are there discounts, rebates or any advantages provided by pharmaceuticals firms (and what is their range)?
7. In your opinion, what are the alternatives for improving the financing system of pharmaceuticals in hospital settings?
8. What is your point on the European Guidelines on Biosimilars?
9. In your opinion, is there a perception that biosimilars are not produce in Europe a reason why physicans do not prescribe them?
10. In your opinion, classic pharmaceutical companies will enter the biosimilar market?

Others points

Appendix 6.6. Questionnaire for interviews for hospital directors

The interview aimed at gaining insights on:1) The weight of the hospital pharmacy within the hospital, 2) tendering procedures for pharmaceuticals and 3)

Weight of the hospital pharmacy within the hospital budget

1. Functioning and financing of the hospital pharmacy: (budget of the hospital pharmacy, pharmaceuticals budget for outpatient and inpatient)
2. Are there discounts, rebates or any advantages provided by pharmaceuticals firms (and what is their range)?
3. Is there a deficit or a surplus in the hospital pharmacy?

Tendering procedures for pharmaceuticals

1. Is there prior experience with tendering in your hospital?

Acceptability of cost-containment policies

1. Are you aware of the discussion concerning the measures for EPO (lump sum and category F)
2. In your opinion, what will be the reaction to mandatory quotas for biosimilars at the hospitals? How can we improve the implementation and acceptability of such a policy?.
3. In your opinion, what will be a long term policy/vision for the hospitals?

APPENDIX 7. WEB SURVEY

Appendix 7.1. Questionnaire

My background

What is your specialty? (multiple answers possible)[1 answer minimum]

- hospital pharmacy
- medical oncology
- nephrology
- rheumatology
- haematology
- paediatrics
- other
- Specify your specialty:

What is your setting ? (multiple answers possible)[1 answer minimum]

- university hospital
- public hospital
- private hospital
- other
- Specify your other setting:

What is your scientific society/association/union ?[1 answer minimum]

- Belgian Hematological Society (BHS)
- Belgian Royal Society for Rheumatology (KBVR/SRBR)
- Belgian Society of Medical Oncology (BSMO)
- Groupement des néphrologues francophones de Belgique (GNFB)
- Nederlandstalige Belgische Vereniging voor Nefrologie (NBVN)
- Vlaamse vereniging van ziekenhuisapothekers (VZA)
- Association Francophone Des Pharmaciens Hospitaliers De Belgique (AFPHB)
- Belgian Study Group for Pediatric Endocrinology (BSGPE)

My current knowledge

Q1-According to the definition in the EU, a biosimilar is... (multiple answers possible)

- a new biopharmaceutical
- a generic medecine of an innovator biopharmaceutical
- a counterfeit copy of a biopharmaceutical
- a biopharmaceutical comparable in quality to the reference biological
- a biopharmaceutical comparable in safety & efficacy to the reference biological
- I do not know

Use of biosimilars

Q2-In my opinion a biosimilar can in general be used to start a treatment instead of the innovator biopharmaceutical... (one single answer possible)

- without any safety and efficacy concerns
- with minor safety and efficacy concerns
- with major safety and efficacy concerns
- never
- I do not know

Q3-In my opinion an ongoing treatment using the innovator biopharmaceutical can in general be switched to a biosimilar... (one single answer possible)

- without any safety and efficacy concerns
- with minor safety and efficacy concerns
- with major safety and efficacy concerns

- never
- I do not know

Q4-Are there biosimilars on the formulary of your hospital? (one single answer possible)

- yes
- no
- I do not know
- not applicable

Q5-Have you prescribed any biosimilars? (one single answer possible)

- never
- rarely
- often
- always
- I do not know
- not applicable

Advantages of biosimilars

Q6-In my opinion biosimilars are... (multiple answers possible)

- not important for the health system
- important to stimulate innovation of biopharmaceuticals
- important to stimulate competition in the biopharmaceutical market
- important to save costs for the health system
- important to offer alternatives in case of drug shortage
- important for other reasons
- Q6a-These other reasons are:
- I do not know

Barriers to use of biosimilars

Q7-In my opinion the reason(s) why physicians do not prescribe a biosimilar is (are): (multiple answers possible)

- biosimilars are not included in the hospital formulary
- there is too much uncertainty over the efficacy of biosimilars
- there is too much uncertainty over the safety of biosimilars
- physicians receive better fringe benefits from innovator drug firms
- Q7a-What type of fringe benefits for physicians ?
- hospitals receive better fringe benefits from innovator drug firms
- Q7b-What type of fringe benefits for hospitals ?
- requirements for market authorization of biosimilars are not stringent enough
- physicians trust more the innovator drug firms
- physicians have a better relationship with the innovator drug firms
- the traceability of origin of biosimilars is not certain
- the naming of the biosimilars is confusing
- biosimilars are no longer an up-to-date treatment
- the implementation of biosimilars removes R&D capital from innovating companies
- other reason
- Q7c-Other reason(s). Specify:
- I do not know

Increasing the uptake of biosimilars

Q8-In my opinion the following intervention(s) could increase the uptake of biosimilars: (multiple answers possible)

- official position paper of professional medical societies on biosimilars
- robust cost-effectiveness data of biosimilar versus innovator drug
- well-monitored post-marketing studies confirming efficacy & safety of biosimilar
- patient registries

- mandatory inclusion of biosimilars on hospital formulary
- public tendering
- pre-defined percentage (quotas) on biosimilar use
- pricing strategies
- other
- Q8a-Other intervention(s) to increase the uptake is(are):

Q9-The uptake of biosimilars could be increased by standardizing the reimbursement for day hospital and classical hospitalization with a lump sum... (one single answer possible)

- equal to the least expensive biopharmaceutical
- lower than the least expensive biopharmaceutical
- reducing the price of the originator by a fixed percentage
- Q9a-Please, specify here which percentage should be used (with a number between 0 and 100) :
- or with other type of pricing strategy
- Q9b-Please, specify here which other type of pricing strategy could increase the uptake of biosimilars:
- Not appropriate
- I do not know

Q10-A minimum pre-defined percentage (quota) of biosimilar use at hospital level could increase the uptake of biosimilars. (multiple answers possible)

- no
- yes in inpatient setting
- yes in day hospital setting
- I do not know

Q11-A minimum pre-defined percentage (quota) of biosimilar use at prescriber level could increase the uptake of biosimilars. (multiple answers possible)

- no
- yes in inpatient setting
- yes in day hospital setting
- yes in outpatient setting
- I do not know

My information

Q12-In general, my main source(s) of information on biosimilars is (are): (multiple answers possible)

- medical scientific literature
- lay press
- innovator company
- biosimilar company
- hospital pharmacist
- RIZIV – INAMI communications
- medical professional association communications
- medical conferences
- Federal agency for medicines and health products (FAGG/AFMPS)
- none
- other
- Q12a-Other main source(s) of information. Specify:

Q13-I need more information on: (multiple answers possible)

- criteria for market authorisation of biosimilars in Europe
- efficacy and safety of biosimilars
- interchangeability and substitution of biosimilars
- stakeholder involvement in biosimilar debate
- effect of biosimilars on cost-savings
- other
- Q13a-Other information needed:

Appendix 7.2. Response rate

Table 31 – Response rate to the web survey on biosimilars

Scientific society or association	N members	N members who were sent the link	N responses	Response rate (%)[3]
Total specialist	1066	945	98	10.4
Belgian Hematological Society (BHS)	308	248	25	10.1
Belgian Society of Medical Oncology (BSMO)	205	205	18	8.8
Belgian Royal Society for Rheumatology (KBVR/SRBR)	251	175	33	18.9
Groupement des néphrologues francophones de Belgique (GNFB)	120	135	14	10.4
Nederlandstalige Belgische Vereniging voor Nefrologie (NBVN)	146	146	6	4.1
Belgian Study Group for Pediatric Endocrinology (BSGPE)	36	36	2	5.6
Total chief hospital pharmacist	183	181	28	15.5
Vlaamse vereniging van ziekenhuisapothekers (VZA)[1]	80-100	80-100	24	24.0
Association Francophone Des Pharmaciens Hospitaliers De Belgique (AFPHB)[2]	83	81	4	4.9
Total specialist and chief hospital pharmacist	1 249	1126	126	11.2

[1]The VZA has a total of 600 members. The association sent a mail to all members mentioning that only chief pharmacist was concerned. Estimated sampling from chief hospital pharmacists was set to 80 to 100 by the association.[2]The AFPHB has 518 members (including students) of which 377 are pharmacist. The associations sent a mail including the survey link only to chief hospital pharmacist (81.) [3] Response rate calculated on the number of members who were sent the link. For the VZA, it was calculated on the maximum estimation of the association (100).

Appendix 7.3. Results

Results on biosimilar web survey

Results are presented per speciality and in number of checked answered unless stated differently

Table 32 – Setting of respondent (per specialty)

	Hospital pharmacists	Physicians	Total
University hospital	5	45	50
Public hospital	13	40	53
Private hospital	10	20	30
Other	1	4	5
Total	29	109	138
Khi2=6,79 ddl=3			

Table 33 – Knowledge of the definition of a biosimilar (per specialty)

	Hospital pharmacists	Physicians	Total
a new biopharmaceutical	5	8	13
a generic medicine of an innovator biopharmaceutical	9	32	41
a counterfeit copy of a biopharmaceutical	2	4	6
a biopharmaceutical comparable in quality to the reference biological	10	38	48
a biopharmaceutical comparable in safety & efficacy to the reference biological	17	48	65
I do not know		5	5
Total	43	135	178
Khi2=2,22 ddl=5			

Table 34 – Attitude on using a biosimilar to start a new treatment (i.e. primary substitution) (per specialty)

	Hospital pharmacists	Physicians	Total
without any safety and efficacy concerns	12	9	21
with minor safety and efficacy concerns	11	47	58
with major safety and efficacy concerns	4	27	31
never		5	5
I do not know	1	10	11
Total	28	98	126
Khi2=15,6 ddl=4			

Table 35 – Attitude on using a biosimilar to switch a treatment (i.e. secondary substitution) (per specialty)

	Hospital pharmacists	Physicians	Total
without any safety and efficacy concerns	2	6	8
with minor safety and efficacy concerns	13	33	46
with major safety and efficacy concerns	8	30	38
never	4	18	22
I do not know	1	11	12
Total	28	98	126
Khi2=2,01 ddl=4			

Table 36 – Summary of results for primary and secondary substitution

	Primary substitution			Secondary substitution		
	No or minor concerns	Major concerns or should never be used	I do not know	No or minor concerns	Major concerns or should never be used	I do not know
Overall	62.7%	28.6%	8.7%	42.9%	47.6%	9.5%
Pharmacists	82.1%	14.3 %	3.6 %	53.6%	42.9%	3.6%
Physicians	57.1%	32.6%	10%	42.9%	47.6%	9.5%

Table 37 – Awareness of biosimilar on hospital formulary (per specialty)

	Hospital pharmacists	Physicians	Total
yes	6	12	18
no	20	53	73
I do not know	1	29	30
not applicable	1	4	5
Total	28	98	126
Khi2=8,11 ddl=3			

Table 38 – Biosimilars prescription habits (per specialty)

	Hospital pharmacists	Physicians	Total
never	8	67	75
rarely		10	10
often		7	7
always		1	1
I do not know		4	4
not applicable	20	9	29
Total	28	98	126
Khi2=46,7 ddl=5			

Table 39 – Attitude on the importance of biosimilars (per speciality)

	Hospital pharmacists	Physicians	Total
not important for the health system	1	11	12
important to stimulate innovation of biopharmaceuticals	9	10	19
important to stimulate competition in the biopharmaceutical market	17	30	47
important to save costs for the health system	21	64	85
important to offer alternatives in case of drug shortage	16	21	37
I do not know	2	12	14
Total	66	148	214
Khi2=11 ddl=6			

Table 40 – Reasons not to prescribe a biosimilar (per specialty)

	Hospital pharmacists	Physicians	Total
biosimilars are not included in the hospital formulary	12	31	43
there is too much uncertainty over the efficacy of biosimilars	11	58	69
there is too much uncertainty over the safety of biosimilars	14	58	72
physicians receive better fringe benefits from innovator drug firms	8	6	14
hospitals receive better fringe benefits from innovator drug firms		5	5
requirements for market authorization of biosimilars are not stringent enough	5	29	34
physicians trust more the innovator drug firms	21	41	62
physicians have a better relationship with the innovator drug firms	16	26	42
the traceability of origin of biosimilars is not certain	2	32	34
the naming of the biosimilars is confusing	2	14	16
biosimilars are no longer an up-to-date treatment	3	7	10
the implementation of biosimilars removes R&D capital from innovating companies	5	37	42
other reason	1	3	4
I do not know	1	7	8
Total	101	354	455
Khi2=31,7 ddl=13			

Table 41 – Summary: Reasons not to prescribe a biosimilar (percent of respondents of specialty who checked that reason)

	Pharmacists		Physicians	
1	physicians trust more the innovator drug firms	75%	there is too much uncertainty over the safety of biosimilars	59%
2	physicians have a better relationship with the innovator drug firms	57%	there is too much uncertainty over the efficacy of biosimilars	59%
3	there is too much uncertainty over the safety of biosimilars	50%	physicians trust more the innovator drug firms	42%
4	biosimilars are not included in the hospital formulary	43%	the implementation of biosimilars removes R&D capital from innovating companies (33.3%)	38%
5	there is too much uncertainty over the efficacy of biosimilars	39%	biosimilars are not included in the hospital formulary	32%
6	the implementation of biosimilars removes R&D capital from innovating companies	18%	the traceability of origin of biosimilars is not certain	33%
7	requirements for market authorization of biosimilars are not stringent enough	18%	requirements for market authorization of biosimilars are not stringent enough	30%
8	biosimilars are no longer an up-to-date treatment	11%	physicians have a better relationship with the innovator drug firms	27%
9	the traceability of origin of biosimilars is not certain	7%	the naming of the biosimilars is confusing	14%
10	the naming of the biosimilars is confusing	7%	biosimilars are no longer an up-to-date treatment	7%
11	dont know	0.4%	dont know	7%
12	physicians receive better fringe benefits from innovator drug firms	0 %	physicians receive better fringe benefits from innovator drug firms	5%

Table 42 – Interventions to increase the uptake of biosimilars

	Hospital pharmacists	Physicians	Total
official position paper of professional medical societies on biosimilars	16	52	68
robust cost-effectiveness data of biosimilar versus innovator drug	19	63	82
well-monitored post-marketing studies confirming efficacy & safety of biosimilar	21	71	92
patient registries	3	21	24
mandatory inclusion of biosimilars on hospital formulary	4	8	12
public tendering	5	4	9
pre-defined percentage (quotas) on biosimilar use	3	7	10
pricing strategies	8	19	27
other	1	4	5
Total	80	249	329
Khi2=5,85 ddl=8			

Table 43 – Summary of interventions to increase the uptake of biosimilars

	respondents
well-monitored post-marketing studies confirming efficacy & safety of biosimilar	73.0%
robust cost-effectiveness data of biosimilar versus innovator drug	65.1%
official position paper of professional medical societies on biosimilars	54.0%
pricing strategies	21.4%
patient registries	19.0%
mandatory inclusion of biosimilars on hospital formulary	9.5%
pre-defined percentage (quotas) on biosimilar use	7.9%
public tendering	7.1%
other	4.0%

Table 44 – Lump sum to increase the uptake of biosimilars

	Hospital pharmacists	Physicians	Total
equal to the least expensive biopharmaceutical	8	11	19
lower than the least expensive biopharmaceutical	4	12	16
reducing the price of the originator by a fixed percentage	7	17	24
or with other type of pricing strategy	1	2	3
Not appropriate	3	27	30
I do not know	5	27	32
Total	28	96	124
Khi2=7,3 ddl=5			

Table 45 – Effectiveness of quota at hospital level to increase the uptake of biosimilars

	Hospital pharmacists	Physicians	Total
no	8	34	42
yes in inpatient setting	5	15	20
yes in day hospital setting	6	15	21
I do not know	12	41	53
Total	31	105	136
Khi2=0,535 ddl=3			

Table 46 – Effectiveness of quota at prescriber level to increase the uptake of biosimilars

	Hospital pharmacists	Physicians	Total
no	7	32	39
yes in inpatient setting	7	17	24
yes in day hospital setting	5	20	25
yes in outpatient setting	6	24	30
I do not know	10	36	46
Total	35	129	164
Khi2=1,21 ddl=4			

Table 47 – Main source(s) of information on biosimilars

	Hospital pharmacists	Physicians	Total
medical scientific literature	16	59	75
lay press	1	5	6
innovator company	9	12	21
biosimilar company	18	38	56
hospital pharmacist	3	5	8
RIZIV – INAMI communications	5	15	20
medical professional association communications	5	29	34
medical conferences	13	42	55
Federal agency for medicines and health products (FAGG – AFMPS)	7	9	16
none	1	11	12
other		1	1
Total	78	226	304
Khi2=11,1 ddl=10			

Table 48 – Subjects around biosimilars on which more information is requested

	Hospital pharmacists	Physicians	Total
criteria for market authorisation of biosimilars in Europe	11	50	61
efficacy and safety of biosimilars	22	86	108
interchangeability and substitution of biosimilars	23	52	75
stakeholder involvement in biosimilar debate	4	21	25
effect of biosimilars on cost-savings	15	52	67
other		4	4
Total	75	265	340
Khi2=4,95 ddl=5			

REFERENCES

1. Rovira J, Espín J, García L, Olry de Labry A. The impact of biosimilars' entry in the EU market. Granada: Andalusian School of Public Health; 2011. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_market_012011_en.pdf
2. ICH Expert Working Group. ICH Harmonised tripartite guideline comparability of biotechnological/biological products subject to changes in their manufacturing process Q5E. 2004. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf
3. European Medicines Agency (EMA). EMA Procedural advice for users of the Centralised Procedure for Similar Biological Medicinal Products applications. 2012. (EMA/940451/2011) Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125166.pdf
4. International Federation of Pharmaceutical Manufacturers Associations (IFPMA). Encouragment of new clinical drug development: the role of data exclusivity. Geneva: 2000. Available from: http://www.who.int/intellectualproperty/topics/ip/en/DataExclusivity_2000.pdf
5. European Medicines Agency (EMA). Concept paper on extrapolation of efficacy and safety in medicine development. Draft. 2012. (EMA/129698/2012) Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129285.pdf
6. 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.
7. European Medicines Agency (EMA). Questions and answers on biosimilar medicines (similar biological medicinal products). 2012. (EMA/837805/2011) Available from:

http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf

8. Food and Drug Administration (FDA). Guidance for Industry Scientific Considerations in Demonstrating Biosimilarity to a Reference Product- Draft guidance. In: (CDER) CfDEaR, (CBER) CfBEaR, editors.; 2012.
9. European Medicines Agency (EMA). Glossary (terms and abbreviations) London: European Medicines Agency (EMA); 2010. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/12/WC500099907.pdf
10. Folino-Gallo P, Muscolo L, Vogler S, Morak S. PHIS Glossary. Italian Medicines Agency – AIFA and h Gesundheit Österreich GmbH; 2011. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/MethodologyTemplate/PHIS%20Glossary_UpdatedApril2011.pdf
11. Standing Committee of European doctors (CPME). Project group on Market Access and Uptake of Biosimilars Work Area G: "Develop information material directed to healthcare professionals". 2011. Available from: http://cpme.dyndns.org:591/database/2012/FINALPUBLIC.CPME.Info.material.to.health.professionals.on.Biosimilars.DEC.2011.pdf
12. RIZIV - INAMI Minimum voorschrijven van goedkope geneesmiddelen - Inhoud en doelstelling [[cited 02/16/2013]. Available from: http://www.riziv.be/care/nl/doctors/promotion-quality/feedbacks/feedback-generica/intro.htm
13. SPP intégration sociale. Rapport social national 2012. Belgique. Bruxelles: Service Public Fédéral de Programmation Intégration sociale; 2013. Available from: http://www.mi-is.be/sites/default/files/doc/national_social_report_2012_belgium_fr.pdf
14. 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
15. Bioportafolio Biopharmaceuticals - news, views, blogs and reports [2012 [cited 01/02/2013]. Available from: http://www.bioportfolio.com/channels/biopharmaceuticals
16. U.S. Food and Drug Administration CFR - Code of Federal Regulations Title 21 [04/01/2012 [cited 2013/01/02]. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=210.3
17. Project Group on Market Access and Uptake of Biosimilars. What you need to know about Biosimilar Medicinal Products. A consensus information document. Brussels: 2013. 201313/02/2013 Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/tor_biosimilars_en.pdf
18. Schiestl M, Stangler T, Torella C, Cepeljnik T, Toll H, Grau R. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nature Biotechnology. 2011;29(4):310-2.
19. Minghetti P, Rocco P, Del Vecchio L, Locatelli F. Biosimilars and regulatory authorities. Nephron. 2011;117(1):c1-7.
20. Saenger P. Current status of biosimilar growth hormone. International Journal of Pediatric Endocrinology. 2009;2009:370329.
21. Schiestl M. A biosimilar industry view on the implementation of the WHO guidelines on evaluating similar biotherapeutic products. Biologicals. 2011;39(5):297-9.
22. European Medicines Agency (EMA). Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process: non-clinical and clinical issues. 2007. (EMEA/ CHMP/BMWP/101695/2006) Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003935.pdf
23. BIOTECanada Subsequent Entry Biologics [2011 [cited 13/02/2013]. Available from: http://www.biotech.ca/en/policy-matters/health-bio/seb.aspx

24. Schellekens H, Moors E. Clinical comparability and European biosimilar regulations. Nature Biotechnology. 2010;28(1):28-31.
25. Dowlat HA. Perceptions and realities of clinical safety of biosimilars - EU and US perspectives: Part 2. Regulatory Rapporteur 2012;9:16-9.
26. European Medicines Agency (EMA). Applications for new human medicines under evaluation by the Committee for Medicinal Products for Human Use. February 2013. 2013. (EMA/100806/2013) Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/02/WC500139241.pdf
27. World Health Organisation. Guidelines on the use of International Nonpropietary Names (INNs) for pharmaceutical substances. Geneva: World Health Organisation; 1997. Available from: http://www.who.int/medicines/services/inn/innquidance/en/index.html
28. Rader RA. Nomenclature of new biosimilars will be highly controversial. BioProcess International,. 2011;9:26-33.
29. Chantelot E. Introduction - Naming of Biotechnology Medecines. Geneva: WHO; 2006. Available from: http://www.who.int/medicines/services/inn/WHO_INN-Research-basedIndustriesPPT.pdf
30. World Health Organization (WHO). WHO Informal Consultation on International Nonproprietary Names (INN) Policy for Biosimilar Products. Geneva: 2006 4-5 September 2006. Available from: http://www.who.int/medicines/services/inn/BiosimilarsINN_Report.pdf
31. Miletich J, Eich G, Grampp G, Mounho B. Biosimilars 2.0: guiding principles for a global "patients first" standard. mAbs. 2011;3(3):318-25.
32. Directive 2010/84/EU of the European parliament and of the council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, OJ L 348/74
33. European Generic Medicines Association (EGA). EGA position paper on naming of biopharmaceuticals: a contribution to WHO “Review of International Nonproprietary Names (INN) for Biological and Biotechnological Substances”. 2006. Available from: http://www.who.int/medicines/services/inn/WHO_INN-EGAposition.pdf
34. Regulation (EC) No 726/2004 of the European Parliament of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ 30 april 2004 L 136/1
35. Regulation (EU) No 1235/2010 of December 2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products, OJ 31 L 348/1
36. European Commission The EU pharmacovigilance system [[cited 18 december 2012]. Available from: http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm
37. Huberlant B, Kwade Z, Annick VR. Post Authorization Safety Studies (PASS); Updated EU regulations. Life Science 2011(42).
38. Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council, OJ L 159/5
39. Wet van 3 augustus 2012 tot wijziging van de wet van 25 maart 1964 op de geneesmiddelen 11 september 2012.
40. Agence Fédérale des Médicaments et des Produits de Santé - Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (AFMPS - FAGG) Pharmacovigilance

[[cited 23-10-2012]. Available from: http://www.fagg-afmps.be/fr/pharmacovigilance/

41. U.S. Food and Drug Administration. Guidance for Industry: Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); 2005. Available from: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128076.pdf
42. Chertkow J. Regulatory and Development Issues: Hurdles exist but are surmountable. 2007. Biosimilars Series
43. European Medicines Agency (EMA). Guideline on similar biological medicinal products. London: European Medicines Agency (EMA); 2005. (CHMP/437/04) Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf
44. European Medicines Agency (EMA) European public assessment reports [London;2012 [cited 01/02/2013]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125
45. Dalli J Healthy and Active Ageing through improved access to affordable generic medicines (Speech) [Malta;2012 [cited 15 June 2012]. Available from: http://ec.europa.eu/commission_2010-2014/dalli/docs/speech_15062012.pdf
46. European Medicines Agency (EMA) European Medicines Agency - Q&A: Similar biological products - Questions 1-10 [London [cited 23-10-2012]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000125.jsp&mid=WC0b01ac0580533e0c
47. Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Giezen TJ, et al. Biosimilars: what clinicians should know. Blood. 2012;120(26):5111-7.
48. European Medicines Agency (EMA). Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (revision). 2010. (EMEA/CHMP/BMWP/301636/2008 Corr.*) Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089474.pdf
49. Shapiro M. Quality Considerations for Biosimilars. In: Advisory Committee for Pharmaceutical Science and Clinical Pharmacology; 2012.
50. Barbosa MDFS. Immunogenicity of biotherapeutics in the context of developing biosimilars and biobetters. Drug Discovery Today. 2011;16(7-8):345-53.
51. European Medicines Agency (EMA). Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins. 2008. (EMEA/CHMP/BMWP/14327/2006) Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003946.pdf
52. European Medicines Agency (EMA) European Medicines Agency finalises guidance on medicines containing monoclonal antibodies [London;2012 [cited 08 november 2012]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/06/news_detail_001527.jsp&mid=WC0b01ac058004d5c1
53. Agence nationale de sécurité du médicament et des produits de santé (ANSM). Des Médicaments issus des biotechnologies aux médicaments biosimilairs: état de lieu. Paris: Agence française de sécurité sanitaire des produits de santé; 2011. Rapport d'expertise Available from: http://ansm.sante.fr/var/ansm_site/storage/original/application/132b69b9562106e97fb1516417326fce.pdf
54. European Medicines Agency (EMA). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2006. (EMEA/CHMP/BMWP/42832/2005) Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf
55. European Medicines Agency (EMA). 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 granulocyte-colony stimulating factor. 2006. (EMEA/CHMP/BMWP/31329/2005) Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003955.pdf

56. European Medicines Agency (EMA). Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. 2012. (EMA/CHMP/BMWP/403543/2010) Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

57. Declerck P. Biologicals and biosimilars: a review of the science and its implications. Generics and Biosimilars Initiative Journal. 2012;1(1):13-6.

58. Shaw BE, Confer DL, Hwang WY, Pamphilon DH, Pulsipher MA. Concerns about the use of biosimilar granulocyte colony-stimulating factors for the mobilization of stem cells in normal donors: position of the World Marrow Donor Association. Haematologica. 2011;96(7):942-7.

59. European Medicines Agency (EMA). Questions and answers on biosimilar medicines (similar biological medicinal products) 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf

60. Schellekens H, Klinger E, Muhlebach S, Brin JF, Storm G, Crommelin DJA. The therapeutic equivalence of complex drugs. Regulatory Toxicology and Pharmacology. 2011;59(1):176-83.

61. U.S. Senate. Biologics Price Competition and Innovation Act of 2009. In; 2009.

62. Dowlat HA. Perceptions and realities of clinical safety of biosimilars: EU and US perspectives: Part 1. In; 2012. p. 20-5.

63. Chow SC, Lu Q, Tse SK, Chi E. Statistical methods for assessment of biosimilarity using biomarker data. Journal of Biopharmaceutical Statistics. 2010;20(1):90-105.

64. Chow SC, Yang LY, Starr A, Chiu ST. Statistical methods for assessing interchangeability of biosimilars. Statistics in medecines. 2012.

65. le Polain M, Franken M, Koopmanschap M, Cleemput I. Drug reimbursement systems: international comparison and policy recommendations. Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010 2011-03-07 (2nd print; 1st print: 2011-01-11). KCE Reports 147C (D/2010/10.273/90) Available from: http://kce.fgov.be/index_en.aspx?SGREF=5211&CREF=18732

66. Van De Sande S, De Ryck D, De Gauquier K, Hilderson R, Neyt M, Peeters G, et al. Feasibility study of the introduction of an all-inclusive case-based hospital financing system in Belgium - Supplement Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010 25/01/2010. KCE Reports 121S (D/2010/10.273/04) Available from: https://kce.fgov.be/publication/report/feasibility-study-of-the-introduction-of-an-all-inclusive-case-based-hospital-fin

67. Koninklijk besluit tot vaststelling van de procedures, termijnen en voorwaarden inzake de tegemoetkoming van de verplichte verzekering voor geneeskundige verzorging en uitkeringen in de kosten van farmaceutische specialiteiten, B.S. 21 december 2001.

68. Arrêté ministériel modifiant la liste jointe à l'arrêté royal du 21 décembre 2001 fixant les procédures, délais et conditions en matière d'intervention de l'assurance obligatoire soins de santé et indemnités dans le coût des spécialités pharmaceutiques, M.B. 17 août 2012.

69. Gerkens S, Kerkur S. Belgium: Health system review. Brussels: 2010. Health Systems in Transition, Available from: http://www.euro.who.int/en/who-we-are/partners/observatory/health-systems-in-transition-hit-series/countries-and-subregions/belgium-hit-2010

70. DeSwaef A, Antonissen Y. PHIS Hospital Pharma Report - Belgium. Vienna: Gesundheit Österreich GmbH; 2009. Pharmaceutical Health Information System (PHIS) Available from: http://whocc.goeg.at/Literaturliste/Dokumente/CountryInformationR

eports/V4%20PHIS_Hospital%20Pharma_BE_draft_version_for_publication.pdf

71. Koninklijk besluit van 4 maart 1991 houdende vaststelling van de normen waaraan een ziekenhuisapotheek moet voldoen om te worden erkend., B.S. 23 maart 1991.

72. Vloger S, Habl C, Leopold C, Mazag J, Morak S, Zimmermann N. Pharmaceutical Hospital Pharma Report 2010. Vienna: Gesundheit Österreich GmbH; 2010. Available from: http://ec.europa.eu/health/healthcare/docs/phis_hospital_pharma_report_en.pdf

73. Vogler S, Zimmermann N, Habl C, Piessnegger J, Bucsics A. Discounts and rebates granted to public payers for medecines in European countries. Southern Medical Review. 2012;5(1):6.

74. Vrijens F, Van de Voorde C, Farfan-Portet M-I, le Polain M, Lohest O. The reference price system and socioeconomic differences in the use of low cost drugs. Health Services Research (HSR). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010 02/04/2010. KCE Reports 126C (D/2010/10.273/20) Available from: http://kce.fgov.be/index_en.aspx?SGREF=14851&CREF=15353

75. Directive 2004/18/EC of the European Parliament and of the Council of 31 March 2004 on the coordination of procedures for the award of public works contracts, public supply contracts and public service contracts, OJ L 134 30 April 2004, p. 114–240 Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32004L0018:en:NOT

76. Directive 2007/66/EC of 11 December 2007 amending Council Directives 89/665/EEC and 92/13/EEC with regard to improving the effectiveness of review procedures concerning the award of public contracts, O.J. L 335/31 20 December 2007.

77. Council of the European Union, Brussels, 16 February 2012 Interinstitutional File: 2011/0438 (COD) 6436/12, Available from: http://register.consilium.europa.eu/pdf/en/12/st06/st06436.en12.pdf

78. Wet van 24 december 1993 betreffende de overheidsopdrachten en sommige opdrachten voor aanneming van werken, leveringen en diensten B.S. 22 januari 1994.

79. Wet van 16 juni 2006 betreffende de gunning, informatie aan kandidaten en inschrijvers en wachttermijn inzake overheidsopdrachten en bepaalde opdrachten voor werken, leveringen en diensten, B.S. 15 februari 2007.

80. Organieke wet van 8 juli 1976 betreffende de openbare centra voor maatschappelijk welzijn, B.S. 5 augustus 1976.

81. Wet van 14 januari 2002 houdende maatregelen inzake gezondheidszorg, B.S. 22 Februari 2002.

82. Van de Gronden JW, Szyszczak E, Neergaard U, Krajewski M. Health Care and EU Law. Springer; 2011.

83. Koninklijk besluit tot bepaling van de algemene uitvoeringsregels van de overheidsopdrachten en van de concessies voor openbare werken, B.S. 14 januari 2013.

84. Hostenkamp G. The Market for hospital pharmaceuticals in Denmark. Nordic Journal of Health Economics. 2012;Vol. 1(s. 57).

85. Ministerieel besluit van 29 december 1989 betreffende de prijzen van de terugbetaalbare geneesmiddelen, B.S. 6 januari 1990.

86. Wet van 25 maart 1964 op de geneesmiddelen, B.S. 17 april 1964

87. Koninklijk besluit van 7 april 1995 betreffende de voorlichting en de reclame inzake geneesmiddelen voor menselijk gebruik B.S. 12 mei 1995.

88. Pharma.be. Code voor deontologie. 2012. Available from: http://www.pharma.be/assets/files/940/940_129872488174732499.pdf

89. Patient protection and affordable care act, United States Public Law, 2010, HR 3590. Available from: http://www.gpo.gov/fdsys/pkg/PLAW-111publ148/pdf/PLAW-111publ148.pdf

90. Loi du 29 décembre 2011 relative au renforcement de la sécurité sanitaire du médicament et des produits de santé, L'Assemblée nationale et le Sénat, 2011, 22667. Available from: http://www.journal-

officiel.gouv.fr/verifier/explication.php?fic=joe_20111230_0302_0001.pdf.sig&basedir=../publication/2011/1230&joDate=30/12/2011&sommairePage=#

91. Wet betreffende marktpraktijken en consumentenbescherming, B.S. 6 april 2010.
92. Koninklijk besluit van 19 april 2001 betreffende de parallelinvoer van geneesmiddelen voor menselijk gebruik en de parallelle distributie van geneesmiddelen voor menselijk en diergeneeskundig gebruik, B.S. 30 mei 2001.
93. Wet tot wijziging van de wet van 25 maart 1964 op de geneesmiddelen M.B. 3 Augustus 2012.
94. Ministerieel besluit tot wijziging van de lijst gevoegd bij het koninklijk besluit van 21 december 2001 tot vaststelling van de procedures, termijnen en voorwaarden inzake de tegemoetkoming van de verplichte verzekering voor geneeskundige verzorging en uitkeringen in de kosten van farmaceutische specialiteiten, 14 januari 2013.
95. Koninklijk besluit nr 78 betreffende de uitoefening van de gezondheidszorgberoepen, B.S. 14 november 1967.
96. Hurtado P, Vieta A, Espinos B, Badia X. Market access barriers for biosimilars in Spain and Germany: Epoetin ALFA example. Value Health. 2011;14(7):A336.
97. Kani C, Litsa P, Alexopoulou E, Hatzikou M, Delibasi S, Geitona M. Striving for affordable treatments within the Greek environment: Do epoetin biosimilars help? Value Health. 2011;14(7):A412-A3.
98. Lebboroni M, Rosti G, Cerchiari A, Katz P. Health economics analysis of pegfilgrastim in the prophylaxis of febrile neutropenia (FN) in Italy. European Journal of Hospital Pharmacy: Science and Practice. 2012;19(2):172.
99. Lindner L, Gimenez E, Rovira J, Espin J, Olry A, Leticia G. Biosimilars in the European market. Value Health. 2011;14(7):A338.
100. Loiacono C, Sgroi C, Coppolino S, Cannata A, Ferrara R, Arcoraci V, et al. How much are biosimilars used in southern Italy?: A retrospective analysis of epoetin utilization in the local health unit of Messina in the years 20102011. BioDrugs. 2012;26(2):113-20.
101. Long M, Trout J, Akpinar P. Biosimilars: HGH to tnfs, how will payers respond? Value Health. 2009;12(7):A240.
102. Shepelev J, Rauland M, Krattiger C. Biosimilars are not generics from payer perspective. Value Health. 2011;14(7):A351.
103. Toscani M, Vogenberg R, Nash D, Peskin S. Issues associated with biologic agents:healthcare stakeholder survey. Value Health. 2011;14(3):A14.
104. Viejo Viejo I. Does launch price actually matter? Value Health. 2011;14(7):A353.
105. Blackstone EA, Fuhr JP, Jr. Biosimilars and innovation: an analysis of the possibility of increased competition in biopharmaceuticals. Future Medicinal Chemistry. 2010;2(11):1641-9.
106. Howell PR. Patient access issues and opportunities. Contract Pharma. 2012(4).
107. Jommi C. Biosimilar drugs: Economic issues and Italian market perspectives. PharmacoEconomics - Italian Research Articles. 2010;12(1):17-31.
108. Aapro MS. What does a prescriber think of biosimilars? Oncologie. 2011;13(5):234-8.
109. Doloresco F, Fominaya C, Schumock GT, Vermeulen LC, Matusiak L, Hunkler RJ, et al. Projecting future drug expenditures: 2011. American Journal of Health-System Pharmacy. 2011;68(10):921-32.
110. Grabowski HG, Kyle M, Mortimer R, Long G, Kirson N. Evolving brand-name and generic drug competition may warrant a revision of the Hatch-Waxman Act. Health Affairs. 2011;30(11):2157-66.
111. Heinzl S. Epoetin biosimilar: Cost-saving potential is still not exhausted. Pharmazeutische Zeitung 2008;153(42):23.
112. Hoffman JM, Li E, Doloresco F, Matusiak L, Hunkler RJ, Shah ND, et al. Projecting future drug expenditures--2012. American Journal of Health-System Pharmacy. 2012;69(5):405-21.

113. Howell P, Burich M. Will biosimilars fulfill their promise of affordability? Pharmaceutical Processing. 2012;27(9):36-9.

114. Mellstedt H. Biosimilar products--cheaper version of biological drugs. New possibilities within several therapeutic fields. Lakartidningen. 2009;106(23):1563-6.

115. Aapro M, Cornes P, Sun D, Abraham I. Comparative cost efficiency across the European G5 countries of originators and a biosimilar erythropoiesis-stimulating agent to manage chemotherapy-induced anemia in patients with cancer. Therapeutic Advances in Medical Oncology. 2012;4(3):95-105.

116. Simoens S. Health economics of market access for biopharmaceuticals and biosimilars. Journal of Medical Economics. 2009;12(3):211-8.

117. Simoens S. Biosimilar medicines and cost-effectiveness. ClinicoEconomics and Outcomes Research. 2011;3(1):29-36.

118. Simoens S, Verbeken G, Huys I. Market access of biosimilars: Not only a cost issue. Oncologie. 2011;13(5):218-21.

119. Simoens S, Verbeken G, Huys I. Biosimilars and market access: a question of comparability and costs? Targeted Oncology. 2012:1-5.

120. Chauhan D, Towse A, J. M-F. The market for biosimilars: evolution and policy options. . Office of Health Economics OHE reserach; 2009. Briefing

121. Moran N. Fractured European market undermines biosimilar launches. Nature Biotechnology. 2008;26(1):5-6.

122. Grabowski HG, Ridley DB, Schulman KA. Entry and competition in generic biologics. Managerial and Decision Economics. 2007;28(4-5):439-51.

123. Ruiz S, Calvo G. Similar biological medicinal products: Lessons learned and challenges ahead. Journal of Generic Medicines. 2011;8(1):4-13.

124. Borget I, Grivel T. Biosimilaires et facteurs medico-economiques. Bulletin du Cancer. 2010;97(5):589-95.

125. Sheppard A. Navigating the biosimilars market: The market landscape for biosimilars is in flux, with limited penetration now, but with the potential for growth for those who can navigate the market. BioPharm Int. 2011;24(9 SUPPL.):s12-s3.

126. Jönsson B. Introduction. In: Matisson N M-FJ, Towse A,, editor. Biosimilars: How much entry and price competition will result? London: Office of Health Economics (OHE); 2009. p. 6-1.

127. Towse A, Mestre-Ferrandiz J. The Market for Biosimilars: Evolution and Policy Options. In: Matisson N M-FJ, Towse A,, editor. Biosimilars: How much entry and price competition will result? London: Office of Health Economics (OHE); 2009. p. 25-35.

128. Grabowski H, Long G, Mortimer R. Implementation of the biosimilar pathway: economic and policy issues. Seton Hall law review. 2011;41(2):511-57.

129. Cornes P. The economic pressures for biosimilar drug use in cancer medicine. Targeted Oncology. 2012;7(SUPPL.1):S57-S67.

130. Hughes DA. Biosimilars: evidential standards for health technology assessment. Clinical Pharmacology & Therapeutics. 2010;87(3):257-61.

131. Liefner M. Biosimilars: Price Dynamics in Europe. In: Matisson N M-FJ, Towse A,, editor. Biosimilars: How much entry and price competition will result? London: Office of Health Economics (OHE); 2009. p. 51-65.

132. Haustein R dMC, Ariane H, Haeussler B. . Saving money in the European healthcare systems with biosimilars. . Berlin: IGES; 2011.

133. Thirstrup S. Market Access to Biosimilars - Authorities point of view. In: Proceedings of Emergence des médicaments biosimilaires; 2012; Brussels. Available from: http://www.sympobiosimilars.be/fr/docs/Symposium_Biosimilars_22112012_Presentation_4.pdf

134. RIZIV-INAMI Médicaments [Brussels,: National Institute for Health and Disability Insurance;2012 [cited November, 2012]. Available from: http://www.inami.fgov.be/drug/fr/drugs/index.htm

135. Befrits G. Biosimilars in Sweden from a payer perspective. In: Proceedings of 10th EGA International Symposium on Biosimilar

Medicines; 2012; London: TLV, Tandvårds- och läkemedelsförmånsverket.

136. Dylst P, Vulto A, Simoens S. How can pharmacist remuneration systems in Europe contribute to generic medicine dispensing? Pharmacy Practice. 2012;10(1):3-8.

137. Haag-Weber M, Vetter A, Thyroff-Friesinger U, Group IN-S. Therapeutic equivalence, long-term efficacy and safety of HX575 in the treatment of anemia in chronic renal failure patients receiving hemodialysis. Clinical Nephrology. 2009;72(5):380-90.

138. Glaeske G, Schicktanz C. BARMER GEK Arzneimittelreport 2011. Bremen: Universität Bremen. Abteilung für Gesundheitsökonomie, Gesundheitspolitik und Versorgungsforschung; 2011. Available from: http://www.zes.uni-bremen.de/uploads/News/110713_Kurzfassung.pdf

139. Kohn L, Christiaens W. The use of Qualitative Research Methods in KCE studies. Brussels: Belgian Health Care Knowledge Centre (KCE); 2012. 197C Available from: https://kce.fgov.be/sites/default/files/page_documents/KCE_187C_qualitative_research_methods.pdf

140. Board ME. Biosimilars, meer van hetzelfde of toch anders? Antwoorden op stellingen. In: (CBG) CtBvG, editor. Collegedag CBG-MEB 2012; 2012.

141. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. The Journal of the American Medical Association. 1999;282(15):1458-65.

142. Zelenetz AD, Ahmed I, Braud EL, Cross JD, Davenport-Ennis N, Dickinson BD, et al. NCCN Biosimilars White Paper: regulatory, scientific, and patient safety perspectives. Journal of the National Comprehensive Cancer Network. 2011;9 Suppl 4:S1-22.

143. Commission Regulation (EU) No 1251/2011 of 30 November 2011 amending Directives 2004/17/EC, 2004/18/EC and 2009/81/EC of the European Parliament and of the Council in respect of their application thresholds for the procedures for the awards of contract, O.J. 319/43 2 December 2011.

144. Koninklijk besluit van 15 juli 2011 plaatsing overheidsopdrachten klassieke sectoren, B.S. 9 augustus 2011.

145. Code de la santé publique, Journal Officiel 1953. Available from: http://www.legifrance.gouv.fr/affichCode.do?cidTexte=LEGITEXT000006072665&dateTexte=20130322

146. L' Assurance Maladie (Améli) Base des médicaments et informations tarifaires [Paris: L'assurance maladie en ligne;2012 [cited September 26, 2012]. Available from: http://www.codage.ext.cnamts.fr/codif/bdm_it/index_presentation.php?p_site=AMELI

147. Agence nationale de sécurité du médicament et des produits de santé (ANSM) Médicaments biosimilaires - Point d'information [Saint Denis: Agence nationale de sécurité du médicament et des produits de santé;2011 [cited September 26, 2012]. Available from: http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Medicaments-biosimilaires-Point-d-information

148. Chevreul K, Durand-Zaleski I, Bahrami SB, Hernandez-Quevedo C, Mladovsky P. France: Health system review. Health systems in transition. 2010;12(6):1-291, xxi-xxii.

149. Cubaynes MH, Noury D, Dahan M, Falip E. Le circuit du médicament à l'hôpital. Tome I. Paris: Inspection générale des affaires sociales; 2011. RM2011-063P

150. Groupe permanent d'étude des marchés soins et laboratoires (GPEM/SL). Guide d'approvisionnement des médicaments, des dispositifs médicaux stériles et autres produits du domaine pharmaceutique. Paris: Ministère de l'économie et des finances. Groupe permanent d'étude des marchés soins et laboratoires; 2002. Available from: http://www.economie.gouv.fr/files/files/directions_services/daj/marches_publics/oeap/gem/dispomedic/dispomedic.pdf

151. Guéniot C Médicaments génériques [Paris: Encyclopaedia Universalis;2012 [cited September 26, 2012]. Available from: http://www.universalis.fr/encyclopedie/medicaments-generiques/1-la-promotion-du-generique-en-france/

152. Kanavos P, Taylor D. Pharmacy discounts on generic medicines in France: is there room for further efficiency savings? Current Medical Research and Opinion. 2007;23(10):2467-76.

153. Lopes S, Marty C, Berdai D. PHIS Hospital Pharma Report - France. Paris: Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAMTS); 2009. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/CountryInformationReports/PHIS%20Hospital%20Pharma%20France%202009.pdf

154. MEDISPAR Médicaments à dispensation particulière. [Paris: Ordre national des pharmaciens;2012 [cited November, 2012]. Available from: http://www.meddispar.fr/Medicaments/

155. Ministère des affaires sociales et de la santé Les spécialités pharmaceutiques prises en charge en sus des prestations d'hospitalisation [Paris: Ministère des affaires sociales et de la santé,;2009 [cited November, 2012]. Available from: http://www.sante.gouv.fr/les-specialites-pharmaceutiques-prises-en-charge-en-sus-des-prestations-d-hospitalisation.html

156. Safon MO, Suhard V, Pichetti S. La politique du médicament en France. Paris: Institut de recherche et documentation en économie de la santé (IRDES); 2012.

157. College voor Zorgverzekeringen (CVZ) Preferentiebeleid biologische geneesmiddelen [Utrecht: College voor Zorgverzekeringen;2011 [cited November 2012]. Available from: http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/standpunten/2011/sp1109-preferentiebeleid-biologische-geneesmiddelen.pdf

158. CVZ Farmacotherapeutisch Kompas. [Diemen: College voor zorverzekeringen;2012 [cited November 2012]. Available from: http://www.fk.cvz.nl/

159. Kanavos P, Seeley L, Vandoros S. Tender systems for outpatient pharmaceuticals in the European Union: Evidence from the Netherlands, Germany and Belgium. London: London School of Economics; 2009. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/study_pricing_2007/tendering_systems_en.pdf

160. Nederlandse Vereniging voor Hematologie Biosimilars [Nederlandse Vereniging voor Hematologie,;2012 [cited November 2012]. Available from: http://www.hematologienederland.nl/biosimilars

161. Nederlandse Vereniging van ziekenhuizen (NVZ) Add Ons Dure geneesmiddelen [Utrecht: Nederlandse Vereniging van ziekenhuizen;2012 [cited December 2012]. Available from: http://www.nvz-ziekenhuizen.nl/prestatiebekostiging-2012/add-ons-dure-geneesmiddelen/

162. Schafer W, Kroneman M, Boerma W, van den Berg M, Westert G, Deville W, et al. The Netherlands:s: Health system review. 2010. Health System in Transition Available from: http://www.euro.who.int/__data/assets/pdf_file/0008/85391/E93667.pdf

163. Storms H, Schreurs M. PHIS Hospital Pharma Report. The Netherlands. The Hague: Ministry of Health, Welfare and Sport; 2009. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/CountryInformationReports/PHIS%20NL%20Hospital%20Pharma%20Report%202009.pdf

164. Zuidberg C, Vogler S, Mantel A. The pharmaceutical system of the Netherlands. Utrecht: University of Utrecht, Faculty of Pharmaceutical Sciences; 2010.

165. Deutsches Institut für Medizinische Dokumentation und Information (DIMDI) Arzneimittel-Festbeträge [Cologne: Deutsches Institut für Medizinische Dokumentation und Information;2012 [cited 18 december 2012]. Available from: http://www.dimdi.de/static/de/amg/fbag/index.htm

166. GKV-spitzenverband. Rahmenvertrag über die Arzneimittelversorgung nach § 129 Absatz 2 SGB V in der Fassung vom 15. Juni 2012. Berlin: GKV Spitzenverband; 2012. Available from: http://www.gkv-spitzenverband.de/media/dokumente/krankenversicherung_1/arzneimittel/rahmenvertraege/apotheken/AM_20120615_S_RVtg_129_Abs2.pdf

167. Hoffmann F, Glaeske G, Pfannkuche MS. The effect of introducing rebate contracts to promote generic drug substitution, on doctors' prescribing practices. Deutsches Ärzteblatt International. 2009;106(48):783-8.

168. Institut für das Entgeltsystem im Krankenhaus(InEK) Fallpauschalen-Katalog [Siegburg: Institut für das Entgeltsystem im Krankenhaus 2012 [cited 18 december 2012]. Available from: http://www.g-drg.de/cms/G-DRG-System_2012/Fallpauschalen-Katalog

169. Anell A, Glenngard AH, Merkur S. Sweden health system review. Health Syst Transit. 2012:1-159.

170. Chu R, Torstensson D, Pugatch M, . Patient Safety and Comfort. The challenges of Switching Medicines. Stockholm: 2012. Available from: http://www.stockholm-network.org/downloads/publications/Patient_Safety_and_Comfort__The_Challenges_of_Switching.pdf

171. Läkemedelsverket (Medical Products Agency). Utredning av förutsättningar för utvidgat utbyte respektive utbyte vid nyinsättning. Läkemedelsverket. Uppsale: 2011 2011-09-26. Available from: http://www.lakemedelsverket.se/upload/nyheter/2011/Regeringsuppdrag%20utbytbarhet%20rapport%20sept%202011.pdf

172. Pharmaceuticals benefit board (LFN). The Swedish pharmaceutical reimbursement system. 2007. Available from: http://www.tlv.se/Upload/English/ENG-swe-pharma-reimbursement-system.pdf

173. Organisation for Economic Co-operation and Development (OECD). Generic Pharmaceuticals 2009. Paris: OECD; 2010. Policy Roundtables Available from: http://www.oecd.org/competition/abuse/46138891.pdf

174. Sierakowiak A, Syed T. Key decision makers - characterization and analysis of their attitudes toward the authorization process and market of biosimilars in Sweden and Denmark. Stockholm: Karolinska Institutet; 2009.

175. Svensson J. PHIS Hospital Pharma Report. Sweden. Lund: The Swedish Institute for Health Economics; 2009. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/CountryInformationReports/V5%20PHIS%20Hospital%20Pharma%20report%20SE_final%20version.pdf