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Maarit Simi

BIOSIMILAR MEDICINES IN FINNISH HOSPITALS

Introduction of Biosimilar Infliximab

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Introduction of Biosimilar Infliximab

Maarit Simi
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Biologisten lääkkeiden hintakilpailu on ollut vaatimatonta ennen biosimilaarien tuloa markkinoille. Ensimmäinen biosimilaari, somatropin, sai EU:ssa myyntilupansa 2006 ja vuonna 2013 sai myyntiluvan ensimmäinen biosimilaari monoklonaalinen vasta-aine, infliximab. Suomi oli yksi ensimmäisistä maista, johon tuote Euroopassa 2013 lanseerattiin. Esimerkiksi, Pohjoismaista Ruotsi ja Tanska lanseerasivat myöhemmin, 2015 helmikuussa. Infliximabin alkuperäisvalmiste, Remicade, oli Suomessa tukkuohjehinnoin vuoden 2014 ja 2015 tilastoissa suomen viiden myydyimmän lääkevalmisteen joukossa.

Infliximab on sairaalavalmiste ja biosimilaarin infliximabin tultua markkinoille, oletettiin sen aiheuttavan hintakilpailua ja tuovan sairaaloille säästöjä. Opinnäytetyön tarkoituksena oli selvittää biosimilaarien käyttöönottoa Suomen sairaaloissa, selvittää toteutuiko hintakilpailu, saavutettiinko säästöjä ottamalla biosimilaari käyttöön, sekä mihin säästetyt rahat käytettiin. Tutkimus toteutettiin Word-pohjaisella kyselyllä, ja lähetettiin sähköpostitse ryhmille, joilla on käyttökokemusta biosimilaarista infliximabista, tai jotka ovat vastuussa lääkehankinnoista tai budjeteista. Teoriaosuudessa on selvitetty mitä biologisilla ja biosimilaareilla lääkkeillä tarkoitetaan, kartoitettiin biosimilaarien asemaa muissa Euroopan maissa sekä selvitettiin biologisten lääkkeiden käyttöä ja kustannuksia Suomessa. Tiedon lähteinä käytettiin mm. IMS-tilastoja, Fimean ja EMA:n julkaisuja, sekä alan lehtiä. Tietoja etsittiin myös PubMedin kautta. Mielenkiinto tehdä opinnäytetyö aiheesta lähti kirjoittajasta itsestään.

Tutkimuksista saatujen tulosten mukaan, infliximab oli vuonna 2015 sairaaloiden kolmanneksi kalleimpien biologisten lääkkeiden joukossa (ostohinnoin laskettuna) ja biosimilaarin infliximabin aiheuttaman hintakilpailun avulla sairaaloissa saavutettiin lääkekustannussäästöjä, jotka useimmiten käytettiin lääkekustannusten hallintaa. Toisaalta biosimilaarin infliximabin käyttöönotto mahdollisti myös uusien lääkkeiden käyttöönoton sairaalan valikoimassa sekä useamman potilaan hoidon infliximab-valmisteella. Myös yritys, joka markkinoi infliximabin alkuperäisvalmistetta, Remicadea, lähti hintakilpailuun mukaan laskemalla hintaansa ainakin osissa sairaaloissa jo ennen kuin biosimilaari infliximabi osallistui ensimmäisen kerran tarjouskilpailuun. Apteekkareilta saatujen arvioiden mukaan markkinoille tulevien uusien biosimilaarien odotetaan mahdollistavan kustannussäästöjä seuraavan viiden vuoden aikana yksittäiselle sairaalalle enimmillään jopa 5 miljoonaa euroa.

Uusia biosimilaareja on tulossa markkinoille lähitulevaisuudessa ja olisikin mielenkiintoista selvittää myös näiden valmisteiden osalta millaiseksi hintakilpailu sairaaloissa muodostuu. Lähtevätkö käytettävät alkuperäisvalmisteet hintakilpailuun mukaan ja millainen hintaero on biosimilaariin. Toisaalta markkinatilanne on myös muuttumassa biosimilaarien osalta, kun biosimilaareja, jolla on sama vaikuttava aine, tulee markkinoille ja tuotteet alkavat kilpailla keskenään. Olisi mielenkiintoista tietää, miten tämä tulee vaikuttamaan lääkkeiden hinnoitteluun.

Asiasanat: Biosimilaari, biologinen lääke, kustannussäästöt, kustannuspaineet, lääkekustannukset

ABSTRACT

Oulu University of Applied Sciences
Technology Business

Author: Maarit Simi
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Price competition for biological medicines has been modest before the arrival of biosimilars on the market. In Europe, the first biosimilar, somatropin, was approved in 2006 and the first biosimilar monoclonal antibody, infliximab, more complex biological medicinal product, was approved in 2013. Finland was one of the first European countries to able to launch the biosimilar infliximab in the autumn of 2013. Several other countries, such as Denmark and Sweden, launched the product in February 2015. The originator infliximab, Remicade, was one of the ten best-selling pharmaceuticals in wholesale prices in Finland in 2014 and 2015.

Infliximab is a hospital product and after biosimilar infliximab entered the markets, it was assumed to cause price competition and to generate savings for hospitals. The purpose of the thesis was to find out about the introduction of biosimilars in Finnish hospitals, to determine whether price competition was achieved, whether savings were achieved by using the biosimilar and how the savings were used. The study was carried out using a Word-based questionnaire which was emailed to groups with clinical experience of biosimilar infliximab or who are responsible for budgets or drug purchasing. In the theoretical part, what is meant by biological and biosimilar medicines,
the situation of biosimilars in other European countries, and the use and cost of biological medicines in Finland were investigated. The sources of information were, IMS statistics, Fimea and EMA publications, and professional magazines. Information was also searched through PubMed. The author's own interest in and familiarity with the topic were the reasons for the choice of subject.

According to the results of the studies, in 2015, infliximab was among the third most expensive biological medicines in the hospitals (at purchasing prices). Hospitals were able to achieve cost savings by using biosimilar infliximab and in most cases savings were used to manage medication costs. In addition, the cost savings did enable commissioning of new medicinal products to the pharmaceutical formulary and made also possible to treat more patients with the infliximab. Also, a company that markets the infliximab originator product, Remicade, participate in the price competition by lowering its price (at least in some hospitals) already before the biosimilar infliximab took part in the tendering for the first time. According to estimates from pharmacists, new biosimilars entering the market are expected to provide cost savings of up to EUR 3 - 5 million for a single hospital over the next five years.

More biosimilars are coming into the market in the near future, and it would be interesting to follow, how biological medicines price competition in hospitals evolves. Will the originator products participate in the price competition and what will be the price difference between the biosimilar and originator? On the other hand, the market situation is also changing with regards to biosimilars because

more biosimilars with the same active substance enter the market and the biosimilars start to compete against each other. It would be interesting to know how this will affect the pricing of biological medicines.

Keywords: Biosimilar, biological medicines, cost savings, cost pressure, cost of medicines

CONTENTS

ABBREVIATIONS

Abbreviation	Explanation	Page
R&D	Research and development	24, 31
EMA	European Medicines Agency	3, 5, 25 ,28, 38, 40, 42-47, 68, 198
MIA	Manufacturer's and Importer's Authorization	26
GMP	Good Manufacturing Practice	26
IP	Intellectual Property	32
TRIP	Trade-Related Aspects of Intellectual Property Rights	32
EPO	European Patent Office	30, 32, 55-60, 62
PCT	Patent Cooperation Treaty	32
SPC	Supplementary Protection Certificate	33-34, 68
RDP	Regulatory Data Protection	33
EEA	European Economic Area	39, 43, 53, 57-59
WHO	World Health Organization	40, 82, 90, 104
FDA	Food and Drug Administration	40, 48
PK	Pharmacokinetic	43, 45
PD	Pharmacodynamic	45
API	Active Pharmaceutical Ingredient	31, 44
AIFA	Italian Medicines Agency	47
MEB	Medicines Evalution Board	47
FIMEA	Finnish Medicines Agency	49, 72, 88, 90-91, 125-126, 205
NHS	National Health Service	51, 63-64
BSG	The British Society of Gastroenterology	63
NICE	National Institute for Health and Care Excellence	64, 72
RADS	Council for the High-Cost Hospital Medicines?	64-65, 70
DKMA	Danish Medicines Agency	64
LIS	Drug procurement cooperation - Norwegian tender system to reduce cost of expensive medicines	70
DRG	Diagnosis-Related Group	70
ECCO	European Crohn's and Colitis Organization	73
ESMO	The European Society for Medical Oncology	73
mAb	monoclonal antibody	30, 77
ROB-FIN	National register for Biologic treatment in rheumatoid diseases in Finland	78-79
HPV	Human Papillomavirus	79
QALY	Qualite Adjustet Life Year	81
THL	Terveyden ja hyvinvoinnin laitos - National Institute for Health and welfare	81
RA	Rheumatoid Arthritis	81-84

HUS	Hospital District of Helsinki and Uusimaa	71, 81, 85-86
sDMARD	Synthetic Disease-Modifying Anti-Rheumatism Drug	82
bDMARD	Biological Disease-Modifying Anti-Rheumatism Drug	52, 82-85
DMARD	Disease Modifying Anti-Rheumatism Drug	85
HUCH	Helsinki University Central Hospital	86
TUCH	Turku University Central Hospital	86
TAUH	Tampere University Hospital	86
KUH	Kuopio University Hospital	86-87
OUH	Oulu University Hospital	86-87
ERA	Expert Responsibility Area	86
SHA	System of Health Accounts	92
GDP	Gross Domestic Product	82, 93-95, 100-102
OTC	Over the Counter medicines	95
DDD	Defined Daily Dose	58, 60, 62, 65-66, 95, 99-100, 104-105, 107, 114-116
Response rate	Number of completed surveys/number of emails sent	118, 120, 121

LIST OF APPENDICES

1 INTRODUCTION

Pharmaceuticals have a vital role in the healthcare system. The affordability and financing of new medicines challenges governments worldwide and policy makers are balancing the access of patients to new effective pharmaceuticals with limited healthcare budgets.

Biological medicines are often remarkably expensive due to the highly demanding manufacturing processes, high drug development costs and significant therapeutic values. However, one of the main reasons for the high price tag has been the lack of competition in prices. Most biological medicines have been under patent protection, and have not therefore been under price competition which would have lowered their prices. In recent years, first patents of biological products have expired and biosimilars have become to the market.

Biosimilar medicines are an important subclass of biopharmaceuticals, versions of existing biopharmaceuticals, for which marketing exclusivity rights have expired. The active substance of the biosimilar is, from a scientific and regulatory point of view, just another version of the active substance of the originator product. In Europe, first biosimilar was approved in 2006 (somatropin/Omnitrope) and first biosimilar monoclonal antibody (infliximab/Remsima and Inflectra), more complex biological medicinal product, was approved in 2013. Biosimilar infliximab challenged hospital decision-makers and clinicians to think about the status of a biological originator product in a new competitive environment.

Biosimilar products are increasingly entering the market, not only from the so-called generic pharmaceutical companies but also from companies traditionally known as innovative pharmaceutical companies. Biosimilars are expected to increase price competition and reduce prices of biological medicines. Competition in the market resulting from the introduction of cost-effective biosimilars will save the EU several billion euros annually and when biosimilar monoclonal antibodies are included, will potential savings be much greater.

Finland was one of the first European countries to be able to launch the biosimilar infliximab in the autumn of 2013. Several other countries, such as Denmark and Sweden, launched the product in February 2015. Biosimilar infliximab challenged hospital decision-makers and clinicians to think about the status of a biological originator product in a new competitive environment.

2 RESEARCH PROBLEM AND THE OBJECTIVES OF THE STUDY

The author had worked with biosimilar products for several years in pharmaceutical industry and the author's own interest in and familiarity with the topic were the reason for the choice of subject.

The main purpose of this research is to understand the introduction of the biosimilar infliximab in Finnish hospitals, the impact of biosimilar on the pricing of the originator products and to find out how savings, achieved by biosimilar competition, were used and what is expected of future biosimilars. The objective is to reinforce awareness of the potential of biosimilars to promote price competition of biological medicines and to show that biosimilars are seen in the hospitals as a cost-effective alternative to the high-priced branded biologics, offering cost advantages to both payers and patients.

To achieve these objectives, as well as to fill gaps discussed in the previous chapter, the main research questions and sub-questions are described as follows:

1) How biosimilar product is positioned at the present time in hospital pharmaceutical formulary.
2) Are the studies conducted for biosimilars extensive enough, from where the respondents have received information about biosimilars and is there need for more information.
3) What preparations were made before switching patients from originator product to biosimilar product, did switching affect the efficacy and safety and was some follow-up done.
4) What do the respondents think about switching between biosimilars (same active substance) and what should be taken into account in this kind of a switch.
5) What are the main barriers to wider uptake of biosimilars.
6) What did the respondent expect the price difference to be between the originator and the biosimilar product when it was first time selected to the pharmaceutical formulary, what was the real price difference and did the originator product’s price change when compared to the previous purchasing period.
7) Were medicinal cost savings realized and how the saved money was used.

8) What is expected from the future biosimilars in hospital use, are they going to affect the price of the originator product, what might be the price difference between the originator and the biosimilar product and are medicinal cost savings expected to occur.

3 STUDY DESIGN

The research method of this thesis was a qualitative study. Microsoft Word spreadsheet questionnaires were designed to gather information and opinions about biosimilar experiences and the estimates of cost savings achieved. On top of that, medicinal cost saving in the future were questioned about. Questionnaire gathered data from specified target groups, which included chief physicians from rheumatology and gastroenterology and also hospital chief pharmacists. Chief Assessment Physicians, Medical Directors and Heads of Departments were also targeted, but the number of responses received from them was very modest. These target groups were chosen, because they have experience of biosimilar infliximab. When designing the questionnaire, additional expertise was provided by Professor, Department Head Tuulikki Sokka-Isler, Docent, Ph.D. Pekka Kurki and Hospital Chief Pharmacist. Oncologists were also a target group in the beginning, but the responses were not analyzed, due the lack of replies. Only one Specialist Oncology, two Heads of Pharmacy and two Heads of Departments returned the questionnaire.

The survey was conducted by sending a questionnaire to the target group via e-mail. There were two types of questionnaires, which were slightly different from one another. The pharmacists received a different form than the other target groups. The first questionnaire was sent on October 1, 2016 and the reminder was sent from 21 to 25 October 2016.

The biosimilar products chosen for questionnaire were infliximab and filgrastim. Only infliximab responses are analyzed in this thesis. Analysis concerning filgrastim were left out, because of lack the of responses from oncology.

The theoretical part aimed to identify the challenges of the high costs of biological medicines and to explain the reasoning behind of welcoming of biosimilars to the market. In the literature review, the patent system, the exclusive marketing rights of biological medicines and the cost pressures created by biological drugs were investigated. Also as part of the study was the introduction of biosimilars in the Nordic countries, and how the attitudes in different countries to biosimilars have changed in recent years and what is being done to reduce the pressure of increasing costs of medicines in Finland. Information has been searched for an example from PubMed, Fimea and Emea pages, and medical publications.

4 STUDY METHOD

In the fourth chapter, the theory of qualitative research method is briefly presented.

4.1 Research method

The main focus is directed to explorative qualitative research in this study. The basic idea of qualitative research is to reflect the real life. As a research method, it aims for comprehensive information acquisition, in which the research material is compiled in natural or real situations. Qualitative study author often uses people as tools for data collection and trusts both conversations that have taken place and own observations. (Hirsijärvi, Remes & Sajavaara 2007, 157, 160.)

Understanding the perspective of the participants is goal of qualitative research. The author of a qualitative research has an active role and the goal is to find out what the phenomenon to be studied is from the point of view of the people involved in the study, that is, what is reality from their point of view. Through this study, this reality is structured and the theory of reality is formed. (Kylmä & Juvakka 2007, 28-29.)

Qualitative research is guided by questions such as what, why and how. In addition, qualitative research is characterized by the fact that only a small amount of research data is available on the research topic. (Kylmä & Juvakka 2007, 31.) The purpose of qualitative research is to raise unexpected issues and to find or reveal facts, rather than finding arguments for claims already made. Informants are selected appropriately, and therefore, the cases being investigated are treated as unique. Uniqueness is also taken into account when interpreting the collected material. Flexibility and modification of plans when circumstances so require fall into the features of qualitative research. (Hirsijärvi, Remes & Sajavaara 2007, 157, 160.)

4.2 Informers

For qualitative research, it is important that the people from whom the information is to be collected have as much information as possible about the matter being investigated or have personal experience with it. On the basis of this idea, reporting informants are chosen with discretion. (Tuomi & Sarajärvi 2003, 87-89.)

4.3 Collection of material

Generally, a qualitative study is a discretionary sampling. The units, that are being investigated, are not selected a very large amount, are thoroughly explored, and the quality of the material is important. The size of the material is also important and the material should be comprehensive in relation to what kind of analysis and interpretation it is intended to make. The aim is to select the material appropriately and explain it theoretically. (Eskola & Suoranta 2014, 18, 60-61.)

4.4 Handling and analysis of material

When processing the data, the responses were compiled into tables by target group and were summarized. The compilation revealed the dispersion of the closed questions, and all the options for open issues.

5 REVIEW OF LITERATURE

The literature review deals the theory of biological and biosimilar drugs and surveys how biosimilars have affected the market and cost of biological medicinal products.

5.1 What is biological medicinal product?

A biological medicinal product contains one or more active substances made by or derived from a biological source. Some of the active substances of biological medicines may already be present in the human body, like insulin, growth hormone and erythropoietin. The active substances of biological medicines are larger and more complex than those of non-biological medicines and such complexity can be reproduced only by living organisms. Biological medicines complexity and the complex process of the production may result in a degree of variability in molecules of the same active substance, particularly in different batches of the medicine. Because of live cells and complex manufacturing and purification processes, the active substances of the biological medicinal products are often heterogeneous mixtures. (Europeans Medicines Agency (h) 2012, 1; Fimea (a), accessed 6 October 2016, 1.)

Previously biological medicinal products were developed mainly for rare diseases. Nowadays biotechnology has enabled the development of treatments for a variety of serious, common diseases including cancers, heart attacks, stroke, multiple sclerosis, diabetes, rheumatoid arthritis and autoimmune diseases. (European Commission 2015, 2; Fimea (a) 2016, accessed 6 October 2016, 1.)

There is over 30 years of experience with biological medicines in Europe. Biosynthetic "human" insulin was the first approved substance for therapeutic use, first marketed in 1982. Worldwide, many million patients have already benefited from approved biological medicines which are showing to have better long term outcomes with fewer costly side effects. Studies have also shown that biological medicines treatment leads to quicker recovery time and less additional treatments. One of the most important advantages for the patient of being treated with biologic medicines is the improvement in quality of life over the long term. (European Commission 2015, 2 – 4.)

Recent analyses suggest that over 1500 medicines are currently in development, targeting diseases across a wide range of therapeutic areas from cancer to diabetes and infectious diseases (figure 1). Biologics represent 42% of the total number of medicines in the pipeline while accounting just 8% of currently marketed products (figure 2). Biological medicals are typically priced at €10 000–100 000 per patient per year or more. According the analysis from the Tufts Center for the Study of Drug Development, published 2013 November, the pharmaceutical industry has shifted its R&D focus from small molecule drugs to a biotechnology products. For example, only 13 biotechnology products were commercially available in 1989 compared to 2012 when the number of marketed biotechnology products had grown to 210. Between 2001 and 2012 global biotechnology product sales increased from US$36 billion to US$163 billion. Over 245 biologic medicines representing 166 different active substances were authorized in the EU and US by 2014. (WHO 2015, 30; EvaluatePharma 2012, 8-9; Tufts Center for the Study of Drug Development. 2013; Mitragotri et al. .2014, 1; Medicines for Europe (a), accessed 9 November 2017.)

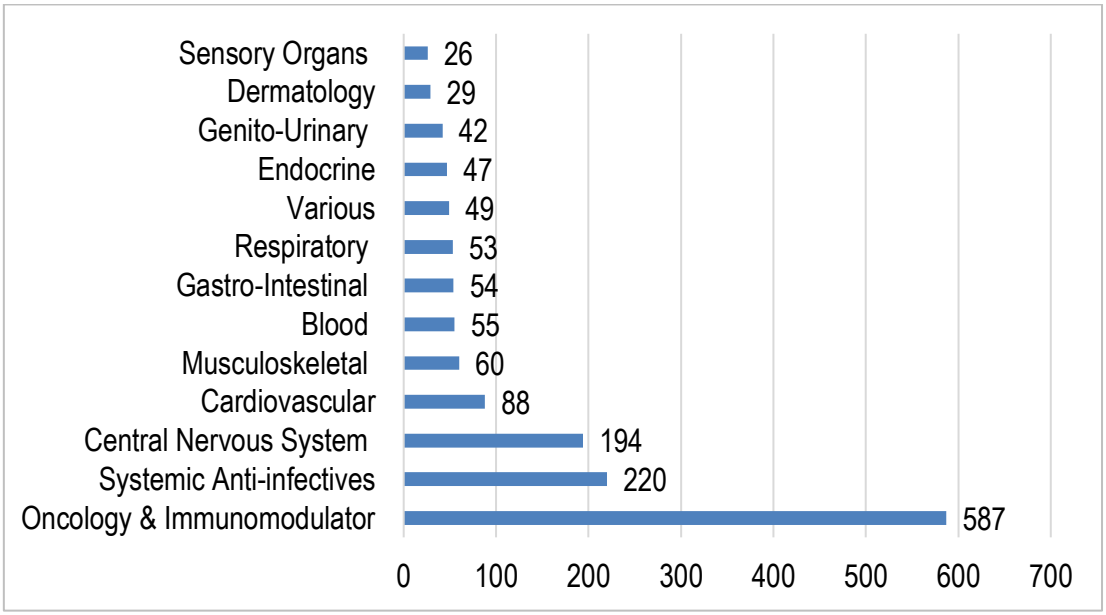


FIGURE 1. New medicines in development/pipeline among the NASDAQ group of companies, by therapeutic area, May 2012 (EvaluatePharma 2012, 9)

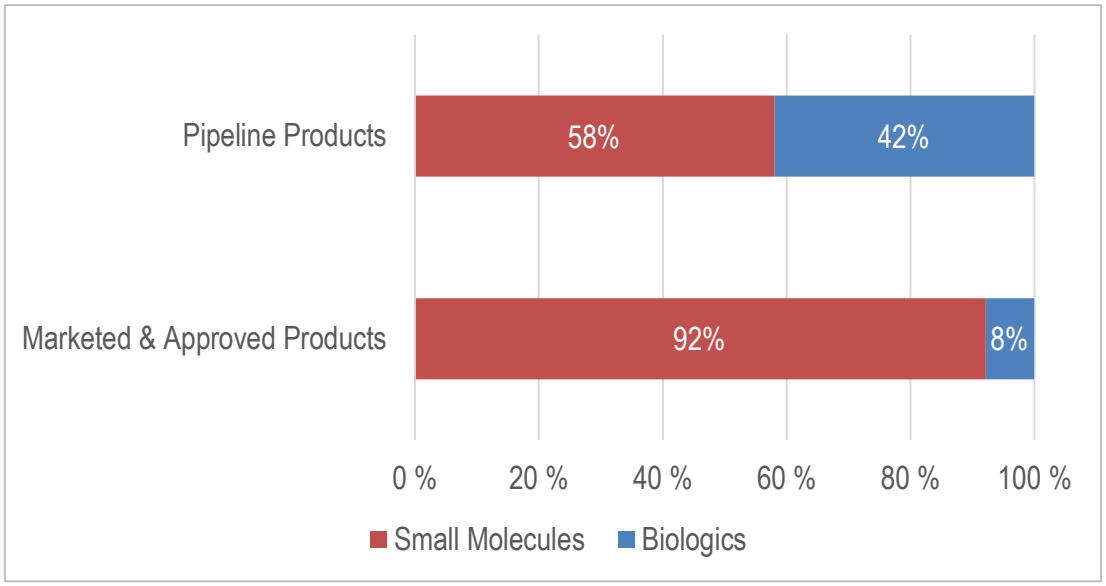


FIGURE 2. Percentage of small molecules and biologics in the pipeline and on the market/approved (EvaluatePharma 2012, 8)

"Biological medicinal products are believed to hold significant position in the future of medication, as already half of the products under development are biological medicinal products" (Fimea (a), accessed 6 October 2016, 1).

5.1.1 Definition of European Medicines Agency

EMA'S (European Medicines Agency) definition of biological medicinal products according Part I of Appendix I of Directive 2001/83/EC is that a biological medicinal product is a product that contains a biological substance. A biological substance is produced by or extracted from a biological source and 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. (European Medicines Agency (g) 2015, 6.)

As biological medicinal products are considered for example, recombinant proteins, monoclonal antibodies, medicinal products derived from human blood and human plasma, immunological medicinal products and advanced therapy medicinal products (gene- and cell therapy medicinal products and tissue engineered products). (European Medicines Agency (g) 2015 ,6; Fimea (a), accessed 6 October 2016.)

It should be noted that all substances which are extracted from a biological source are not biological medicinal products. These products are classified as chemical medicinal products, for example antibiotics which are produced in yeast/mold or polysaccharides, which can be accurately analyzed and for which there is no viral risk. (Fimea (a), accessed 6 October 2016.)

5.1.2 How are biological medicinal products produced?

Biotechnology uses modern technologies and living organisms, such as plant or animal cells, bacteria, viruses and yeast, to produce biological medicines. Many biological medicines are made by using genetically modified cells. Each manufacturer develops their own proprietary manufacturing processes and has their own unique cell lines. A complex process of the manufacturing of biological medicines involves several very sensitive processes (figure 3). It is vital to control those processes to obtain consistent results and to be able to guarantee the safety and the efficacy of the final product. (European Commission (b) 2013, 7-8.)

In the European Union, approved medicine manufacturers and importers, are legally obliged to hold a valid Manufacturer's and Importer's Authorization (MIA)/Good Manufacturing Practice (GMP) certificate issued by an EU national competent authority. An MIA/GMP certificate is granted if the manufacturing or importing site complies with the EU Guidelines on Good Manufacturing Practice, including specific provisions for biological medicinal products. (European Commission (b) 2013, 8; Medicines for Europe (b) 2016, 18.)

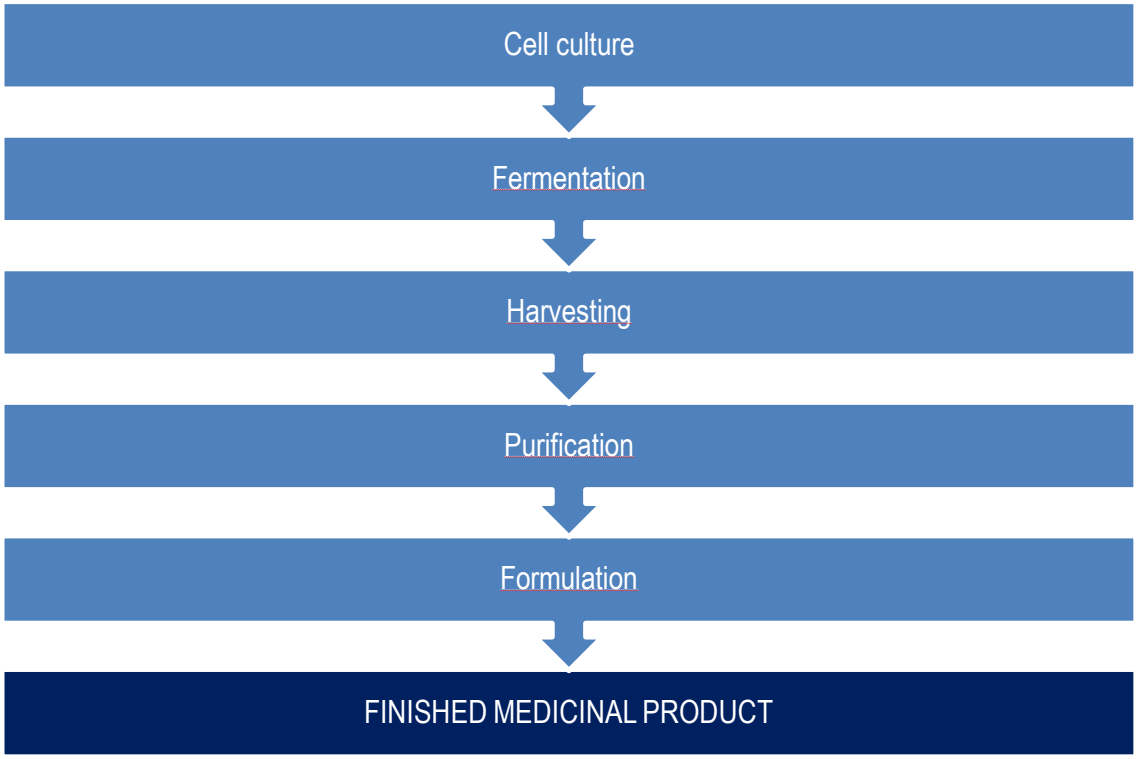


FIGURE 3. Standard production sequence in the manufacture of biopharmaceutical product (adopted from Medicines for Europe (b) 2016, 18)

5.1.2.1 Manufacturing changes of biological medicinal products

Any biological medicine is likely to be modified several times, because the manufacturers of biological medicines frequently make changes to manufacturing processes. These changes can occur during development and after approval of the product and are often seen as improvements. Reasons for the manufacturing changes may for example include improvement of the manufacturing process, increase scale, improve product stability and comply the with changes in regulatory requirements. Changes in manufacturing can be small, like change in the supplier of cell culture media, and range to major ones, like introducing new purification steps or implementing new manufacturing sites. For example, the infliximab biosimilar reference medicine Remicade has had about 40 changes in the manufacturing process for the active substance or the final product since its initial authorization approval (figure 4). It can be argued that the medicine administered to a patient today is not 'identical', but is comparable to the medicine authorized years ago. (Schneider 2013, 315 – 316; European Medicines Agency (a) 2005, 3 – 5; National Institute for Health and Care Excellence 2015, 3; Weise et al. 2014, 3191.)

Any changes in the manufacturing process is to be substantiated with appropriate data and approved by the EMA. When changes are made to the manufacturing process, the manufacturer needs to demonstrate the changes do not adversely impact the safety and efficacy of the drug product. So-called “comparability exercise” is required by the regulatory authorities to evaluate the pre- and post-change product. This evaluation focuses on the relevant quality attributes and depending on the magnitude of the change and the understanding of the existing product, sometimes also comparative data on the non-clinical and clinical level are required. The principles of the comparability exercise are regulated in guidelines such as ICH Q5E, which is issued by International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Q5E is an internationally agreed standard which is intended to assist in the collection of relevant technical information and it provides principles of the comparability of biotechnological and biological products before and after changes are made in the manufacturing process for the drug substance or medicinal product. In the ICH Q5E is stated that “The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are 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 drug product”. The manufacturers and regulators have managed these quality changes for years and have more than 20 years’ experience in assessing the comparability of different versions of a given biological medicinal product. After approval, the products new version is expected to have, in all therapeutic indications, same efficacy and safety. (Fimea (k) 2015, 1; European Medicines Agency (a) 2005, 3 – 5; Schiestl et al. 2011, 310; Schneider 2013, 315 – 316; Weise at al 2014, 3191.)

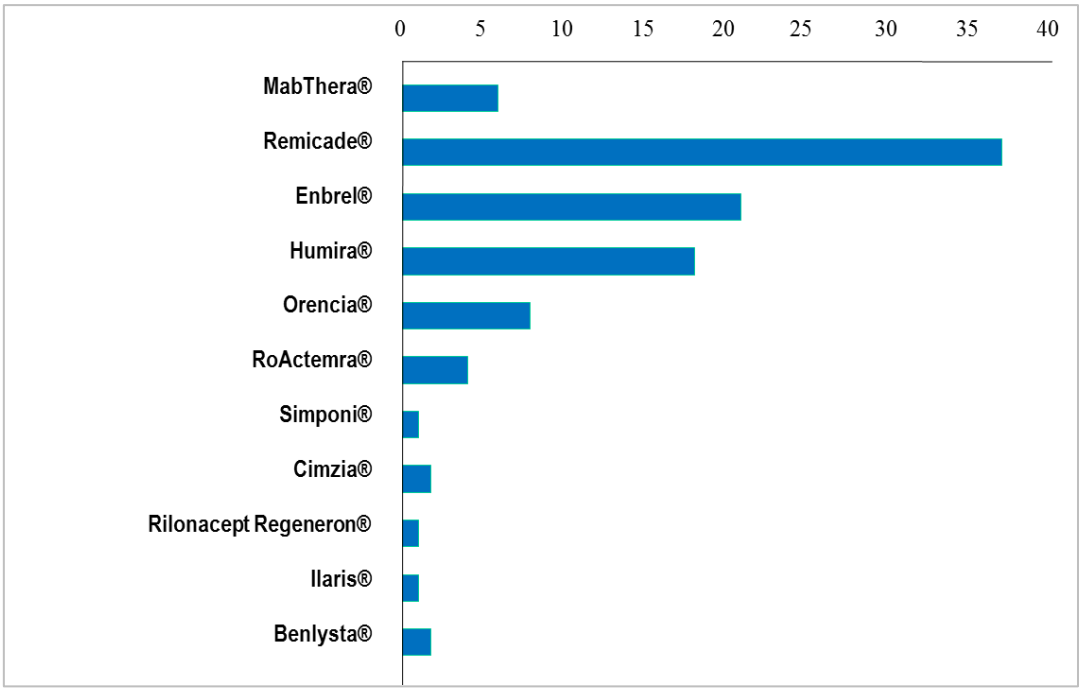


FIGURE 4. Number of manufacturing process changes after regulatory approval (Schneider 2013, 316)

5.2 Biological medicines versus small molecules

Biological medicines differ many ways from small molecule medicines, as shown in table 1. Small molecule medicines are manufactured typically by chemical synthesis whereas biological medicines are generally made in genetically engineered cells. Biologic medicines are significantly more complex structurally than small molecule pharmaceutical medicines and are often 200 to 1 000 times larger. The manufacturing process of biological medicines is more complex than for traditional small molecule medicines and minor changes in manufacturing process can have an impact on medicines efficacy or immunogenicity. Biological medicines are defined as mixtures of many different form of the same protein whereas small molecule medicines have well-defined chemical structure. All the various components of the small molecule medicines can usually be determined while biological medicines are more difficult to characterize due to inherent variability in the molecule. Majority of small molecule compounds are taken orally but administration of most biological medicines must be by injection or infusion because the digestive system affects proteins. (GaBi Online 29 June 2012; European Commission (b) 2013, 8-9; Ganellin et al. 2013, 98; Ezell S 2015, 2.)

Biological medicines contain much larger molecules than conventional pharmaceuticals (figure 5). As an example, a small molecule medicine aspirin measures just 180 Daltons, has 21 atoms and

remains relatively stable over time with little ability to initiate an immune response. Instead a typical monoclonal antibody biological medicine measures 150,000 Daltons and contains 20,000 atoms, degrades over time, and have the inherent potential to induce unwanted immune response. (GaBi Online 29 June 2012; European Commission (b) 2013, 9.)

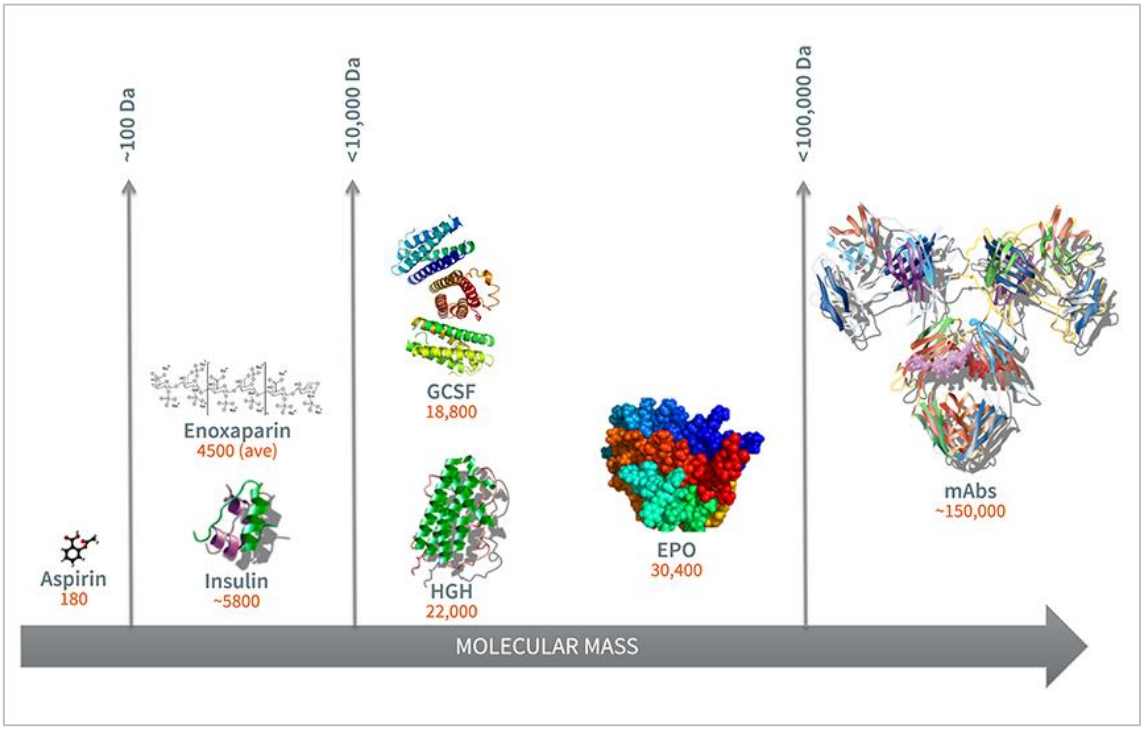


FIGURE 5. Comparison of molecular mass of small molecule medicines versus large biological medicines. Da: Dalton, GCSF: Granylocyte Colony-Stimulating Factor, HGH: Human Growth Hormone, EPO: Erythropoiesis-Stimulating agent, mAbs: Monoclonal Antibodies (Adopted from Amgen (a), accessed 9 October 2016)

TABLE 1. Characteristics of small molecule medications compared to biological medications (GaBi Online 29 June 2012; European Commission (b) 2013, 7-8; Mócsai et al. 2014, 2 - 3, 6; Bechtel 2016, 37)

	Small molecule drugs	**Biological drugs**
Size	Small (single molecule).	Large (mixture of related molecules).
	Generally low molecular weight	Generally high molecular weight

	(< 700 Da).	(> 1 kDa).
Structure	Homogenous drug substance, well defined, independent of manufacturing process.	Heterogeneous mixtures, defined by the exact manufacturing process.
Modification	Well defined	Many options
Manufacturing	Usually produced by organic or chemical synthesis. Predictable chemical process. Fewer critical process steps Identical copy can be made Fewer critical process steps.	Produced with/from live cells/organisms. Difficult to control from starting material to final API. Many critical process steps. Impossible to ensure identical copy.
Characterisation	Well characterised.	Cannot be characterised completely the molecular composition and heterogenicity.
Stability	Stable.	Unstable, sensitive to external conditions.
Immunogenicity	Usually non-immunogenic.	Often immunogenic.
Administration	Oral.	Mostly by injection or infusion.
Manufacturing cost	High.	Low/variable.

5.3 Legal instruments for intellectual property rights protection

In the pharmaceutical sector in the European Union, the industry has different legal instruments at its disposal for intellectual property rights protection. These instruments are patents, supplementary protection certificates, regulatory data protection and a 10-year market exclusivity for orphan drugs (drugs used for the treatment of rare conditions). Patent law grants patent holder a time-limited monopoly for an active pharmaceutical substance in which time originator companies should be able to recoup their R&D investments. Pharmaceutical products can be covered by several patents, sometimes by as many as 30 to 40 patents or more. (Tuominen 2011, 8-9, 24; Roox 2008, 5, 7; GaBi Online 1 July 2011.)

"The large number of patent litigations surrounding launch of generics and biosimilars is a consequence of the difficulty to appreciate the actual date of the loss of Intellectual Property (IP), and the value of some additional patents that research based companies use to reinforce their IP protection" (Creativ-Ceutical 2012, 36). Obstacles with biosimilar entry timing are caused by the facts that there is no centralized listing of biological patents, expiration dates are proprietary information to the companies and each biological medicinal product has formulation patents which are difficult to assess. (Creativ-Ceutical 2012, 36; GaBi Online 30 September 2011.)

5.3.1 Patent system of the EU Pharmaceutical medicinal products

The special characteristics of the patent system influence the pharmaceutical market. The patent system enables pharmaceutical companies, which have research activities, to cope with the competitive pressures of early patent application and the delays in drug approval. (Tuominen 2011, 2.)

Patent system is not completely harmonized within the EU, but it is assumed that the patent systems of the Member States are roughly similar, at least at the level of general principles. This is due to TRIPS Agreement, Member States are parties to the European Patent Convention 2000 and have also adopted some key provisions of the Community Patent Convention. (Tuominen 2011, 9; European commission (d) 2009, 99 – 100.)

Patents in the EU can be obtained either by filing a national application at the national patent offices or by filing application at the European Patent Office (EPO). Most pharmaceutical companies prefer to use the European Patent Office (EPO) which handles centralized patent applications. Most patent filling by European pharmaceutical companies are made in accordance with the Patent Cooperation Treaty (PCT), which gives the possibility of designating almost 140 countries. (Tuominen 2011, 9-10; European commission (d) 2009, 100, 103, 114.)

According Art. 28 of the TRIPs Agreement, third parties are forbidden to manufacture, market or import the product for such purposes. Also, if the patent concerns a process, third parties are precluded from using or marketing that process. (Tuominen 2011, 9 – 10.)

The period of protection is 20 years from the date of the filling from which medicines enjoy roughly 8 to 10 year's effective protection, see figure 6. Usually patent applications are filled early in the

research phase. A branded pharmaceutical derives most profits during the first five- to eight-years of market exclusivity. (Tuominen 2011, 6 – 7.)

5.3.2 Supplementary Protection Certificate (SPC)

For new products, EU has introduced a Supplementary Protection Certificate (SPC), which ensures a maximum of 15 year's market exclusivities, figure 6. Supplementary Protection Certificate extends the initial patent protection by up to 5 years, figure 6. Overall purpose of the Supplementary Protection Certificate regulation is to compensate the patent holder and the holder of the marketing authorization for the time lost while gaining approval for the medicinal product to be placed on the market for human use. (Tuominen 2011, 7, 10 – 11; Intellectual Property Office 2013, 16.)

Regulation EC 1901/2006 grants additional intellectual property protection for exclusive rights against imitation. This regulation aims to facilitate the development and accessibility of medicinal products for use in the pediatric population. As compensation for conducting the pediatric research, the patent holder is entitled to a six-month extension of the protection period. (Tuominen 2011, 11; Official Journal of the European Union 2006, 1.)

5.3.3 Regulatory Data Protection (RDP)

"Regulatory data protection (RDP) is a form of exclusive right enforced through the marketing authorization procedure". When an originator company releases a new medicine on the market it must provide vast amount of information on its product order to obtain the necessary market authorization. When generic manufacturer brings the same product on the market it must either generate its own data or wait a certain period until it would be permitted to rely on the data provided by the innovator. (Tuominen 2011, 11 – 12.)

In practice the exclusivity rendered by the regulatory data protection is weak for several reasons and data protection period would only be relevant if there was no other intellectual property protection. (Tuominen 2011, 12.)

The generic manufacturer's application for authorization can be used after defined periods of time. Application using the abridged procedure cannot be made in the first 8 years from the date of first

authorization in the Community. After this, requests for generic authorization can be made, but actual marketing cannot take place before 10 years from the first Community authorization have elapsed (figure 6). (Tuominen 2011, 12.)

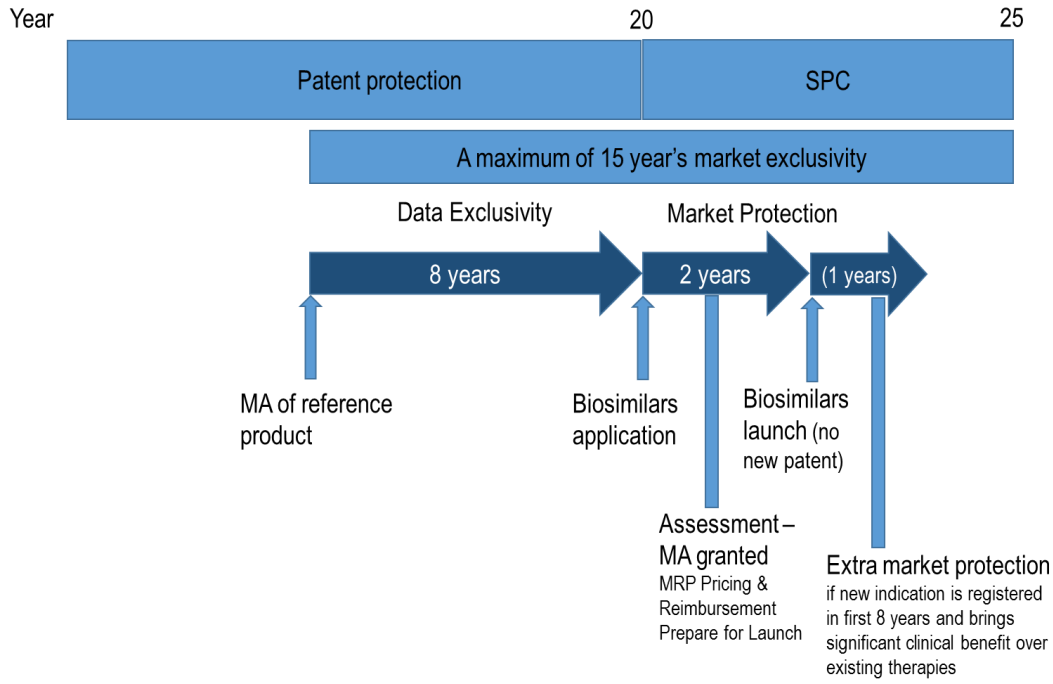


FIGURE *6. Data exclusivity and market protection of the originator product. The 8+2(+1) exclusivity period came into effect in the EU in late 2005 and it does not affect exclusivity periods for products for which applications were submitted before the effective date. SPC = Supplementary Protection Certificate, MA = Marketing Authorization, MRP = Mutual Recognition Procedure (Kurki et al. 2016; Europeans Medicines Agency (e) 2013, 3-5, 31; European Commission (a) 2013, 39 – 40; GaBi Online 1 July 2011)*

5.3.4 Examples of market exclusivity of medicines

In EU in some countries, medicines have experienced as long as 21 years, such as Genotropin in Slovenia, and as low as six years, like Neupogen in Romania, exclusivity times. Genotropin was the first biological medicine facing biosimilar competition in the EU and experienced the largest exclusivity times of the three biological medicines, Genotropin, Eprex/Erypo and Neupogen. When comparing the market exclusivity period of three biological medicines, the median was 17 years and did not differ much among the three products, corresponding medians ranging from 16 to 18 year (table 2). (Labry et al. 2013.)

TABLE 2. Market exclusivity time of biological product (Labry et al. 2013)

Name of biological product	Median time
Genotropin	18
Eprex/Erypo	18
Neupogen	16

All three biological products mentioned have been exposed to biosimilar competition in EU. Genotropin's biosimilar did receive its marketing authorization 2006, Eprex/Erypo's biosimilar 2007 and Neupogen's biosimilar 2008 (table 3).

5.4 What Is biosimilar medicine?

Biosimilar medicines are an important subclass of biopharmaceuticals, versions of existing biopharmaceuticals, for which marketing exclusivity rights have expired (figure 7). The active substance of the biosimilar is, from a scientific and regulatory point of view, just another version of the active substance of the originator product. Weather a biologic medicinal product is classified as a biosimilar medicine or as an original biological medicinal product is related to the degree of innovation of the product and/or its therapeutic application. In other words, original product may be either a new molecular entity, or a slightly modified existing molecule (typically called biobetters, figure 10) and biosimilar is aimed at replicating a well know reference original medicinal product. Biosimilar is intended to contain essentially the same active substance as to original product, to come in the same pharmaceutical form and to be administered via the same route at the same dose for the same, or fewer, indications. (Fimea (i), accessed 27 January 2017; Medicines for Europe (b) 2016, 8; Mora 2015, 952 – 953; Weise et al. 2014, 3191.)

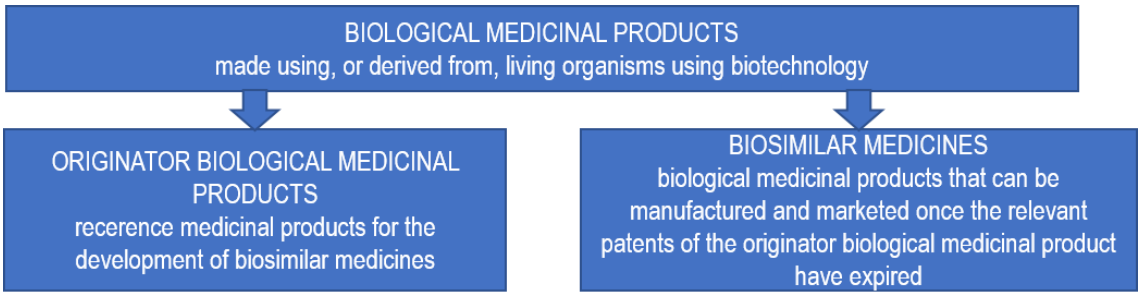


FIGURE 7. Biosimilar medicines are a subclass of biological medicinal products (adopted from Medicines for Europe 2016 (b), 9)

The expiration of data protection or patents for the first-generation original biotherapeutics, followed by patent expiration on the first approved monoclonal antibodies, has led to the development and authorization of copy versions, termed "similar biological medicinal products" (biosimilars) by the European Medicines Agency in the European Union (EU). European Union was first to establish an approval pathway for biosimilars with the publication of the Guideline on Similar Biological Medicinal Products (CHMP/473/04) in October 2005. In Europe, first biosimilar was approved in 2006 (somatropin/Omnitrope) and first biosimilar monoclonal antibody (infliximab/Remsima and Inflectra), more complex biological medicinal product, was approved in 2013 (table 3). (Creativ-Ceutical 2012, 53; European commission 2015, 4; European Medicines Agency (f) 2013; Olech 2016, S1 - S 2, S6).

TABLE 3. List of EU approved medicines (January 2017). In red written products are marketed in Finland (21 December 2016) (Fimea (j), accessed 27 January 2017; VFA 2016; European Medicines Agency (b), accessed 27 January 2017; European Medicines Agency (c), accessed 31 January 2017; European Medicines Agency (d), accessed 31 January 2017, European Medicines Agency (l), accessed 27.1.2017)

Name of biosimilar product	Active substance	Therapeutic area	Date of authorization	Marketing authorization holder (biosimilar)	Reference product	Marketing authorization holder (reference)
Omnitrope®	somatropin	- Pituitary dwarfism - Prader-Willi syndrome - Turner syndrome	12 April 2006	Sandoz	Genotropin®	Pfizer

Abseamed®	epoetin alfa	- Anemia - Autologous blood transfusion - Cancer - Chronic kidney failure	28 August 2007	Medice	Erypo® /Eprex®	Janssen-Cilag
Binocrit®			28 August 2007	Sandoz		
Epoetin Alfa Hexal®			28 August 2007	Hexal		
Retacrit®	epoetin zeta		18 December 2007	Hospira		
Silapo®			18 December 2007	Stada		
Ratiograstim®	filgrastim	- Cancer - Hematopoietic stem cell trans-plantation - Neutropenia	15 September 2008	Ratiopharm	Neupogen®	Amgen
Tevagrastim®			15 September 2008	Teva		
Filgrastim Hexal®			06 February 2009	Hexal		
Zarzio®			06 February 2009	Sandoz		
Nivestim®			08 June 2010	Hospira		
Grastofil®			18 October 2013	Apotex		
Accofil®			18 September 2014	Accord Healthcare		
Inflectra®	infliximab	- Ankylosing spondylitis - Crohn's disease - Psoriasis - Psoriatic arthritis - Rheumatoid arthritis - Ulcerative colitis	10 September 2013	Hospira	Remicade®	Janssen Biologics
Remsima®			10 September 2013	Celltrion		
Flixabi®			26 May 2016	Samsung Bioepis		
Ovaleap®	follitropin alfa	- Anovulation	27 September 2013	Teva	Gonal-f®	Merc Serono
Bemfola®			27 March 2014	Finox Biotech		
Abasaglar®	insulin glargine	- Diabetes mellitus	09 September 2014	Eli Lilly	Lantus®	Sanofi-Aventis
Lusduna®			04 January 2017	Merck Sharp & Dohme		

Benepali®	etanercept	- Ankylosing spondylitis - Psoriasis - Psoriatic arthritis - Rheumatoid arthritis	14 January 2016	Samsung Bioepis	Enbrel®	Pfizer
Inhixa®	enoxaparin sodium	- Venous Thromboembo-lism	05 September 2016	Techdow Europe AB	Clexane	Sanofi-Aventis
Thorinane®			05 September 2016	Phar-mathen S.A.		
Truxima®	rituximab	- Chronic lympho-cytic leukaemia - Granulomatosis with polyangiitis and microscopic polyangiitis - Non-Hodgkin's lymphoma - Rheumatoid arthritis	Initial authorization 15 December 2016	Celltrion	MabThera®	Roche
Amgevita® / Solymbic®	ada-limumab	- Rheumatoid arthritis - Juvenile idio-pathic arthritis - Axial spondyloar-thritis - Psoriatic arthritis - Psoriasis - Pediatric plaque psoriasis - Hidradenitis suppurativa - Crohn's disease - Ulcerative colitis - Uveitis	Initial authorization 26 January 2017	Amgen	Humira®	AbbVie

October 2014, the European Medicines Agency (EMA) defined biosimilar medicinal products as follows (CHMP/437/04 Rev 1): "A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference

medicinal product) in European Economic Area (EEA). Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established." (European Medicines Agency (i) 2014, 4.)

The European Commission has noted that biosimilars have observed enhanced price competition from the original biologics, leading to cost savings for patients, healthcare systems and payers, potentially improving patient access to these treatments. Many governments have, or are in process, enacting legislation to allow for the regulation and licensing of biosimilars with intend to reduce healthcare expenditures while preserving the quality of patient care. Competition in the market resulting from the introduction of cost-effective biosimilars will save the EU several billion euros annually and when biosimilar monoclonal antibodies are included, potential savings are even greater. (Kurki 2015; Olech 2016, S2; Medicines for Europe (b) 2016, 9; Research Advocacy Network, 47, accessed 25 January 2017.)

At the moment, uptake of biosimilars in the EU varies widely between countries and therapeutic areas. Of global spending on biosimilars, Europe accounts for 80 percent. (Ekman et al. 2016.)

5.4.1 Biosimilar is not a generic

Biosimilars cannot be considered generics. The active substance of biosimilar is demonstrated to be similar to its originator, but due to complex nature and production in living systems, it is not feasible to exactly duplicate the approved originator biologicals. Generics, on the other hand, are chemically synthesized small-molecules and are considered to be chemically identical to their reference product. (Heinemann et al. 201, 510; Olech 2016, S3, S4.)

The regulatory pathway pursued to demonstrate equivalence is longer and more complex for biosimilar than for generics. The requirements for marketing authorization of a generic (identical chemical structure, dosage formulation, route of administration and bioequivalence) is not generally sufficient for biosimilars. Instead biosimilars must undergo head-to-head comparison with the originator at every step during development to ensure high similarity in physicochemical and functional characteristics, as well as safety and efficacy (figure 10). (Heinemann et al. 2015, 511; Olech 2016, S3, S5.)

5.4.2 Regulatory pathways of biosimilars

Biosimilar regulatory pathways have been established around the world to provide an abbreviated route for biosimilars. The European Medicines agency (EMA) pioneered the development of regulatory framework for the development and approval of biosimilars in 2005. In 2009, the World Health Organization (WHO) issued global guidelines, "Guideline on evaluating of similar biotherapeutic products", generally following similar principles and requirements to those of the EMA, in attempt to harmonize regulations worldwide. For example, Japan, Korea, Canada, Australia and New Zealand have issued guidance documents and regulations that are generally in line with either WHO or EMA regulations (figure 8). At the moment, regulations vary substantially across countries, but many countries are striving towards harmonization of accepted criteria, such as those set forth by the EMA, FDA and WHO. It should also be noted that in some countries, synthetic copies of brand compounds have been approved without comparative clinical studies with the originator. Developing countries have long-treated copies of biologics primarily as generic equivalents and in many of these market, these underregulated copies of some biologics have been manufactured and even marketed as biosimilars. (Heinemann et al. 2015, 510 – 511, 523; Olech 2016, S7 - S8.)

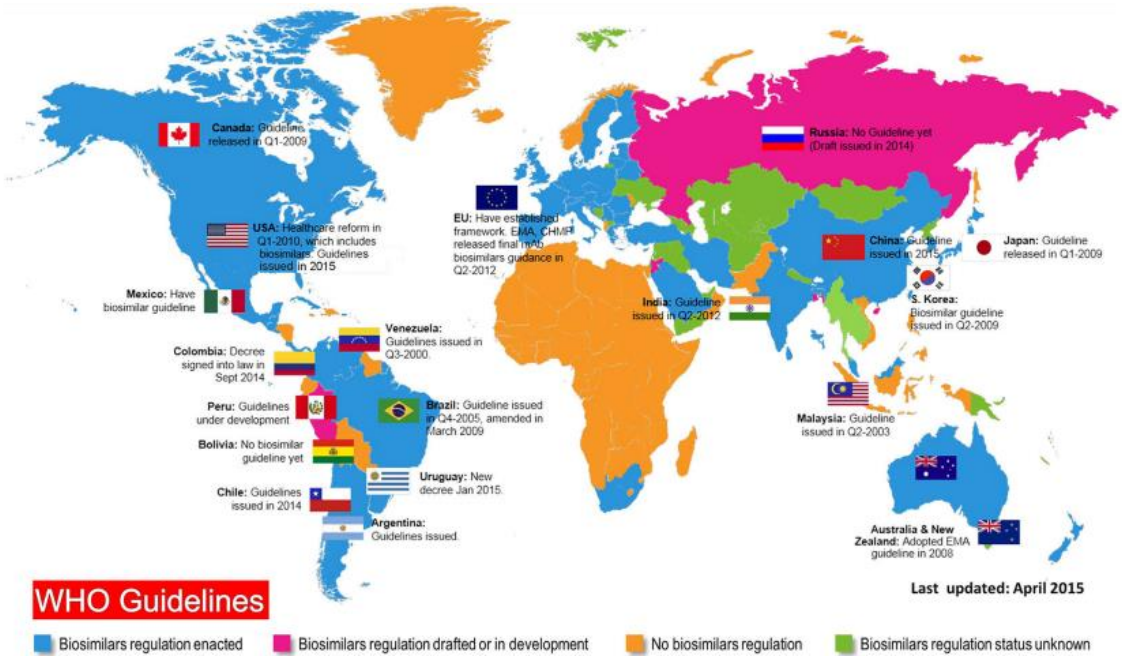


FIGURE 8. Global overview of availability of biosimilar regulatory pathways (adopted from Olech 2016, S8)

5.4.3 Development of a biosimilar medicine

Pharmaceutical company, which plans to develop a biosimilar, has several advantages. Primacy structure, i.e. the amino acid sequence, and expected biological activity of the originator are known. Company can acquire the reference product to analyze its composition and assess it in detail structurally and functionally and is able to analyze batch-to-batch variation (figure 9). It has also access to a wide range of real world clinical data of the original biologic product, licensed and marketed for many years, and has therefore a large body of knowledge of safety and efficacy available. The historical data available helps to determine what evidence and which studies are required for the biosimilar candidate. Also, regulators, responsible for deciding whether a biosimilar candidate is comparable, have extensive knowledge of the original reference product and have often access to information which is not publicly available. Biosimilar manufacturer has no access to the complex production and purification techniques used for the reference product and thus must develop its own manufacturing processes (figure 9). (Heinemann et al. 2015, 510; Mora 2015, 952; Olech 2016, S5.)

Biological medicinal products manufacturing processes are likely to be modified several times throughout their life cycle and thus, originator biological products are not anymore identical to the original version at the time of marketing authorization. Therefore, pre- and post-change version of the biological product needs to be demonstrated to be comparable through a comparability exercise to ensure that quality, efficacy, and safety are not adversely affected. Over the past decades of biotechnology developments, regulators and manufacturers have accumulated extensive experience in assessing the impact of such changes. When a new version of the biological product is approved, it is expected to have the same efficacy and safety in all therapeutic indications. ICH Q5E is an internationally agreed standard intended to assist in the collection of relevant technical information and provide principles of the comparability of biotechnological and biological products before and after changes are made in the manufacturing process for the medicinal substance or medicinal product. The scientific principles of a biosimilar comparability exercise are based on same standard, ICH Q5E, except that the testing is much more extensive (figure 9). (Ekman et al. 2016; European Medicines Agency (i) 2014, 4; European Medicines Agency (a) 2005, 3 – 5; Fimea (k) 2015, 1; Kurki et al. 2013, 208; Weise et al. 2014, 3191.)

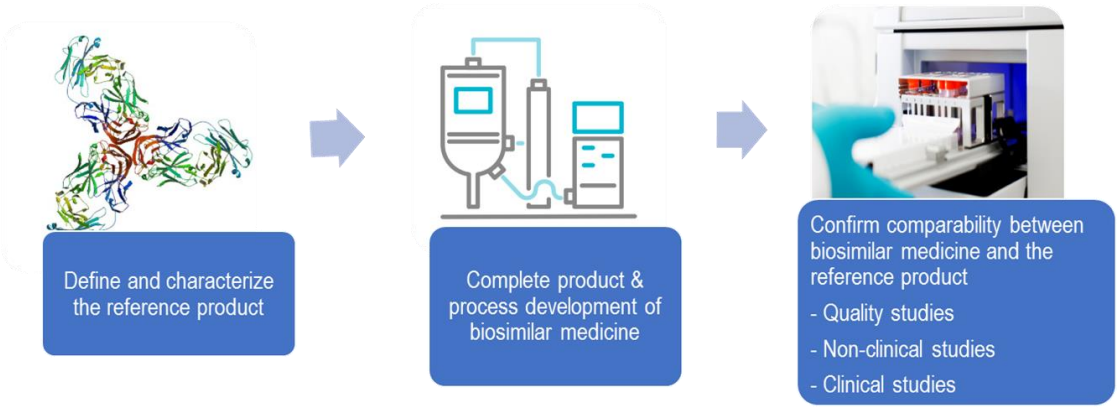


FIGURE 9. Biosimilar development stages (Medicines for Europe (b) 2016: 23; T3DB, accessed 24 January 2017; mAbxience, accessed 24 January 2017; GE Healtcare Life Sciences, accessed 24 January 2017)

All existing EMA quality guidelines for biologicals are also applicable to biosimilars and thus the same quality requirements apply for biosimilars as for any biological medicinal products. The biosimilar specific EU guidance is quite extensive. There is a guideline which gives the general principle relevant to all biosimilars, below that, two general guidelines dealing with biosimilar biotechnology-derived proteins (one for quality, other for non-clinical and clinical issues) and below those are product-class-specific guidelines for the non-clinical and clinical requirements. (Table 4)

TABLE 4. EMA guidelines for biosimilars (Kurki et al. 2015, 650, 652).

Guideline	Main topics	Cover
Overarching guideline CHMP/437/04 Rev 1	- Definition of a biosimilar - Reference medicinal product - General requirements for demonstration of biosimilarity	Biosimilars in any biological product class
General guidelines	- Biosimilar physicochemical and structural comparability exercise - Stepwise development of the non-clinical program - Comparability of human pharmacokinetics - Pharmacodynamic studies - Clinical efficacy and safety studies - Post-marketing risk management	Quality, non-clinical and clinical aspects of biosimilars for biotechnology-derived proteins

Product-class-specific guidelines	- Non-clinical comparability - Comparable pharmacokinetics - Pharmacodynamic markers and surrogates - Recommended study designs and clinical endpoints - Special safety issues, including immunogenicity	Made for product-classes: somatropins, filgrastims, epoetins, insulins, follitropins, alfa-interferons, beta-interferons, monoclonal antibodies, low-molecular-weight heparins

5.4.3.1 Reference product (original biologic medicinal product)

Originally the EMA stated that the biosimilarity exercise must be conducted with a reference product authorized in the EEA. The updated guideline on similar biological medicinal products (CHMP/437/04 Rev 1) has made also possible to use non-EEA-authorized reference products when the aim is to promote global development of biosimilars and avoid unnecessary clinical trials. In this case, certain clinical and in vivo non-clinical studies may be alternatively conducted with non-EEA-authorized reference products if both scientific justification is provided and bridging studies are performed. The Non-EEA-authorized reference product will need to be authorized by a regulatory authority with similar scientific and regulatory standards as EMA (e.g. ICH countries). Bringing data between the proposed biosimilar, the EEA-, and the non-EEA-authorized products should always include a 3-way analytical comparison (structural and functional data) and may also include a 3-way pharmacokinetic (PK) and/or pharmacodynamic (PD) comparison. (European Medicines Agency (i) 2014, 5 – 6; GaBi Online 20 January 2017 (a); Olech 2016, S6.)

5.4.3.2 Comparability to establish biosimilarity

Development process for both originator biological products and biosimilars involve analytical, non-clinical and clinical testing (figure 10). Originators must establish patient de novo and require extensive clinical trials to demonstrate efficacy and safety. The goal of biosimilar is not to re-establish patient benefit per se, but to prove that its safety and efficacy are comparable with the originator biologic's (reference biological medicinal product) and therefore, clinical trials efficacy endpoints differ from those requested for an innovative product. (Mora 2015, 953; Olech 2016, S4 – S5.)

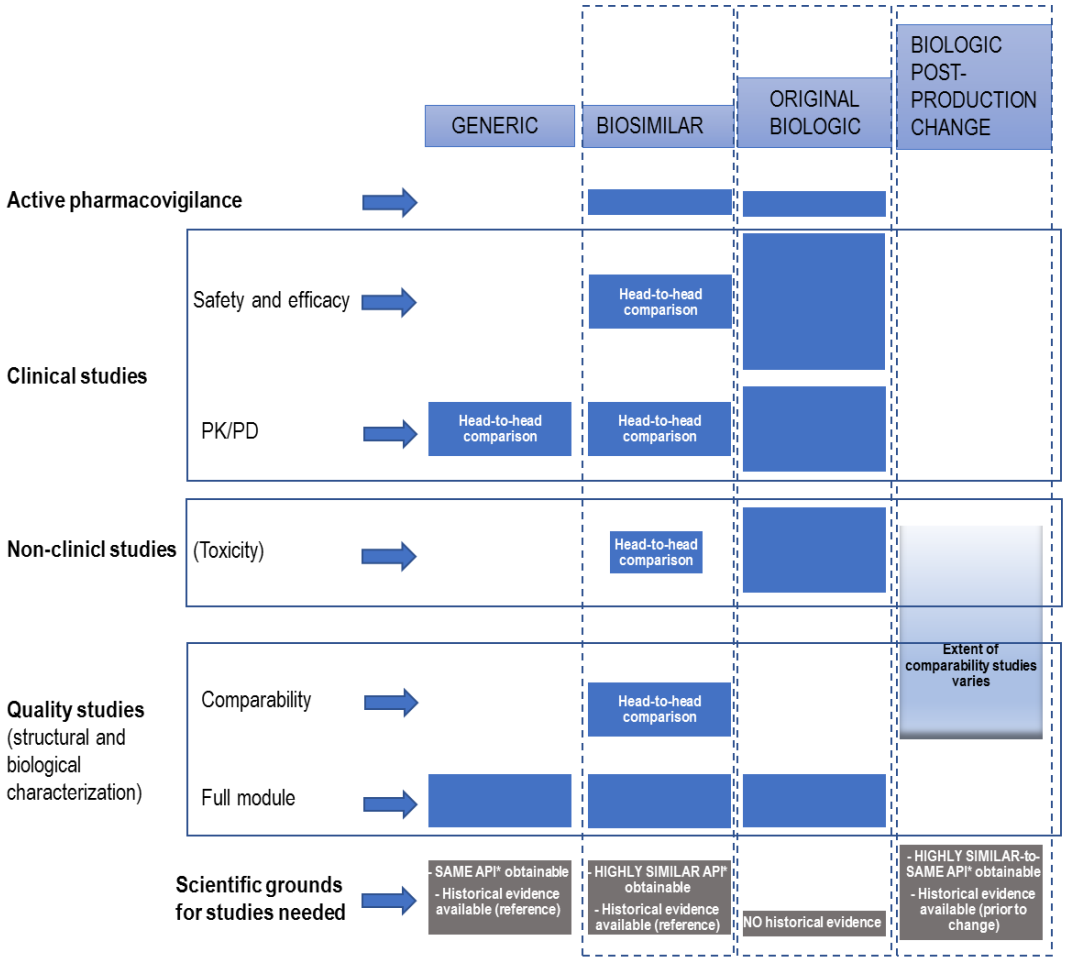


FIGURE *10. Comparative EMA requirements for biosimilar studies vs. studies defined for generics, original biological medicinal product and biologics after manufacturing changes (post-production change), API* = Active Pharmaceutical Ingredient (adopted from Mora 2015, 951)*

For a new innovative biological product with new active substance, the applicant should demonstrate acceptable quality, non-clinical pharmacology and toxicology (figure 10). Also, human pharmacokinetics and pharmacodynamics, safety and efficacy need to be studied in all indications (figure 10). To establish that a biosimilar meets the requirements for biosimilarity, EMA require a rigorous, stepwise biosimilarity assessment, with each step building on previous step (figure 11). A biosimilar has to demonstrate similarity to the reference biological product in terms of quality characteristics, biological activity, pharmacokinetic profile, safety and efficacy based on comprehensive comparability exercise (figure 10, figure 11). The goal of comprehensive comparability exercise is to exclude any relevant differences between the biosimilar and the reference medicinal product. After the comparability has been demonstrated, the holder of the marketing authorization of the biosimilar can refer to the documentation of the reference product. EMA specifies that intended

changes to improve efficacy (biobetters) are not compatible with the biosimilarity approach, and "differences that could have an advantage as regards safety (for instance lower levels of impurities or lower immunogenicity) should be addressed, but may not preclude biosimilarity'". (Ekman et al 2016; European Medicines Agency (i) 2014, 5 - 6; Kurki et al. 2015, 651; Olech 2016, S5.)

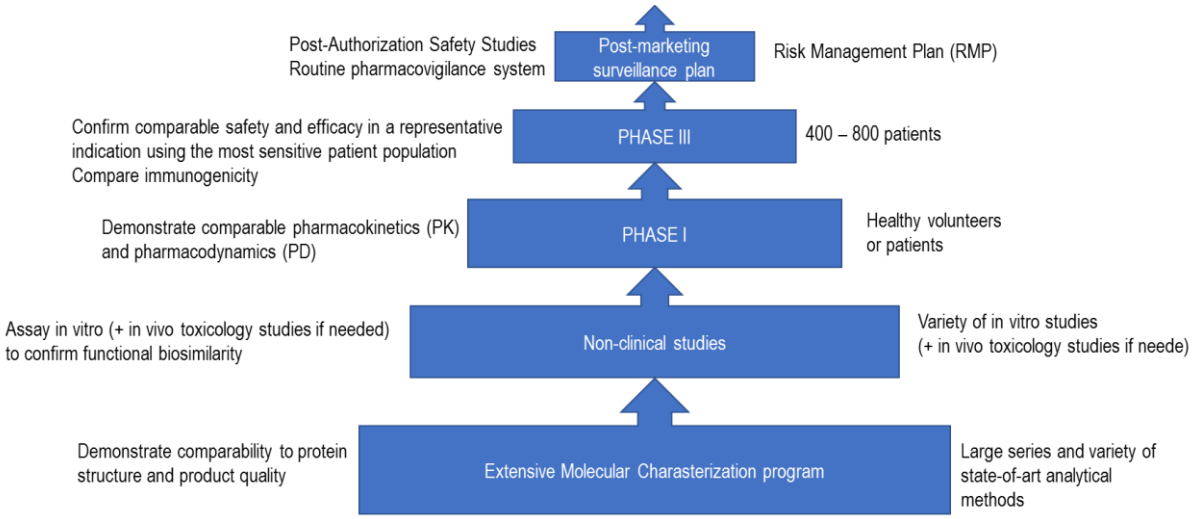


FIGURE 11. The EMA development and approval pathway for biosimilars. A stepwise approach to demonstrate comparability between a biosimilar and the originator reference product (Kurki 2014, 103; Kurki et al. 2013, 209 - 211; Kurki et al. 2015, 653 -656; Ekman et al. 2016)

According to EMA guidelines, a confirmatory clinical trial may not be necessary if similar efficacy and safety can be clearly deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and reference product and the impurity profile and the nature of excipients of biosimilar have not risen a concern. Also, EMA guidance states that if relevant differences are observed between a biosimilar and a reference product, it is unlikely that biosimilarity will be established and instead, a stand-alone development to support a full marketing authorization should be considered. (European Medicines Agency (i) 2014, 6 – 7.)

5.4.3.3 Extrapolation of data

Extrapolation of data has been an established scientific and regulatory principle that has been used for many years. For example, in the major changes in the manufacturing process of originator biological products, clinical data is typically generated in one indication and is extrapolated to the other indications, after the overall information gained from the comparability exercise has been taken in

to account. So far, the authors are not aware of any case where additional clinical studies with the changed product in other or even all approved indications have been provided by the marketing authorization holders, or have been considered by regulators. (Weise et al. 2014, 3192.)

For biosimilars, clinical comparability is usually confirmed in randomized, preferably double-blind clinical trial(s). The selected therapeutic approach should correspond to one of the approved reference product's therapeutic indications, suitable to detect potentially clinically relevant differences (figure 11). However, the originator biological products are often used in more than one indication. According to EMA's guideline on similar biological medicinal products (CHMP/437/04 Rev 1), when biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable with adequate scientific justification. It should be kept in mind that biosimilars cannot automatically claim all indications of the reference product. Extrapolation is the foundation of the biosimilar regulatory framework and this tailored regulatory package allows biosimilars to be marketed at competitive prices. (European Medicines Agency (i) 2014, 5; Ebbers et al. 2016, 1; Kurki et al. 2015, 655; Weise et al. 2014, 3192.)

The extrapolation is usually not problematic, if the relevant mechanism of action of the active substance and the target receptors involved in the tested and in the extrapolated indications are same and the selected therapeutic indication is representative of other therapeutic indications. Instead, when the mode of action is complex and involves multiple receptors or binding sites, the contribution of which may differ between indications or may not be well known, additional data need to be delivered. Also, extrapolation of immunogenicity data is not self-evident and always requires convincing justification. (Weise et al. 2014, 3192.)

Several learned societies have taken the position that extrapolation of indications should not be allowed and clinical data should be required for all indications, despite the fact that no problems have been encountered with the extrapolated therapeutic indications of the current biosimilars in the EU. (Ebbers et al. 2016, 2; Kurki 2015.)

5.4.4 Interchangeability and substitution of biosimilars

Recommendations on interchangeability and substitution of biosimilars and originator biologicals are not included on EMA regulatory guidelines, but are regulated at the national level. Many countries in the EU have avert automatic substitution of innovator biologics with biosimilars, and for example Italy, Spain and the UK have enacted laws or introduced rules to prohibit the practice (figure 12). However, the Italian Medicines agency (AIFA) has stated that physicians should consider prescribing biosimilars to treat naïve patients, if considerable healthcare savings are achieved. Dutch Medicines Evaluation Board (MEB) accepts interchangeability and switching between biologics (whether originators or biosimilars) is permitted when adequate clinical monitoring is performed and the patient is properly informed. MEB also recommends that detailed product and batch information should be recorded in the patient file so that the traceability of the product is guaranteed. France has been the pioneer in allowing to substitute a biosimilar for the prescribed (reference) biologic, under certain conditions. Substitution is allowed when initiating a course of treatment, if the biosimilar belongs to the same group as the prescribed product and the prescriber has not explicitly prohibited substitution. France was the first European country to explicitly permit a restricted form of biosimilar substitution. (GaBi Online 19 April 2013; GaBi Online 21 February 2014; GaBi Online 1 June 2015; Olech 2016, S6)

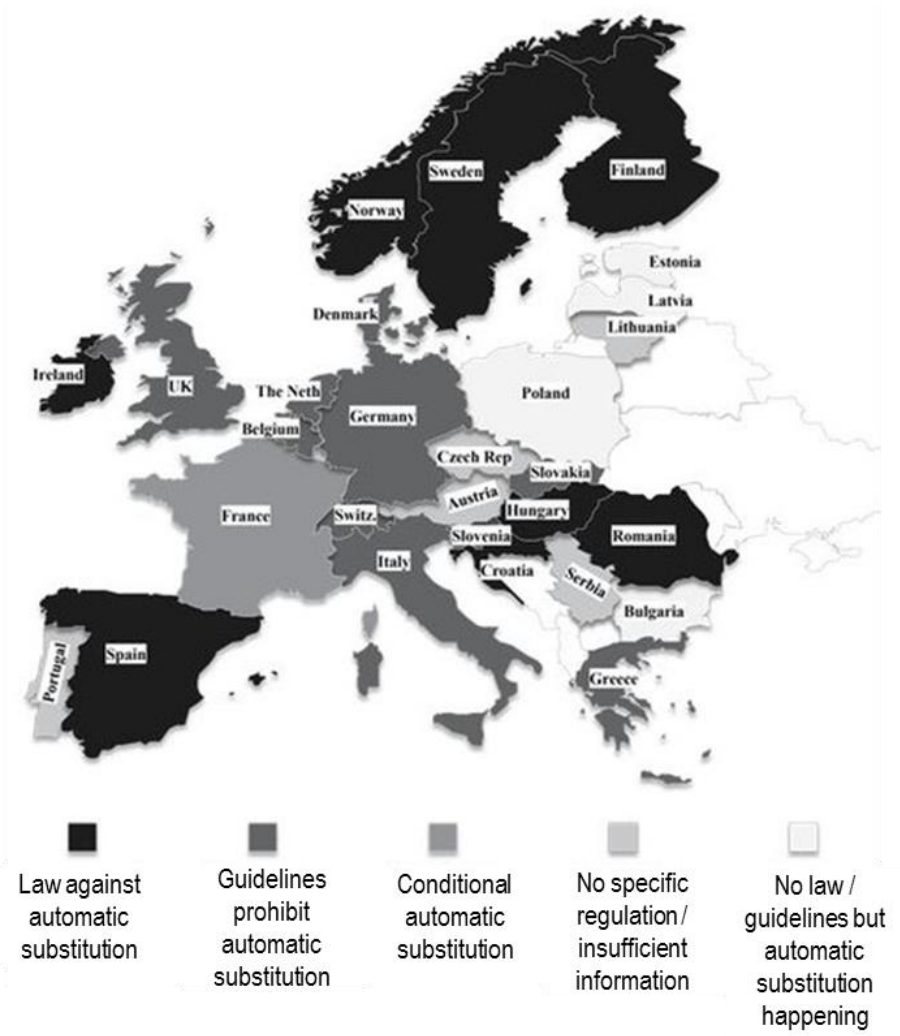


FIGURE 12. Regulators approach towards automatic substitution issues (adopted from GaBi Online 1 June 2015)

The US Food and Drug Administration (FDA) published in the Federal Register on 18 January 2017 draft guidance on biosimilar interchangeability. In order to claim interchangeability, firstly biomilar has to be proven to be biosimilar to the reference biological product and secondly additional information must be submitted. The additional information should show that the biological product can be expected to produce the same clinical result as the reference product in any given patient and also for a biological product 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. (GaBi Online 20 January 2017 (b))

5.4.5 Position of FIMEA – interchangeability of biosimilars

The current position of FIMEA is that EU biosimilars are interchangeable with their reference biologicals under the supervision of a health care person. The patient should be informed of the change of medication and switch should be documented, including brand name and batch number. The announcement was made in May 2015. Automatic substitution at the pharmacy level is not included in Finnish Medicines Agency recommendation. (Ekman et al 2016; Fimea (k) 2015, 1, 3 – 4.)

The FIMEA position paper concludes that switches between biological products, for example in context of hospital tendering processes, are common and usually not problematic. In paper is mentioned that the switches between reference products and biosimilars have been commonly associated with hospital tendering in some EU Member States and no safety signals are associated with the switches in the European EudraVigilance data base for serious adverse effects. Also, the conducted clinical crossover studies have not given evidence of adverse effects due to a switch from a reference product to a biosimilar (somatotropin, epoetin alpha, filgrastim, insulin glargine, infliximab). The risk of adverse effects is expected to be similar to the risk associated with changes in the manufacturing process of any biological products. (Ekman et al 2016; Fimea (k) 2015,3 – 4.)

In Fimea position paper interchangeability is defined as follows: “the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber.” (Fimea (k) 2015, 1.)

5.5 Pharma Industry Finland statement about biological medicines

Lääketeollisuus ry (Pharma Industry Finland) comments that biological medicines have opened new possibilities for the treatment of many serious and chronic diseases and novel medicines also mean revised treatment practices. Lääketeollisuus ry has listed diseases in which most important biological medicines are used to treat. List includes diabetes by substituting for the body’s own insulin production, various cancers, difficult skin and joint diseases, asthma and inflammatory bowel diseases (IBD). (Lääketeollisuus ry (c), accessed 2 October 2016)

Biological medicines are normally administered as infusions or injections to remain their effective and efficient, but the administration of biomedicines is undergoing development to simplify the methods. Lääketeollisuus ry states, that pharmaceutical industry's major aim is to be able to crystallize the large-molecule biological pharmaceutical substances and turn the injectable solutions into orally administered tablets and this way help to transfer the treatments from hospitals to homes. Pharmaceutical development has been possible to lighten the healthcare structures, when wards, and even entire hospitals, have been replaced by treatments given in outpatient care. (Lääketeollisuus ry (c), accessed 2 October 2016.)

Lääketeollisuus ry sees that biological medicines might seem expensive if only price is considered. They argue that the medicine is inexpensive and efficient if all the societal impacts are taken into the calculations. Through biological pharmacotherapies the patients gain additional working years, costs of the invalidity pension and sick leave are reduced and also because therapies work faster, less hospital beds are needed. Lääketeollisuus ry states the cost-effectiveness perspective should be taken, when using biological medicines. (Lääketeollisuus ry (c), accessed 2 October 2016.)

5.6 Biosimilar pricing

Biosimilars can lead to significant savings, but because biosimilar medicines have a more sophisticated and costly development program, those cannot offer the same price reductions as generic medicines. While generic medicines are estimated to cost 2 - 5 million dollars to develop and take 2 – 3 years to produce, are biosimilars development costs much higher, 100 - 200 million dollars, and take longer to produce, 8-10 years (figure 13). Despite of this, the absolute price difference for expensive originator biopharmaceuticals can be substantial between biosimilar and originator products. For example, it's been estimated that a 20 percent price reduction of 5 off-patent biopharmaceuticals would save the EU 1.6 billion euros annually and the US federal government 9 - 12 billion dollars over the next 10 years. (European Commission (c) 2015, 4; Weise et al 2012, 5115.)

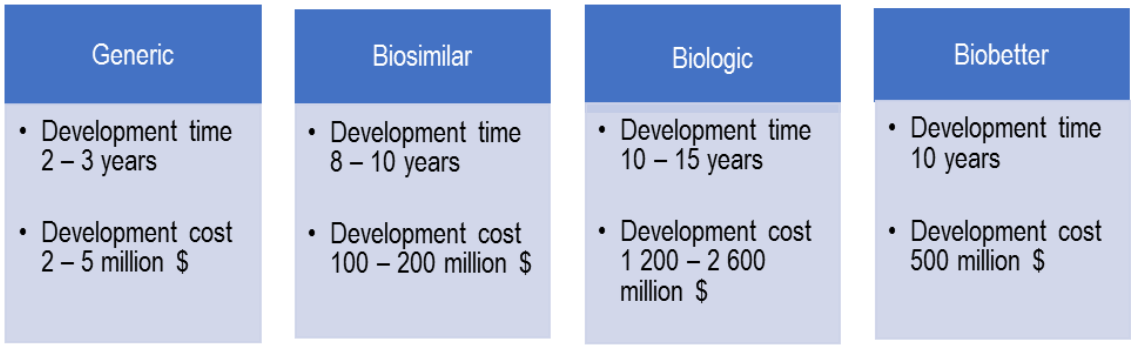


FIGURE 13. Development time and cost of biologics, biobetters, biosimilars and generics (OP-TUM 2016; Pharmaceutical Research and Manufacturers of America: Key Facts)

The hospital markets, through tenders, have received dramatic price discounts, but at the same time the discounts through the retail distributions have remained fixed and limited. For example, for erythropoietin and filgrastim, which price discounts at hospital level were an 85 percent on brand price, retail market discount was only an average of a 30 percent. In EU, some countries have set biosimilar prices at a fixed percentage below the price of the reference biological. In Spain, the mandatory discount is 30%, in Italy at least 20%, in Austria 40–70% and in France 15%. (Creativ-Ceutical 2012, 73; Fuhr et al 2015.)

Biosimilar infliximab (Remsima/Inflectra) was launched in March 2015 in the UK. There, a 100 mg vial of Remicade costs 419,62 British pounds and the list price of a 100 mg vial of Remsima and Inflectra is only 377,66 British pounds. The NHS (National Health System) has further negotiated lower prices for the biosimilars and discount has approached 50 percent of the cost of the originator medicine, Remicade, price. (GaBi Online 7 October 2016; GaBi Online 5 February 2016.)

In France, the price of medicines is negotiable in the hospital setting and for example for filgrastim, the discount is currently more than 90%. In French hospitals, this has led to the widespread and almost exclusive use of biosimilars. By contrast in the outpatient setting (community pharmacies), the price of reimbursed medicines is fixed and concerning biosimilar filgrastim and epoetin alfa, the discount is far less than that obtained in hospitals, being only 10–15% of the reference product's price. (GaBi Online 2 September 2016.)

National tendering has decreased infliximab prices in Norway. In 2014, the Norwegian Medical Agency published the hospital tender prices for the biosimilar infliximab's, Inflectra being offered at a 33% discount and Remisima offered a 39% discount over the Remicade tender price (45 % discount compared with the Remicade list price). Remsima was chosen because it provided the government the lowest priced product. In 2015, prices were further reduced, being 69 percent lower than the reference product tender price (72 % compared with the Remicade list price). This made biosimilar infliximab the preferred bDMARD for all six indications when initiating a bDMARD or switching to a TNF-infliximab in naive patients. In the Norwegian tender for 2016, biosimilar infliximab was still the cheapest alternative, price difference being about 60 percent lower than Remicade. Also, biosimilar version of etanercept (Benepali) was offered with 47 percent lower price compared to regular price of reference etanercept (Enbrel) and as of May 2016, etanercept biosimilar has garnered 40 percent of overall market share. (Collins 2016; Dörner et al. 2016, 2, 5; Fuhr et al. 2015; GaBi Online 13 March 2015; Mack 2015; Welch 2016.)

In Norway, biosimilar epoetin and filgrastim have high discounts in hospital tender prices, up to 89 %. The discounts for use outside of hospitals are lower than tender discounts, around 50 % for filgrastim and even lower for epoetin, around 25 %. Somatropin is not included in any tenders in Norway. The prices for biosimilar somatropin has varied 18-29 % below the average for the originator's somatropin. (Mack 2015.)

Biosimilar version of Lantus (insulin glargine), Abasaglar, entered to Finnish markets in November 2015. The price of Abasaglar was set 22 percent lower than the reference product. Infliximab biosimilar has had similar discounts in Finland than introduced in Norway. In May 2016, Council for Choices in Health Care in Finland (COHERE Finland) gave its recommendation of biosimilars. It recommends that biosimilars are included in the publicly funded healthcare services, according to the principles of the overall economy. Also, on the basis of government proposal HE 184/2016, a set of amendments, intended to create savings to public medical costs in Finland, have been introduced in the Finnish Health Insurance Act (1224/2004). The amendments entered into force on 1 January 2017. The New Health Insurance Act involves price regulation concerning biosimilars. In order to increase the use of and price competition between biological medicines and biosimilars, the suggested reimbursable price for the first biosimilar entering the reimbursement system cannot exceed 70 percent of the list price of the original biologic. Also, the list price of the reference medicine will be re-examined, after the biosimilar is launched (Choices in Health Care 2016; Fimea (g); Finlex 2016; GaBi Online 13 March 2015; Kela (b) 2016, 3.)

5.6.1 Price differences between biosimilar and originator medicines in Finland

In Finland, first recorded biosimilar sales are from year 2008, when biosimilar versions of somatropin and erythropoietin got sales (IMS Health June 2016, 9,13). In beginning of 2017, the price differences between biosimilar and reference product (biosimilar less expensive) vary between therapeutic areas quite hugely, 4% - 43% (table 5). Omnitrope, the oldest biosimilar had lowest difference in price when compared to its reference product Genotropin and highest difference was seen between Remsima and Remicade. Of the EEA countries, Finland, along with Norway, was one of the few countries able to launch biosimilar infliximab in Q4 2013, and managed to have sales at same year (IMS Health November 2015, 9; IMS Health June 2016, 16). Loss of exclusivity in most countries in the EEA occurred as late as February 2015 (IMS Health November 2015, 9). It should be noted that Infliximabs (Remicade, Remsima, Inflectra) are sold only to hospitals in Finland, and hospital discounts are not included here.

Biosimilar filgrastim's (Ratiograstim, Zarzio, Nivestim, Accofil) reference product Neupogen (for dosages 30MU, 48MU) has no price available, but as seen in table 5, prices of biosimilars vary also. For example, 30MU Ratiograstim price is 299,96€ and Accofil 222,87€. First recorded biosimilar filgrastim sales are from year 2009 (IMS Health June 2016, 11).

Eprex has lost its reimbursement, but both biosimilar versions of erythropoietin's (Binocrit, Retacrit) are reimbursed. Slight price difference can be seen between biosimilars, and price difference grows when dosage increases. (Table 5)

Abasaglar's price is 16 percent lower than its reference product (Lantus) price (table 5). It has been reimbursed since February 2016 (Vuorisalo 2015). In Finland, first recorded Abasaglar sales are from year 2015 (IMS Health June 2016, 21).

TABLE 5. Biosimilar products marketed in Finland (January 2017). Originator biological medicine price is price of the company which is the holder of the marketing authorization (table 3). The prices shown are based on price notifications submitted by pharmaceutical companies. The Price column

shows the retail price including value-added tax (VAT). If a product is not reimbursable, the pharmaceutical company can price it freely (Kela (a), accessed 31 January 2017)

Name of biosimilar product	Price of biosimilar, €	Reimbursability	Reference product	Price of reference product, €	Reimbursability	Price difference, % (biosimilar less expensive)
Omnitrope®	635,18/5x5mg (Cartridge)	Special	Genotropin®	663,93/5x5mg (powder for concentrate)	Special	4
Binocrit®	113,99/6x2000IU (syringe)	Special	Eprex®	173,12/6x2000IU (syringe)	No	34
Retacrit®	113,99/6x2000IU (syringe)	Special				34
Binocrit®	211,51/6x4000IU (syringe)	Special		309,72/6x4000IU (syringe)	No	32
Retacrit®	215,73/6x4000IU (syringe)	Special				30
Binocrit®	307,05/6x6000IU (syringe)	Special		449,08/6x6000IU (syringe)	No	32
Retacrit®	315,03/6x6000IU (syringe)	Special				30
Binocrit®	403,68/6x8000IU (syringe)	Special		582,27/6x8000IU (syringe)	No	31
Retacrit®	414,51/6x8000IU (syringe)	Special				29
Binocrit®	483,60/6x10 000IU (syringe)	Special		669,79/6x10 000IU (syringe)	No	28
Retacrit®	513,57/6x10 000IU (syringe)	Special				23
Ratiograstim®	299,96/5x30mu (syringe)	Special	Neupogen®	Not available	Not available	Not available
Zarzio®	296,51/5x30mu (syringe)	Special				Not available
Nivestim®	268,00/5x30mu (syringe)	Special				Not available
Accofil®	222,87/5x30mu (syringe)	Special				Not available

Ratiograstim®	469,62/5x48mu (syringe)	Special				Not available
Zarzio®	466,10/5x48mu (syringe)	Special				Not available
Nivestim®	436,00/5x48mu (syringe)	Special				Not available
Accofil®	349,99/5x48mu (syringe)	Special				Not available
Inflectra®	567,31/100mg (powder for concentrate)	No	Remicade®	793,18/100mg (powder for concentrate)	No	28
Remsima®	457,41/100mg (powder for concentrate)	Special				42
	1303,56/3x100mg (powder for concentrate)	No		2298,90/3x100mg (powder for concentrate)	No	43
Bemfola®	103,64/300iu (prefilled pen)	Basic	Gonal-f®	145,39/300iu (prefilled pen)	Special	29
	151,80/450iu (prefilled pen)	Basic		209,48/450iu (prefilled pen)	Special	28
Abasaglar®	55,95/5x100u (prefilled pen)	Special	Lantus®	66,51/5x100u (prefilled pen)	Special	16

Table 5 does not include all dosages available in Finnish market, just the ones which biosimilar and reference product have common.

5.6.2 Price reductions following the launch of biosimilar

Price reductions (for originators as well as biosimilars, i.e. accessible market) have varied considerably between EU5 countries and therapeutic areas. In Italy and Germany, the observed price reduction for EPOs, following the introduction of biosimilar competition varied hugely, being lowest in Italy, 10 % and highest in Germany, 56 %. For G-CSFs, price reduction has been highest in Spain, 41 % and lowest in UK, 5 %. For Anti-TNF, the price reduction was really mild in 2015, varying between 0 % to only 10 % and also the uptake of biosimilar infliximab's has been low in EU5 countries. (Figure 14.) It should be noted, that highest price reduction may not be same as the lowest price (IMS Health June 2016, 4).

Same trend which is seen in EU5 countries can also be seen in Nordic countries (Finland, Sweden, Norway and Denmark). Price reduction for EPOs ranged from 12 % in Denmark to as high as 41 % in Norway, being in Finland 34 %. The price reduction of filgrastim medicines, was in 2015 lowest in Finland 31 % and highest in Norway 56 %. Infliximab price reduction was mild in Finland and Sweden, only 10 %, and differentiates from Norway, where reduction was much higher, 48 %. (Figure 14.) As will be mentioned later, the hospital tender discounts for infliximab have been much higher in Finland than discounts seen in list prices (infliximab is hospital-only product in Finland) and hospital discounts are not included here.

One exception in price reduction can also be seen in figure 14. In Germany, the rise can be seen in somatropin average price, 3%, since launch of biosimilar version.

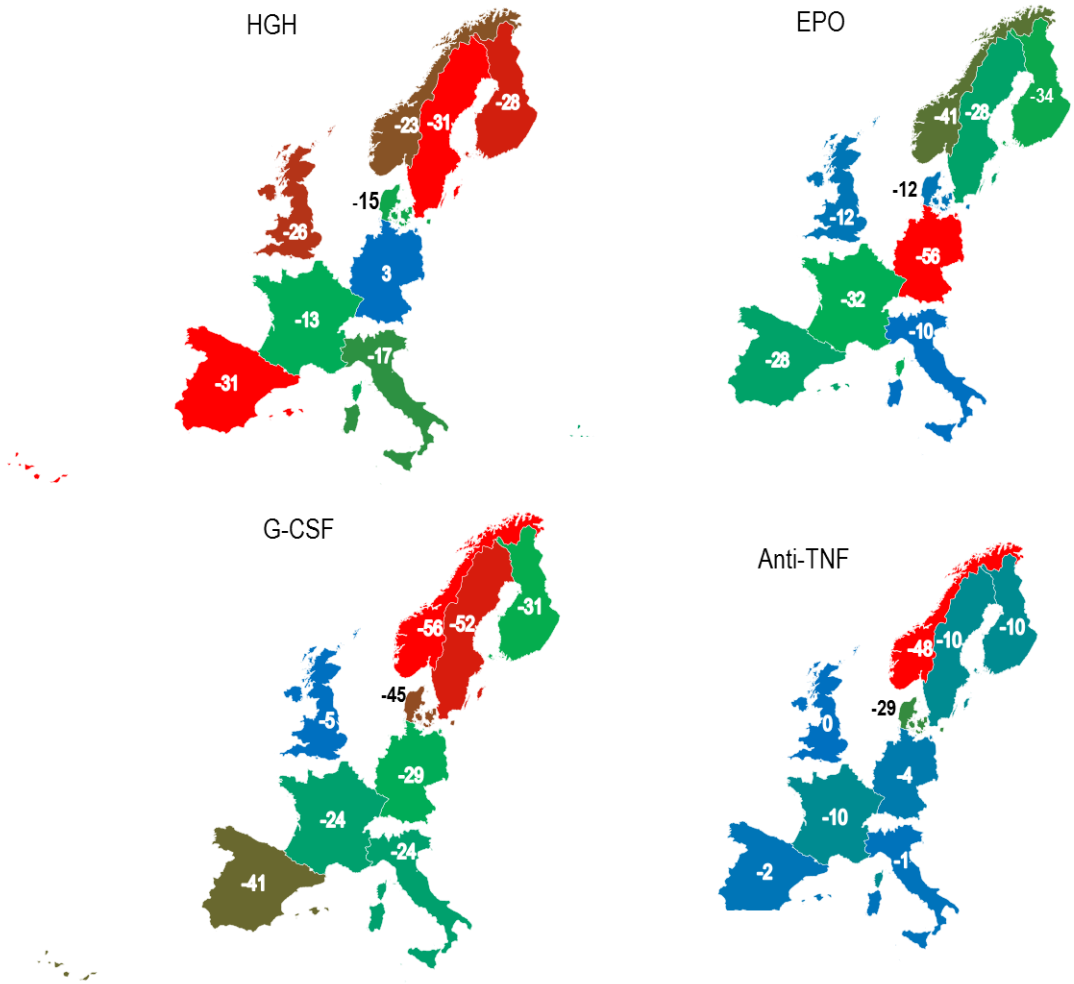


FIGURE 14. Price changes per treatment days (%) across the medicine class (biosimilar accessible market) for HGH, EPO, G-CSF and anti-TNF in Nordic and EU5 countries in 2015, following the launch of the biosimilar versions. Price development is calculated as price per TD 2015 compared

with price in the year before the first biosimilar medicinal product was launched. Prices are a volume weighted ex-manufacturing price averages, without taking into account rebates or discounts (IMS Health June 2016, 8 - 14,16, 24; Appendix 13)

Biosimilars are expected to increase price competition and reduce prices of biological medicines. Biosimilar competition in therapeutic areas of EPOs, G-CSFs, HGHs and Anti-TNF show a consistent reduction in average prices in European Economic Area countries (figure 15). The increased competition has affected, not only the price of reference products, but also price of the whole product class. Price competition might also have similar impact on the total therapy area price as it has on the biosimilar/reference products price (IMS Health June 2016, 4).

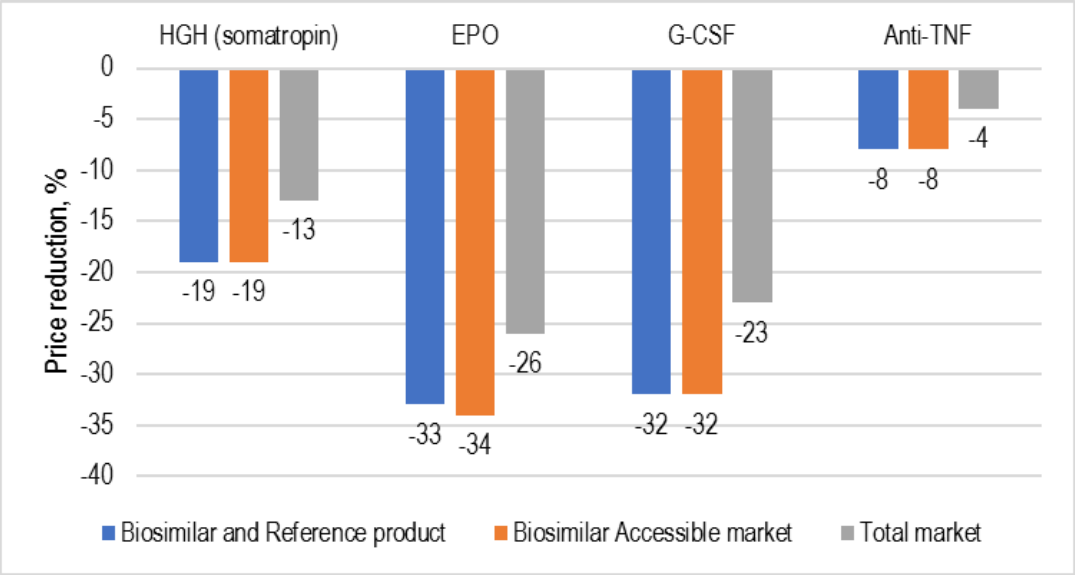


FIGURE 15. Price changes per treatment days in 2015 (%) in European Economic Area (EEA) countries. Price development is calculated as price per TD 2015 compared with price in the year before the first biosimilar medicinal product was launched (IMS Health June 2106, 3 - 4, 8- 14, 16, 24; Appendix 13)

In Finland, a consistent reduction in prices can also be seen in different therapeutic areas. Reduction in prices in Finland has been comparable or even slightly higher than average price reduction in EEA countries. (Figure 16.)

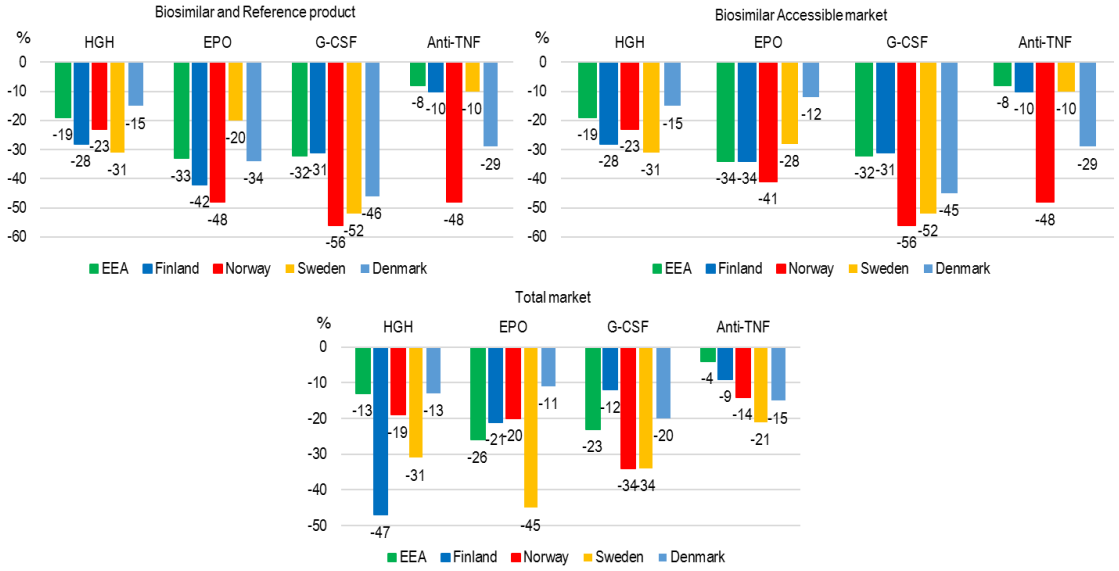


FIGURE 16. Price reductions (%) in Nordic and EEA countries (HGH, EPO, G-CSF and Anti-TNF products). Price development is calculated as price per treatment days (TD) 2015 compared with price in the year before the first biosimilar medicinal product was launched (IMS Health June 2016, 4, 9, 11, 13, 16; Appendix 13)

5.6.3 Lower prices increase patient access?

In Finland, Norway and Sweden Biosimilar and the Reference product volume of EPO, G-CSF and Anti-TNF products have increased compared the year before their first biosimilar medicinal products were launched (figure 17). The Biosimilar and Reference product volume increase of EPOs has been highest in Finland,1033%, same time the full accessible market volume has decreased 48 % (only shorter acting EPOs) and total market volume has increased 2 % (shorter and longer acting EPOs). For example, in renal anemia in 2011, the share of patients with longer acting erythropoiesis-stimulating agents was 72 %, while shorter acting EPOs accounted only 28 % of the patients (Kastarinen et al 2013, 2768). Same trend can be seen with cancer patients, of which 66 % of all patients use longer acting EPO and only 34 % are using shorter acting agents (Kiviniemi et al 2013, 10). 2012, biosimilar EPOs accounted little under 30 % of total short acting epoetin consumption (DDD) and little over 5 % of total erythropoiesis-stimulating agent's consumption (Kastarinen et al 2013, 2769). Even though biosimilar EPOs are not used much and total consumption on erythropoiesis-stimulating agents is shifted to longer acting EPOs, still the price reduction in total market of EPO analogs has been 21 % and in biosimilar accessible market 34 % in 2015 compared to year before the first biosimilar version of Eprex (shorter acting EPO) was launched

(figure 16, Kela (b) 2016, 3). The same pattern can also be seen in Sweden and Norway, both in volume and price (figure 16; figure 17).

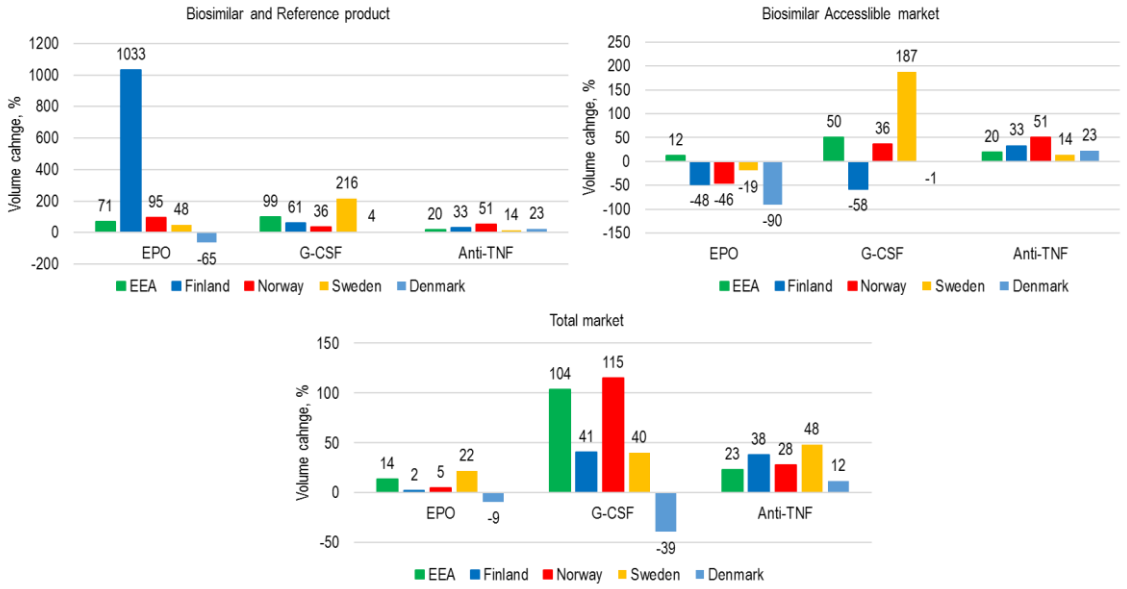


FIGURE 17. Volume development of EPO, G-CSF and Anti-TNF products in treatment days comparing 2015 versus the year before the first biosimilar product was launched in Nordic and EEA countries (IMS Health June 2016, 8 - 11, 13, 14 – 16, 24; Appendix 13)

With G-CSF medicinal products, Biosimilar and Reference product volume has increased in Finland 61 %, which is less than average increase, 99%, in EEA countries. Sweden has highest increase 216%. In Biosimilar accessible market (only shorter acting G-CSF agents) Finland differentiates from Norway and Sweden where consumptions have increased 36 % and 187 % and in Finland it has instead decreased 58 %. Of the total market volume (shorter and longer acting G-CSF agents), highest increase has been in Norway 115 % while the increase in Finland was lower, 41 %. (Figure 17.) In Finland, longer acting G-CSF agent pegfilgrastim has clearly the highest consumption of G-CSF medicinal products in 2015. Its hospital consumption has decreased from 16 % in 2012, to 7 % in 2015 (Fimea (d), 33). Shorter acting filgrastim consumption has done vice versa, hospital consumption has increased to 97 % compared to 2012 when it was just 33 %. (Fimea (d), 33). Same pattern can be seen with G-CSF agents than with EPOs. Short acting G-CSF agents (including biosimilars) are not used much compared to longer acting agents and total consumption on G-CSF agents is shifted to longer acting agents (Kela (b) 2016, 3). Still the price reduction in total

market of G-CSF analogs has been 12 % and in biosimilar accessible market 31 % in 2015 compared to year before the first biosimilar version of Neupogen (shorter acting G-CSF) was launched (figure 16).

In all Nordic countries, Anti-TNF agent's Biosimilar and the Reference product consumption, Biosimilar accessible market consumption and total market consumption have increased compared the year before the first biosimilar medicinal products was launched (figure 17). Same time price reduction has occurred in all Nordic countries, in biosimilar accessible market as well as total Anti-TNF market (figure 16). In Finland consumption of infliximab has increased 2013 – 2015 from 0,60 DDD/1000 inhabitants/day to 0,89 DDD/1000 inhabitants/day (Fimea (d), 34). Biosimilar version of infliximab was launched 2013.

Even if biosimilar product does not end to be the product sold, it may generate a more competitive environment, which leads to lower prices. Reduced prices may increase patient access to the same molecule and/or expand access to other medicines. Also, lower prices make possible in hospitals to treat more patients with in the existing budget of the respective medicine program.

5.7 Penetration of biosimilars in Nordic and EU5 countries

In the EU, uptake of biosimilars varies widely between therapeutic areas and countries mainly because of differences in the healthcare systems between different countries. Eastern Europe is leading the way in biosimilars penetration, maybe driven by economic factors. Acceptance of biosimilars has been dependent on the attitude of physicians, patients, pharmacists, third-party payers and policymakers. (Ekman et al. June 2016; GaBi Online 17 August 2012.)

In Nordic countries biosimilars have higher penetration of G-CSFs and EPOs than for human growth hormones. In 2015, biosimilar EPOs accounted for 90 - 100 % of market (biosimilar + reference product) in treatment days, while somatropin biosimilar accounted only 25 – 33 % in Norway, Sweden and Finland, Denmark being exceptional with 96 % market share. (Figure 18.)

Filgrastim market is also dominated by biosimilars in Nordics. Biosimilar market share was highest in Finland, 97 % and lowest in Norway, 84 % (figure 18). In Finland originator, reference product Neupogen, lost its reimbursement in March 2013 (Apteekkari 2012), which explains the high market

share of biosimilar filgrastims in Finnish market. Beginning of 2017, there is only one Neupogen dosage in market, 0,3mg/ml solution for injection (Kela (a), accessed 31 January 2017).

In United Kingdom (UK), first biosimilar version of the Neupogen was launched in November 2008. After the launch, a number of Strategic Health Authorities opted to reassess their existing guidance of the use of G-CSF-medicines. The updated guidelines reflected the improved cost-effectiveness of biosimilar filgrastim versus alternative treatments. As a result of this, G-CSF was moved to first-line cancer treatment. The impact was that the overall uptake of filgrastim (originator and biosimilar) increased markedly, which was seen in the period between January 2009 and January 2014, when overall consumption of filgrastim short-acting increased by 104%. The launch of biosimilar filgrastim enabled a greater number of patients to be treated with filgrastim therapy in a more cost effective manner than before. Also, biosimilar filgrastim enabled greater number of patients to access these treatments at an earlier stage of the therapy cycle. In 2015 biosimilar filgrastim markets share was in UK, 98 %. (Figure 18; IMS Institute for Healthcare Informatics March 2016, 9.)

In Sweden's Southern Healthcare Region, regional authorities eased restrictions on prescribing filgrastim due to the launch of biosimilar filgrastim and the associated reduction in treatment costs for patients receiving G-CSF therapy for febrile neutropenia. Before introduction of biosimilar filgrastim, the agreement of three physicians was required to commence treatment with the originator product. After the launch of biosimilar filgrastim, individual physicians were permitted to prescribe the biosimilar version without the assent of other medical professionals. Because of this, uptake of G-CSF increased five-fold in the Southern Healthcare Region, driven by usage of biosimilar filgrastim. In Sweden, market share of biosimilar filgrastim was, in 2015, 93 % (figure 18). (IMS Institute for Healthcare Informatics March 2016,14.)

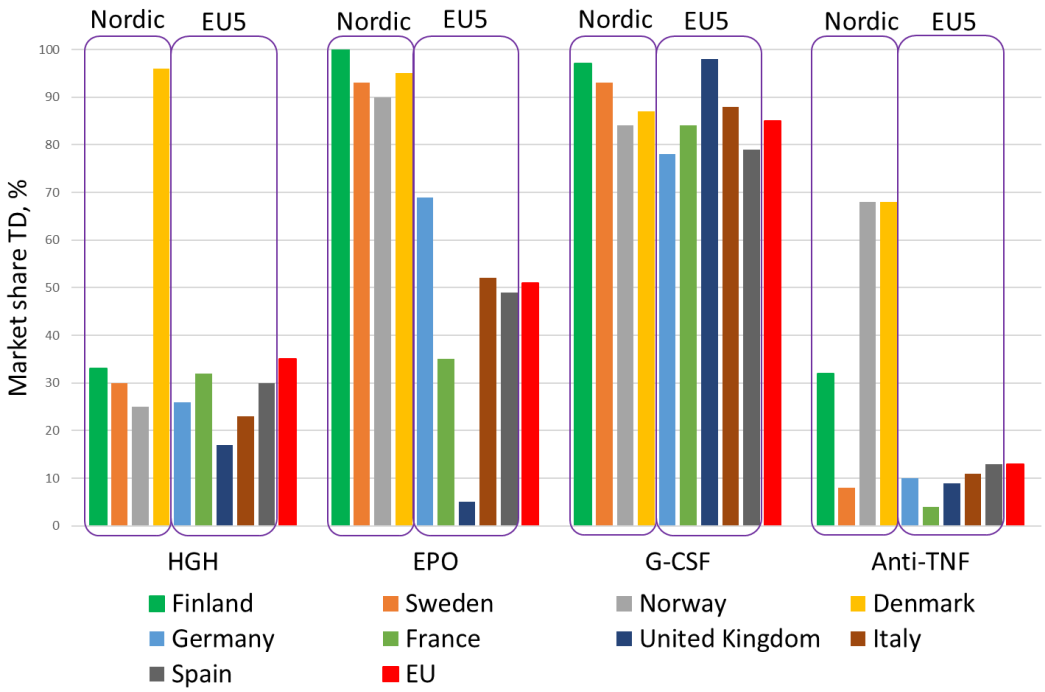


FIGURE 18. Biosimilar market share %, in Nordic and EU5 countries in 2015. Market share is number of biosimilar treatment days (TD) as a share of reference + biosimilar product volume. EPO (epoetin alfa, epoetin zeta), G-CSF (filgrastim), HGH (Genotropin, Humatrope and Omnitrope) and anti-TNF (infliximab). Market share TD (treatment days) is calculated in treatment days/DDDs (IMS Institute for Healthcare Informatics March 2016, 3, 9, 11, 13, 16, 23)

In the beginning of 2015, the market share of infliximab biosimilar versus reference biological medicine (Remicade) was low in Finland, but in 2016 situation in Denmark, Norway and Finland has changed dramatically (market share over 90 %), after originator medicine (Remicade) treatments were nearly totally switched to biosimilars (Inflectra/Remsima) (figure 18, figure 19, Welch 2016). Denmark launched biosimilar version of Remicade over one years later (February 2015) than Finland and Norway (September and December 2013) (Danish Medicines Agency February 2016, 6; Fimea (j); Mack 2015). Because infliximab is only in-hospital treatment in Finland, the purchasing periods of hospital districts have partly affected the uptake of biosimilar infliximab. Purchasing periods vary from two years to four years depending of the district (table 6). There are tough exceptions mentioned in invitations for tender which may allow hospital pharmacies to terminate the existing contract, when biosimilar enters to Finnish market and if market situation is expected to change essentially (HUS apteekki 2015, 8). These exceptions may help biosimilars enter hospital markets quicker, if the discount of the biosimilar is low enough to cause high enough reduction in price level of the medicine. This might accelerate biosimilar medicine's access to hospital markets in future.

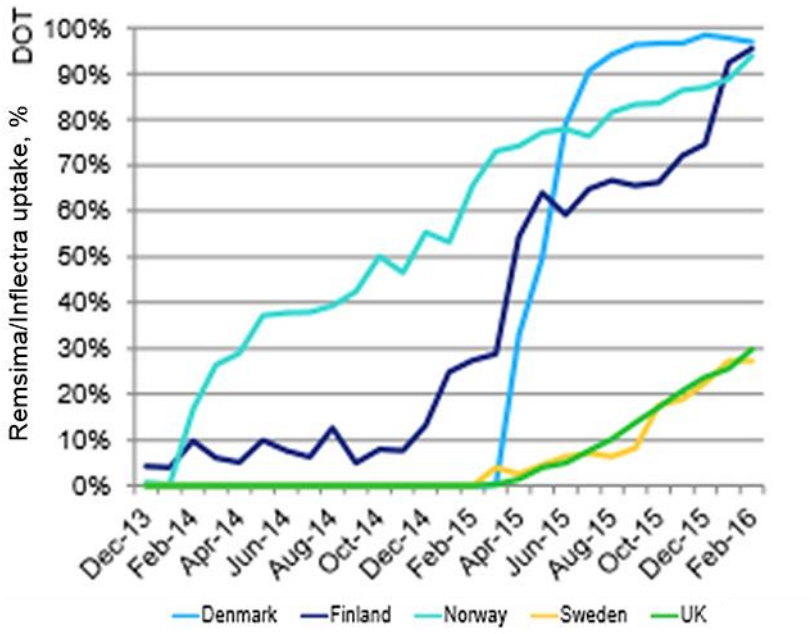


FIGURE 19. Biosimilar infliximab (Remsima/Inflectra) uptake in Nordic countries and United Kingdom (UK) (adopted from Troein 28 April 2016, 8; Troein 17 May 2016)

Compared to Denmark, penetration of biosimilar infliximab has been low in EU5 countries, being lowest in France, 4 % and highest in Spain, 13 % (figure 18). This is even though EU5 countries launched biosimilar infliximab at same time with Denmark, February 2015 and first recorded sales are also in all countries from 2015 (IMS Health June 2016, 16; GaBi Online 20 March 2015). For example, in UK, market share was 2015 only 9 % of reference product, and February 2016 it has increased only up to 30 % despite the fact that UK has one of the highest market shares of generics in Europe (figure 18, figure 19, GaBi Online 29 April 2016). The British Society of Gastroenterology (BSG) did not recommend switching in their 2014 guideline, which was stating that "for patients already on therapy, avoidance of switching from parent drug to biosimilar, or vice versa, at least until we have safety data" (BSG 2014). BSG updated their guideline in February 2016, year after launch of biosimilar infliximab, and is now recommending that "patients who are in a stable clinical response or remission on Remicade therapy can be switched to Remsima or Inflectra at the same dose and dose interval. This should be done after discussion with individual patients, with explanation of the reason for switching" (BSG 2016). NHS England (National Health Service), has made efforts to improve the uptake of biosimilars in the UK. In September 2015, the NHS launched a 'What is a biosimilar' briefing, in collaboration with industry and regulatory partners (GaBi Online 29 April 2016). This document provided an update for key clinical and non-clinical stakeholders

about the developing role of biosimilar medicines in the NHS in England and support the safe, effective and consistent use of all biological medicines, including biosimilar medicines, to the benefit of patients (GaBi Online 29 April 2016; NHS 2015, 5). Also, NICE (National Institute for Health and Care Excellence) has published guideline on January 2016, covering seven biologicals, abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and tocilizumab (GaBi Online 5 February 2016). The NICE recommendation will lead to increased use of biosimilar infliximabs, Inflectra and Remsima, due to their lower price compared to the originator infliximab, Remicade (GaBi Online 5 February 2016).

5.7.1 Uptake of biosimilar infliximab and etanercept in Denmark

In Norway and Denmark, physicians have been at the heart of the decision-making process in relation to biosimilar medicines. In these countries, the uptake of biosimilar infliximab has been rapid and sustained and demonstrates that a key component of ensuring the longer-term sustainability of the market is the trusting and empowering physicians to make the right decisions. (IMS Institute for Healthcare Informatics March 2016,18.)

For example, in Denmark biosimilar infliximab Remsima covered about 98 percent of infliximab consumption in the third quarter of 2016. The biosimilar infliximabs received their marketing date of authorization in Denmark in the beginning of 2015 (Inflectra February and Remsima March 2015). It seems that Danish regions have followed the Council for Use of Expensive Hospital Medicines (RADS) recommendations to switch Remicade treatments to Remsima. It is noteworthy that total consumption of infliximab has increased 2015 and did continue to do so also in 2016 (figure 20). Total consumption increase is caused by RADS' guidelines for biological treatment in the field of rheumatology and gastroenterology, in which infliximab (Remsima) appears as first-line product. In Denmark infliximab medicines are used only in hospitals. Also, Ministry of Health in Denmark did set up an action plan in partnership with the Danish Medicines Agency (DKMA) on "Biological Medicines, Biosimilars and Vaccines for 2015 – 2016", after patients' organizations had approached the Ministry of Health with their concerns regarding of biosimilar information available. The aim of the action plan was to ensure targeted and product-specific monitoring of biologicals. One purpose was also to raise patients and patient organizations awareness on biosimilarity through targeted information and have physician targeted communication activities. (Danish Medicines Agency February 2016, 6; Danish Medicines Agency November 2016, 5, 6; Lunddahl 2016.)

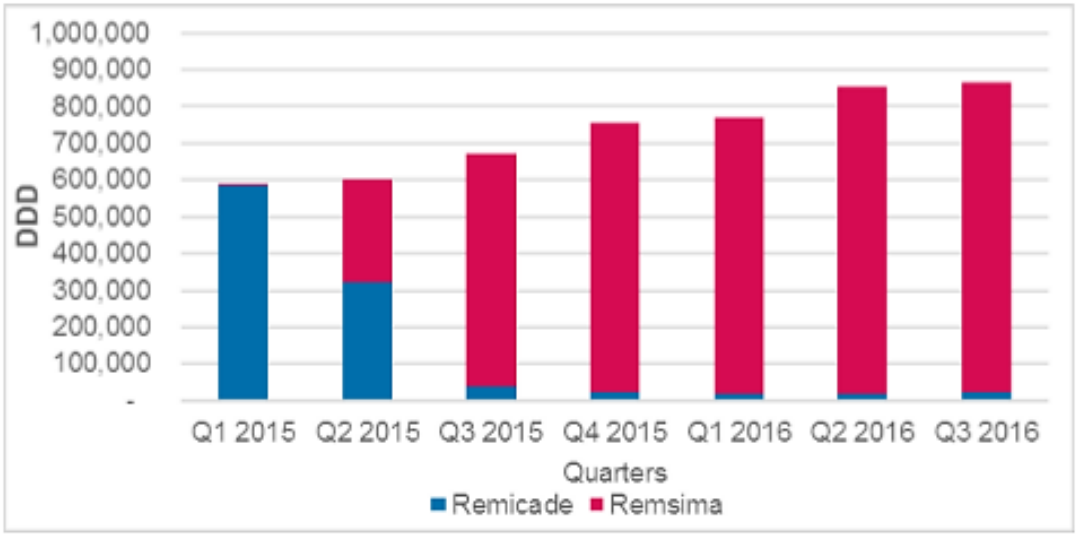


FIGURE 20. DDD consumption of infliximab medicines in Denmark, broken down by Remicade and Remsima between Q1 to Q4 2015 and Q1 to Q3 2016 (adopted from Danish Medicines Agency November 2016, 5)

Another example from Denmark is etanercept-biosimilar uptake. Benepali came to Danish market February 2016 and already in Q3 2016, Benepali accounted 77 percent share of etanercept consumption (figure 21). In the RADS' guideline for patients treated with etanercept, new patients and patients whose other biological treatment has failed, should be treated with the cheapest version of medicine (Benepali), excluding children, because there is no low-dose formulation available. Also, patients who are stable on etanercept treatment should be switched to the cheapest version of the medicine, if there are no exceptional individual concerns. Consumption data shows that regions have switched originator Enbrel to biosimilar Benepali in line with the RADS' guidelines. Etanercept medicines can be used in hospitals and in specialist practices in Denmark. (Danish Medicines Agency November 2016, 6.)

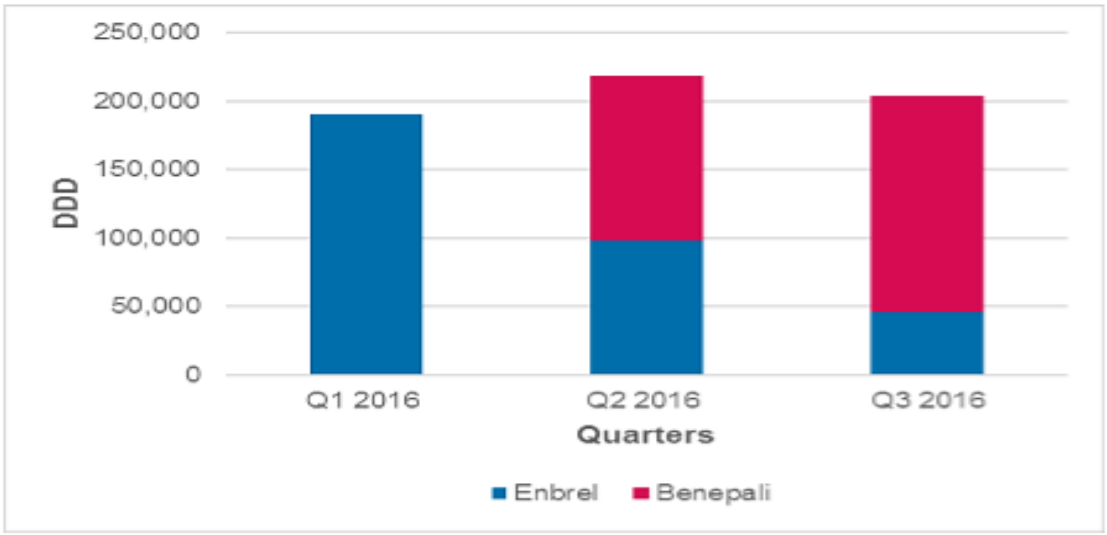


FIGURE 21. DDD consumption of etanercept medicines in Denmark, broken down by Enbrel (originator product) and Benepali (biosimilar product) between Q1 to Q3 2016 (adopted from Danish Medicines Agency November 2016, 6)

5.7.2 What slows down uptake of biosimilars

Several factors have influenced to the penetration of biosimilars. Different stakeholder groups, such as physicians, patients, and payers, have all increasingly important role to play as the biosimilars market develops (figure 22).

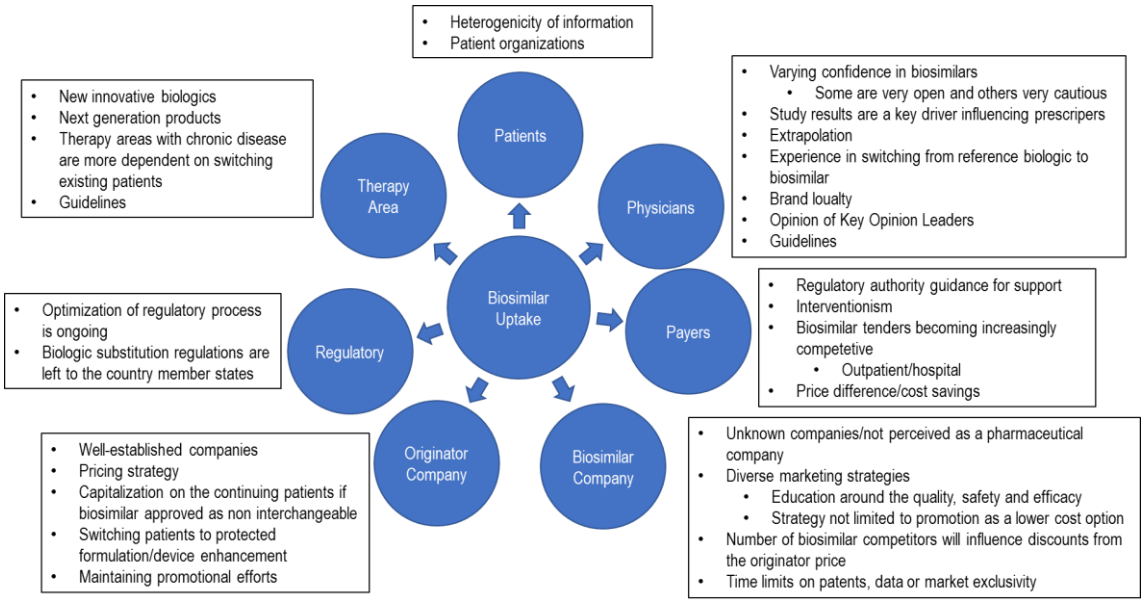


FIGURE 22. Factors influencing the uptake of biosimilars

Biggest problem, which has slowed down uptake of biosimilars, has most likely been lack of knowledge of biological medicines and biosimilars. Without understanding the life cycle/history of biological medicines, the understanding what biosimilars are and why study requirements differ from originators is challenging. Also, the biosimilar information given for payers, physicians, patients, patient organizations, and key decision makers has not been consistent due to fact that originator and biosimilar companies have approached the subject from the perspective which serves their purpose. Biosimilar companies might have, in the beginning, concentrated too much to price difference, and did not educate properly what biosimilarity is. Health authorities should have had more recourses in the beginning with their educations for patient organizations, physicians and payers and this way all stakeholders would have received more objective information about biosimilars. Health authorities should be responsible for providing unbiased, continuously updated information on the use of biosimilars.

Merikoski and Enlund have studied the introduction and use of biological medicinal products in Finland. During the study, Oncologists were already using biosimilar product and Rheumatologists were in the position where first biosimilar monoclonal antibody was entering market. Physicians were willing to use biosimilars, especially if cost savings could be achieved and efficacy, safety and quality of the product can be guaranteed. Some did think biosimilars were different medicines and other considered those to be equivalent to originator medicines. Also, others considered biosimilars as interchangeable and same time some doubted their efficacy and safety. Many of the comments were cautious and physicians wanted to have more information and practical experience. Uncertainties of biosimilar products were related to research processes and manufacturing processes, the country of manufacture and quality of the product. The physicians yearned more objective information relating to basics of biosimilars and their studies. (Merikoski et al. 2016, 66 – 69.)

Even though physicians have expressed their need for real-world-data, their willingness to participate biosimilar studies and their success in recruiting patients to those, has not been high. The reasons might be the lack of innovation for biosimilar medicines, and the limited opportunities to publish on innovative research. Those reasons may remove an invaluable center of influence for the transition from branded biologic to a biosimilar medicine during the commercialization period. This is especially relevant within academic research centers in Western Europe and in the United States, where the need for professional and institutional recognition is marked (Rompas et al 2015,134).

Extrapolation of indications has been one issue with biosimilars. For example, biosimilar infliximab has studies for rheumatoid arthritis (phase III) and ankylosing spondylitis (phase 1) patients and did not have clinical studies for IBD-patients in time of approval of marketing authorization. Still biosimilar version of infliximab received all the same indications than originator product. This made gastroenterologists cautions with IBD-patients and many wanted to wait until more data and experience of the biosimilar version is available. Norway did fund clinical studies in which patients' treatments were switched from originator biological medicines to biosimilars. However, there was some speculation that the NOR-SWITCH study did actually slow the adoption of biosimilar infliximab in Norway (Mack 2015).

Switching originator biological medicine to biosimilar has been big issue. Data on reverse, multiple and cross-switching among biosimilars were lacking as well as switching originator to biosimilar and reverse and many physicians were reluctant to start switching without evidence. EMA has not issued guidance on biosimilar interchangeability or substitution. Many countries in the EU have avert automatic substitution of innovator biologics with biosimilars and some countries have enacted laws or introduced rules to prohibit the practice. Also, several learned societies have published recommendations and position papers advising prescribers to refrain from using biosimilars in therapeutic indications that have not been studied in clinical trials. One concern, for example, with biosimilar infliximab was that tender period changes may cause reverse switching or switching to another biosimilar and that raised for example concerns of immunogenicity. However, published switching data of Lantus to Abasaglar (biosimilar Lantus) did not convince physicians of switching either and uptake of Abasaglar has been slow in Finland. One issue of switching Lantus to its biosimilar has been different prefilled pen. Abasaglar has prefilled KwikPen-pen and Lantus has SoloStar-pen (SPC (a, c), accessed 27 February 2017). Though it would be interesting to know than how many Lantus users are also using rapid-acting Humalog, which has same KwikPen-pen as Abasaglar (SPC(b), accessed 27 February 2017).).

In the beginning, the biosimilar companies have not been necessarily perceived as pharmaceutical companies (for example Samsung Bioepis). Biosimilar companies might have had smaller organizations and less money to spend to marketing compared to bigger and well-established originator companies with much bigger organizations and much more money to spend to protect their originator product. This has led to situations of which originator companies have been able to "dominate" the market with their information while biosimilar companies have not had same potential to

use. Situation is thought now changing, after global big companies have also entered to the biosimilar market. For example, Pfizer completed its acquisition of Hospira on September 2015. Hospira was the world's leading provider of injectable drugs and infusion technologies and a global leader in biosimilars (Hospira 2015). Also, Amgen has large biosimilar pipeline, including for example adalimumab, trastuzumab, rituximab and infliximab (Amgen (b), accessed 21 February 2017). It is very exciting to see, how companies which are competing with biosimilars and originators in same therapy area, will position their educational information about biosimilars.

In addition to the development of new products, manufacturers of originators and biosimilar medicines may differentiate their products by offering value-added services, like patient support or make device enhancements. Also, originator companies are developing second-generation biologics that offer improvements over their older products (for example new formulations and different dosing regiments). These products do compete with biosimilars for market share and payer's, patient's, and prescriber's willingness to switch to these next generation biologics rather than to biosimilars depends of the biosimilar's safety, efficacy, convenience, and cost and not just relative to originator products, but also to the next-generation biologics. Also, how payers structure the relative reimbursement incentives of new generation products will affect the competition. In Finland for example, Toujeo (next generation product of Lantus) reimbursement was limited 1.1.2017, so that a **limited** basic or special reimbursement is available for the product and will be granted if patient has had repeated or severe hypoglycemia during glargine insulin treatment (Lantus/ biosimilar Abasaglar) (Kela (c) 2016). Thought patients' whose Toujeo-treatment was started end of 2016 with special refund category 103, could continue with special rate of reimbursement without having to make new application for reimbursement (Kela (c) 2016).

Price difference between biosimilar and originator product should be high enough to awake interest of different stakeholders. The estimated price reduction of biosimilar has not been as low than with generics, because of their higher manufacturing and development costs. Price reduction varies in different product classes and across countries and in the EU, biosimilars have been typically 15-30% cheaper. Though, much higher price reductions have been seen in hospital tenders and this has possibly affected the biosimilar penetration rates, which have been much higher in hospitals than in retail sector in different therapy areas. If the price reduction is not substantial, price competition will not occur and either payers, physicians or patients will not see the benefit of biosimilar. The question is, what is substantial price difference and does it vary between hospital-only and reimbursed medicines or between therapeutic areas (number of patients treated with originator

product, original price of reference product, total cost of treatment etc.). Also, it might be, that the total cost of biological originator medicine is not seen substantial, especially in smaller hospitals and hospital districts where number of patients may be small, and because of that possible cost savings are also not seen substantial.

The biosimilar medicine might have entered to market after the standard of care has evolved. Manufacturers of second-generation products might have had the ability to shift the standard of care paradigm and convert patients to an improved molecule, for example towards the use of longer acting products, which have limited the need for biosimilar medicines.

When physicians are at the heart of decision-making the uptake of biosimilars has been much higher and faster. In Norway for example, the role of the Norwegian Drug Procurement Co-operation (Legemiddelinnkjøpssamarbeidet, LIS) is critical and physicians are afforded a central role in the decision-making process. LIS is responsible for organizing tenders for the procurement of medicines for state hospitals and LIS' evaluation panels are comprised of physician experts and representatives from all four of the country's healthcare regions. In the LIS model, physicians take into account a range of clinical- and cost-related factors, when deciding to award a tender to a particular product. In addition, as state hospitals are funded via a DRG-system (Diagnosis-Related Group), which includes the cost of the medicines, hospital physicians are able to observe the benefits of the reduced costs associated with biosimilar medicines. This incentive and the trust of hospital physicians to the LIS evaluation system, helps further drive biosimilar uptake. In Denmark, the Council for the Use of High-Cost Hospital Medicines (RADS) has a similar role than LIS in Norway. (IMS Institute for Healthcare Informatics March 2016, 20.)

The problem might have been, that physicians have not necessarily been shared what has been done with the money saved with biosimilars or what will happen the money if they start to use biosimilars. If physicians are able to take part of decision making, and information of the decision and its influence would be shared widely, the idea what society and/or hospital district, hospital, physician and in the end patient will benefit from using biosimilar (more treated patients, new innovative medicine to use etc.), would possibly motivate the individual physician to initiate biosimilar treatments or even to switch stable patients (at least to some extent) to biosimilars.

5.8 Outcomes from the use of biosimilar medicines

The introduction of biosimilar medicines has already had a significant impact on health care costs and patient care. Biosimilars present opportunities to payers, physicians and patients, including cost containment and increased availability of therapeutic options (figure 23).

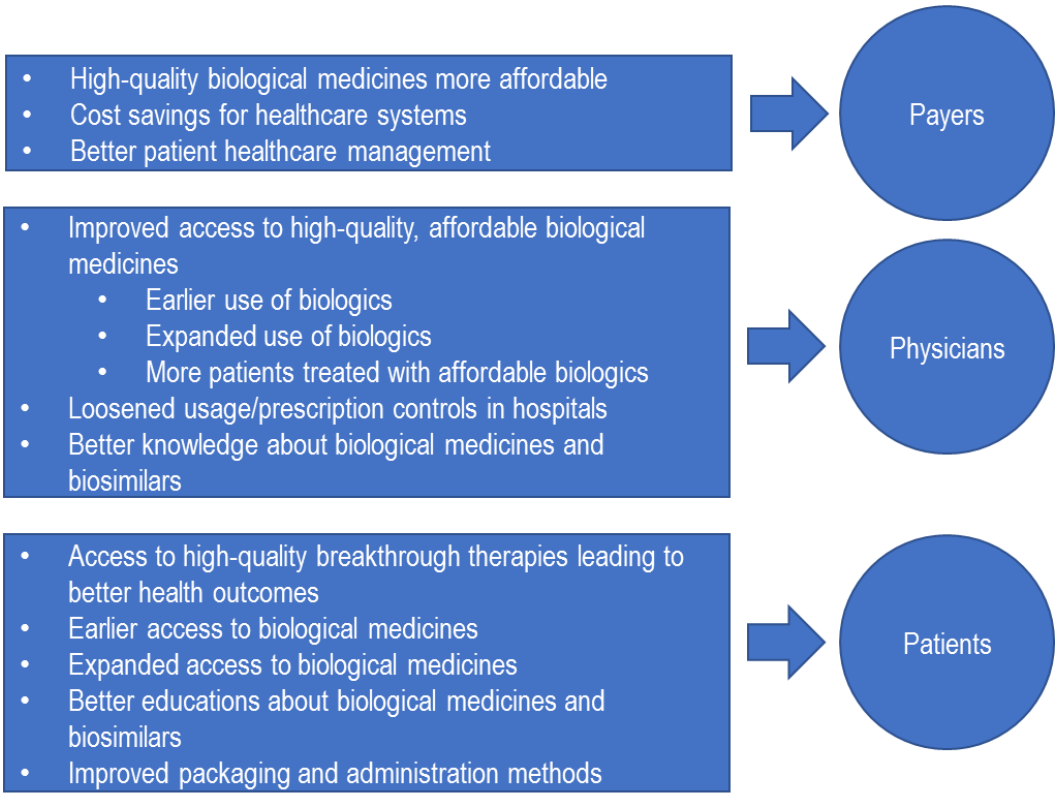


FIGURE 23. The outcomes from the use of biosimilar medicines

Biosimilar competition in different therapeutic areas have showed a consistent reduction in average prices in European Economic Area countries. The increased competition has affected the price of reference products and as well as price of the whole product class.

Biosimilars have the potential to lower costs and for example, in Nordic countries infliximab biosimilar price has been up to 69 % lower than the reference product tender price. From the beginning of 2016, HUS, which is the largest district providing specialized medical care in Finland (table 6), estimated to achieve significant savings (several millions of euros) by switching the use of infliximab treatment mostly to Remsima (biosimilar infliximab), instead of originator product Remicade (HUS 2015, 10). 2009 in Germany, approximately one third of prescriptions for the granulocyte colony-stimulating factor (G-CSF) were for its biosimilar and using the biosimilar over the reference biologic

medicine resulted significant savings (Henry et al. 2014, S14). Also, in the United States, savings from biosimilars are estimated to range from 3,0 to 4,5 billion dollars annually (Henry et al. 2014, S14).

Physicians, payers and patients are more aware what biological medicinal products are and objective biosimilar information provided by health authorities is more available and better targeted to different stakeholders compared to time, when first biosimilar were launched. For example, Fimea (Finnish Medicines Agency) has several publications explaining biosimilars and biological medicines, including a plain language summary of biological medicines and biosimilars.

Earlier and broader use of biologic medicines are seen in markets where biosimilar competition has occurred. As a consequence, biosimilar medicines support improved patient access to certain therapeutic areas compared to the originator. Cost-related restrictions on prescribing of biologics might have been in place for the biologics and after biosimilars have accessed to market and their price has been lower the situation has changed. It can be argued that the launch of biosimilar G-CSF has led to improved patient outcomes, by enabling greater numbers of patients to access these treatments at an earlier stage of the therapy cycle. For example, in the United Kingdom, Germany, and the Netherlands, the availability of a lower cost biosimilar to G-CSF correlated with 10% to 20% increased use of a G-CSF agent and G-CSF was used earlier in the course of therapy, resulting in a shift of its use as a secondary to primary prophylactic agent against febrile neutropenia (Henry et al. 2014, S14).

Lower treatment costs of biosimilar vs. originator medicines has led to loosened usage/prescription controls in hospitals, leading to higher freedom of prescribing for physicians. For example, Southern healthcare region in Sweden relaxed restrictions on prescribing G-CSF for patients receiving G-CSF therapy for febrile neutropenia after biosimilar launch and the associated reduction in treatment costs. As a result, uptake of G-CSF increased five-fold in this region. Also, in 2008 NICE guidance did not recommend use of infliximab for the treatment of ankylosing spondylitis, but following launch of biosimilar infliximab, in new 2016 guidance NICE recommends infliximab in this indication in case the treatment is started with the least expensive infliximab product (NICE 2008; NICE 2016, 4).

As more biosimilar medicines become available, there may be opportunities for manufacturers to improve packaging and administration methods for these medicines. For example, Zarzio (biosimilar version of Neupogen) was the first G-CSF with an innovative automatic needle guard specifically designed for prefilled glass syringes (GaBi Online 2 August 2013). Sandoz was also the only company that provided 'Patient Support Kit' which allowed patients to administer the medicine at home instead of having to go to a clinic or hospital (GaBi Online 2 August 2013).

Several learned societies have updated their recommendations and position papers lately. The European Crohn's and Colitis Organization (ECCO) has published results of a consensus meeting, held October 2016. This statement marks a significant shift in attitude from the previous ECCO position statement, which advised switching from an originator biological medicine to a biosimilar to be inappropriate and emphasized lack of data and benefit of biosimilars in general. The updated ECCO statement is, by contrast, supporting switching from the reference infliximab to a biosimilar infliximab and recommending that switching from originator to a biosimilar should be performed following appropriate discussion between physicians, nurses, pharmacists and patients, and according to national recommendation. (GaBi Online 27 January 2017.) The European Society for Medical Oncology (ESMO) published on January 2017 a position paper on biosimilars, saying that "biosimilars create opportunities for sustainable cancer care". The paper covers several aspects, including switching and interchangeability, which should be permitted if the physician is well-informed about the products, the patient is fully briefed by the physician and a nurse is closely monitoring the changes and tracking any adverse events. The first biosimilar cancer medicines are expected to reach the European market during 2017. (GaBi Online 20 January 2017 (c).) In June 2015, the Finnish Society for Rheumatology published a statement of the use of biosimilars in rheumatological therapeutical indications. It is stating that substitution at pharmacy level is not acceptable and the switch of an original medicinal product to a biosimilar should be based on a decision of the treating specialist and after patient is fully briefed. Also, "for patients who are treatment naive regarding biologicals, either an original or a biosimilar can be initiated on the same rationale". (The Finnish Society for Rheumatology 2015, 1.)

Several countries have updated national and regional guidelines to recommend to start treatment with a more cost-effective option (biosimilar or originator product). Also, increasing number of countries have developed guidelines that specify standards for conducting economic evaluations to be included in reimbursement applications (Henry et al. 2014, S15).

5.9 Biosimilar medicine pipeline for four key original biological medicines

A number of biosimilar players have emerged in the last few years, including innovative companies (Pfizer, Novartis, Boehringer Ingelheim), generics companies (Teva) and some companies with no prior pharmaceutical expertise who are moving into the biosimilar business (Samsung Bioepis, LG Life Sciences). The innovator companies like Pfizer and Amgen have one of the biggest biosimilar portfolios, but also, several Korean companies have entered to biosimilar market, like Samsung Bioepis and Celltrion. (figure 24.)

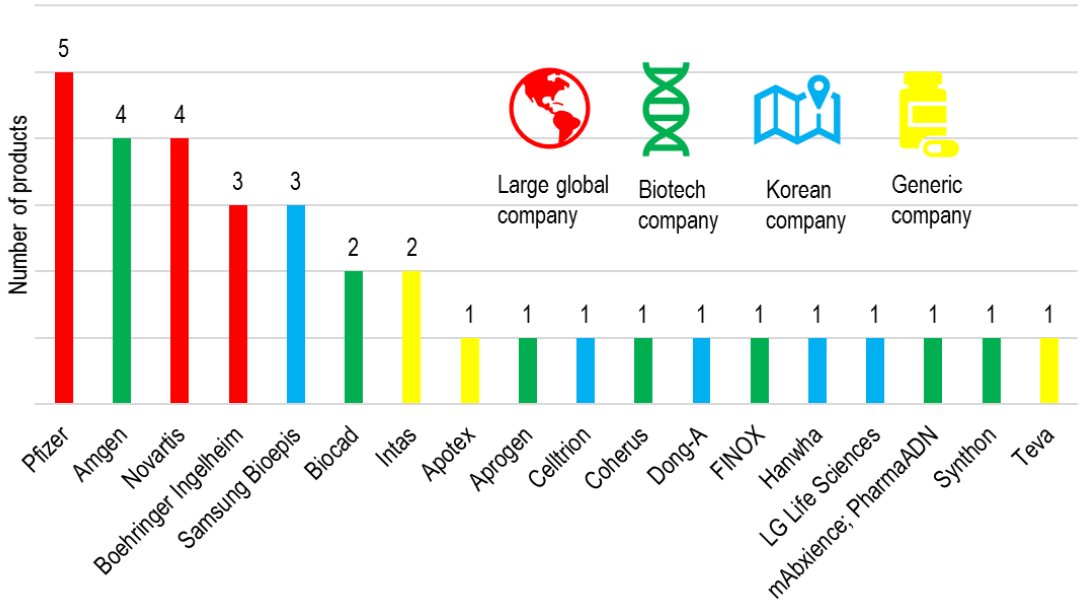


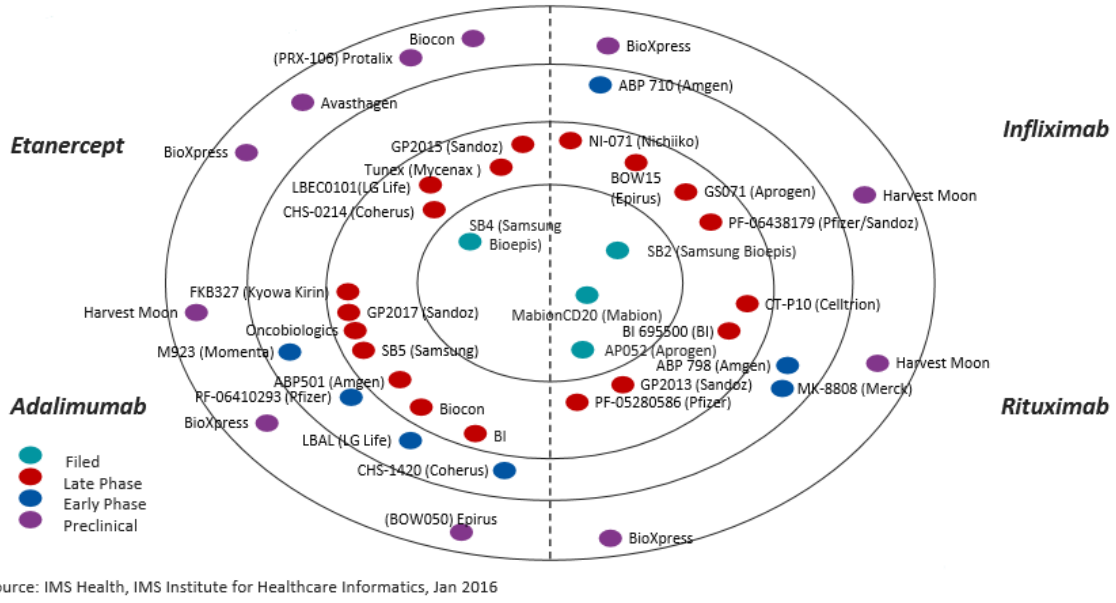
FIGURE 24. Number of biosimilar products in registration, pre-registration and phase III (adopted from Troein 17 May 2016, 8)

There were 41 biosimilar medicines in the pipeline for four key original biological medicines at the end of 2015 from multiple different pharmaceutical companies (figure 25). Of those Samsung Bioepis has received approval in the EU for its biosimilar etanercept, SB4 (refence product Enbrel) January 2016 and biosimilar infliximab, SB2 (reference product Remicade) May 2016.

In December 2016, Celltrion received initial authorization for its biosimilar rituximab, CT-P10 (reference product MabThera) and Amgen received initial authorization for its biosimilar adalimumab, ABP501 (reference product Humira), in January 2017. Amgen applied for marketing authorization for its biosimilar adalimumab under two names, Amgevita and Solymbic. Humira has been blockbuster since 2005 and AbbVie announced 2016 sales to be 16 billion dollars worldwide and sales

increase 16,1 percent on an operational basis with last year (AbbVie 2017; Brennan (a) 2017). More than a dozen other companies are also developing biosimilar adalimumab's, including Boehringer Ingelheim, Momenta Pharmaceuticals, Sandoz and a joint venture between Samsung Biologics and Biogen (Brennan (a) 2017, figure 25).

Additional biosimilar products are also in development for other biologics like tocilizumab (reference product, RoActemra), golimumab (reference product Simponi), and abatacept (reference product Orencia). (IMS Institute for Healthcare Informatics March 2016, 10.)



Source: IMS Health, IMS Institute for Healthcare Informatics, Jan 2016

FIGURE 25. Biosimilar pipeline at the end of 2015 (adopted from IMS Institute for Healthcare Informatics March 2016, 11)

The global biologic medicines market is projected to exceed 390 billion US dollars by 2020 and account for 28% by value of the total global pharmaceutical market. Therefore, biosimilars have an increasingly important role to play. By 2020, biosimilars have the potential to enter markets for a number of key biological medicines, whose current sales account more than 40 billion euros. As a result of biosimilars, the cumulative potential savings for healthcare systems in the five major European Union (EU) markets (i.e. EU5) and the U.S., could exceed 50 billion euros in aggregate over the next five years and reach as much as 100 billion euros. IMS study estimates that almost 50 distinct biosimilars are currently in development and will likely result in a highly competitive marketplace over the next five years. (IMS Institute for Healthcare Informatics March 2016, 1.)

5.10 Challenge of high costs of medicines

Pharmaceuticals have a vital role in the health system. The affordability and financing of new medicines challenges governments worldwide and policy makers are balancing the access of patients to new effective pharmaceuticals with limited health care budgets. At the same time policy makers should provide the right incentives to manufacturers to develop new generations of pharmaceuticals. (OECD 2015, 178; WHO 2015, 17.)

In European countries policy makers consider the high prices of medicines be the main challenge of access to new medicines given the budgetary restraints they have. A special concern is, in the context or pursuing equitable and comprehensive health care and against the backdrop of the global economic crisis, ageing populations and the continuing increase in non-communicable diseases, the continual introduction of new high-price medicines. Some health authorities are already struggling to fund new high-price pharmaceuticals and this has already led to situations where some pharmaceuticals, including pharmaceuticals providing important benefits, may not be available at all, or not accessible to all patients who need them. The IMS Institute of Healthcare information has predicted that worldwide pharmaceutical sales are 30% higher in 2018 than in 2013. The major contributor to pharmaceutical spending growth will continue to be specialty medicines. The reason to this is that there will be more specialty medicines which prices will be in very high levels and more patients need them. Specialty pharmaceuticals are novel drugs and biologic agents that require special handling and ongoing monitoring, are administered by injection or infusion and sold in the marketplace by a small number of distributors and are often considered part of the "personalized medicine" paradigm (right medicine to the right patient at right time). (Hirsch et al. 2014, 1714; OECD 2015, 40-41; WHO 2015, 17, 109, 112.)

Consumption of medicines has increased and pushed pharmaceutical medicine spending up. Rising prevalence of chronic diseases, population ageing, changes in clinical practices (guidelines), coverage extension and new treatment opportunities have increased demand for pharmaceuticals. Recent years cost-containment policies and patent expiries of a many top-selling products have put pressure on pharmaceutical prices. Price pressure has resulted a slower pace of growth over the past decade. Coming years' proliferation of high-cost specialty medicines will be the driver of health care spending growth, expected to account for 50 percent or more of pharmaceutical spending growth in near future. Some of these medicines will bring benefits to patients and others will

have only marginal improvements of patient's outcomes. According to standard thresholds, many of these medicines are not cost-effective. (OECD 2015, 29-30, 34, 41.)

Of the therapeutic areas, cancer has the highest expected spending growth due to the increasing incidence of cancer worldwide and new medicine approvals. Also, many orphan medicines approvals are expected in near future. (OECD 2015, 41.)

5.10.1 Challenge of costs of biological medicines

Increase in the cost of biological medicinal products continues to be strong compared to the cost of traditional medicines. Most biological medicines have been under patent protection, and have not therefore been under price competition which would have lowered their prices. In recent years, first patents of biological products have expired and biosimilars have become to the market. (HE 2016, 10.)

The increase in the number of clinical trials in the past five years is one indicator of the strong growth of biological medicines. The number of blockbusters, i.e. products with sales of more than US$1 billion per year, is another indicator. 2012 there were 33 blockbusters compared to 2006, when there were 20 blockbuster biologicals. (GaBi Online 31 January 2014.)

The global biologic medicines market is estimated to exceed 390 billion US$ by 2020 and going to account up to 28 percent of the total market for pharmaceuticals, while 2002 sales were only 46 billion US$ and share was 11 percent (figure 26). Biological medicines represent 27 percent of pharmaceutical sales in Europe and between 2012 – 2013 market has grown 5.5 percent in value sales compared to 1.9 percent of total market grew. Biologicals growth is driven by monoclonal antibodies (mAbs) and human insulin, with four out of the top five biologicals in 2012 being mAbs. (European Commission (c) 2015, 2; Baelen 2015; GaBi Online 31 January 2014; IMS Institute for Healthcare Informatics November 2013, 9.)

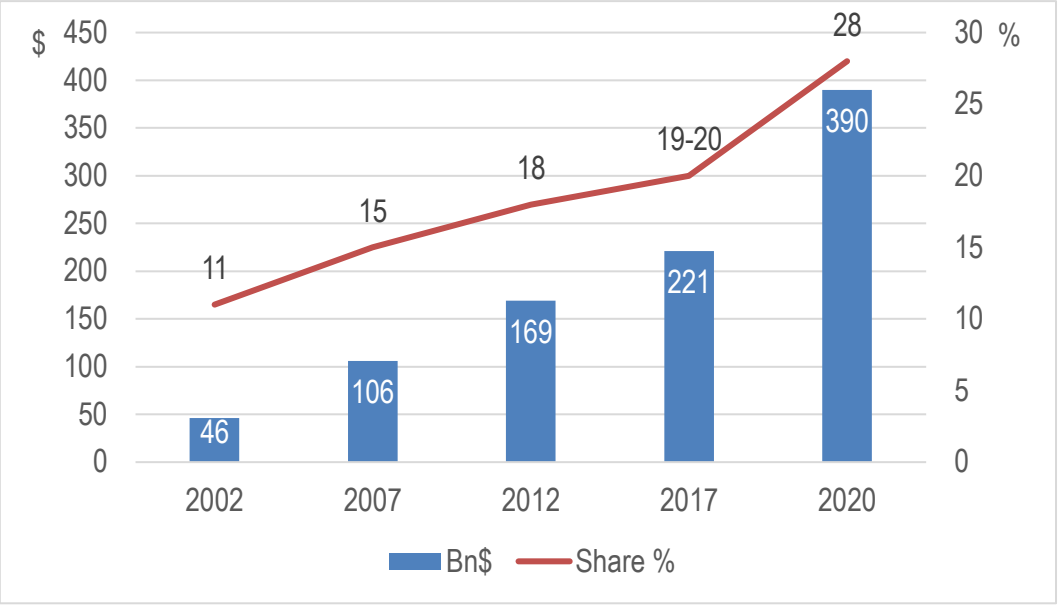


FIGURE 26. The biologics market. (Baelen 2015; IMS Health November 2013, 9; IMS Institute for Healthcare Informatics March 2016, 1)

Biological medicines are often remarkably expensive due to the highly demanding manufacturing process, high drug development costs and significant therapeutic value. One of the main reasons for the high price however is the lack of price competition. (Fimea (l) 2014.)

The high cost of biological medicines and reduced pharmaceutical budgets due to austerity measures mean that biological medicines are not accessible for all patients and they create financial challenges for healthcare systems. On the other hand, the entry of biosimilar medicines into markets, after biological originators' patent expiries, continues to pave the way in providing a sustainable supply of biological medicines across Europe. (European Commission (c) 2015, 2.)

The importance of biological medicines is constantly growing and same time the relatively higher pharmaceutical expenses associated with biological medicines limit their use in hospitals, also impacting their reimbursement status. Lääketeollisuus ry sees that the biosimilars introduced to the market will launch a price competition that brings therapy costs down and this way may increase the opportunities to introduce novel medicines in hospitals, thereby contributing to their entry into the reimbursement system. (Lääketeollisuus ry (c), accessed 2 October 2016.)

For example, biological medicines usage in Rheumatology has increased strongly in the 2010s. End of August 2009 Finnish national register for biologic treatment in rheumatic diseases (ROBFIN) had 3145 patients who had received biological medicine compared to end of year 2012 when

number was 5511. (Reumaliitto 2013.) National register for biologic treatment in rheumatic diseases in Finland (ROB-FIN) is a nation-wide prospective cohort study aiming to provide observational data on safety, effectiveness and costs of biologic treatments in routine healthcare. (DiaGraphIT$_{AS}$, accessed 2 October 2016.)

In Potilaan lääkärilehti (2014) is commented that biological medicine products are not new inventions, because those have been on the market over thirty years. The use of the biological medicines is limited by high price, which is due the challenging production methods and lack of price competition. This is going to change with help of biosimilar products. (Nykopp J 2014.)

The ten best-selling medicines in wholesale prices in Finland 2014 and 2015 are listed in figure 27. There were eight biological medicines in the list both 2014 and 2015. The first, second and fifth places in 2015 were claimed by the TNF-alfa inhibitors Humira (adalimumab), Enbrel (etanercept) and Remicade (infliximab), which are used for the treatment of rheumatoid arthritis, psoriasis and inflammatory bowel diseases. The best-selling antineoplastic agents in the list were Mabthera (rituximab), which is used for example, to treat lymphomas, Herceptin (trastuzumab), for example for breast cancer and Avastin (bevacizumab) for example for metastatic carcinoma of the colon or rectum with other antineoplastic agents. The best-selling antidiabetic medicines in the list were insulin Lantus (glargine) and Levemir (detemir). 2015 Cervarix (vaccine against certain types of cancer-causing human papillomavirus (HPV)) has drop out and Avastin (recombinant humanized monoclonal antibody) has taken its place in top ten. Total sales in wholesale prices of the top 10 products were about 276 million euros and eight biological medicines sales were 233 million euros (figure 27). Total medicine sales in Finland 2015 was 2 958 million euros, of which hospital medicines share was 19 %, 561 million euros (figure 35, figure 49). 2013 total sales of six of essential biological medicines was about 170 million euros, which was 8 % of whole year's medical sales. (Fimea (b) 2016; Ministry of social affairs and health (g) 2016, 3 - 4; Lääketeollisuus ry (a), accessed 13 July 2016; Lääketeollisuus ry (b), accessed 13 July 2016; Talouselämä 2016.)

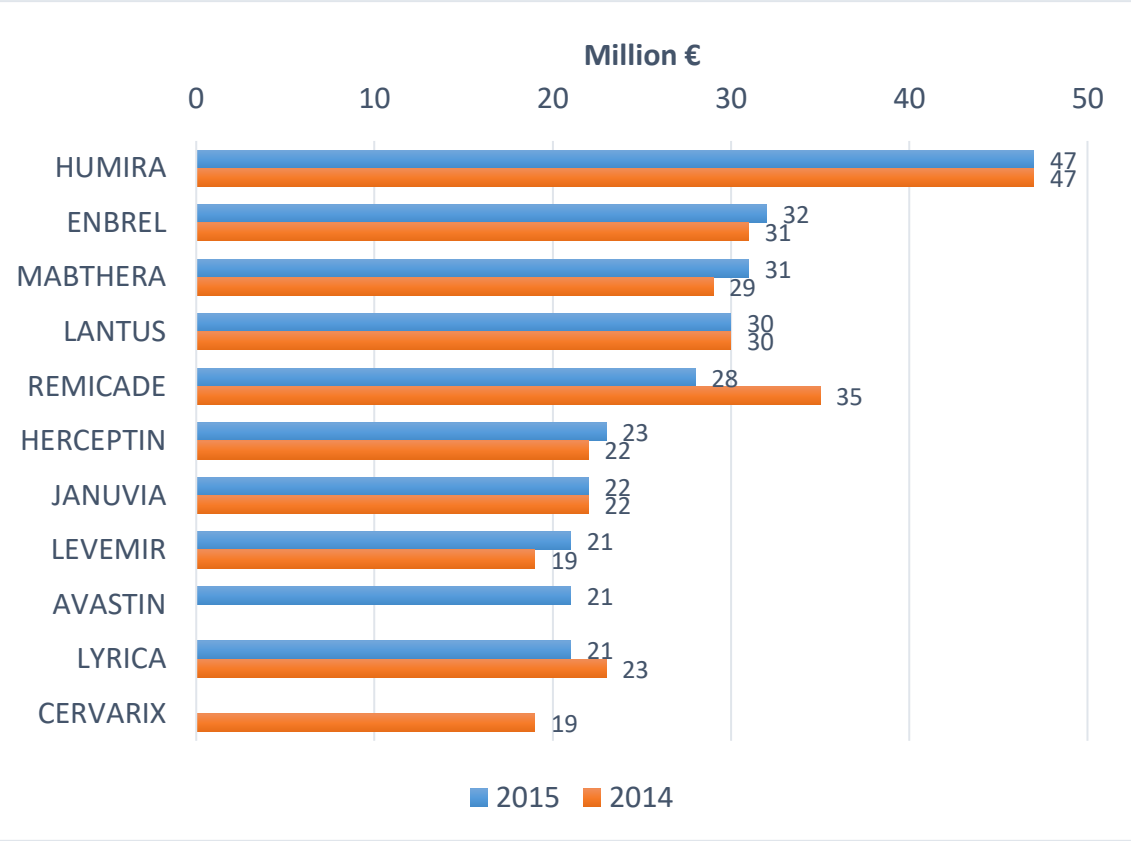


FIGURE 27. Top ten medicinal products in Finland in 2014 and 2015. Wholesale prices in million euros (Lääketeollisuus ry (a), accessed 13 July 2017; Lääketeollisuus ry (b), accessed 13 July 2017)

The link between gross domestic value, health expenditure and global medicine prices leads to large dissimilarities in affordability between countries and in the end, influence patients' access to biologicals. In Central European countries, affordability was a relevant factor that impacted on biologics access. (Laires et al. 2013, 883.)

5.10.2 Examples of costs of new medicines

Specialty pharmaceuticals have already transformed the pharmaceutical industry and the development of pharmaceuticals has shifted towards those. Many of the latest breakthrough treatments, including treatments for cancer, rheumatoid arthritis, HIV and multiple sclerosis have been special pharmaceuticals. (Hirsch et al 2014, 1714.)

New medicines to treat cancer patients cost between 6 000 to 10 000 US$ per month. The cost of new cancer medicines has doubled over the past ten years without necessarily having a concomitant improvement in survival. Requested prices for most new medicines launched are likely to continue to rise due to fact that new cancer medicines are launched for targeted indications, manufacturers seek orphan status and associated high prices. Trastuzumab emtansine costs 90 000£ - 185 600£ per course at an estimated cost per QALY (Qualite Adjusted life year). In Finland trastuzumab emtansine estimated total medicine cost is about 67 700 euros per patient. In the Hospital District of Helsinki and Uusimaa (HUS) the most expensive medications cost more than 200 000 euros per year per patient. They have also estimated the cost of new medicines and for example medicine for chronic lymphocytic leukemia (obinutuzumab) could cost for five patients per year about 140 000 euros and a second-line treatment for lymphoblastic leukemia patients with poor prognosis (blinatumomab) could cost about 150 000 euros per patient. (Helsingin ja Uudenmaan sairaanhoitopiiri 2016, 1; HUS 2015, 9; Härkönen et al. 2015 (a), 18; WHO 2015,14, 104.)

There is about 170 million Hepatitis C patients in the world and in 2013 Finland registered to THL's Register of Infectious Diseases a total of 1 174 new hepatitis C cases. One of the new medicines for hepatitis C, 12-week course of sofosbuvir, costs in the United Kingdom from 35 908£ to 71 816£ depending on genotype. Same treatment costs in Finland 50 940 €. In the United States sofosbuvir costs about 1 000 US$ per tablet equating to 84 000 US$ for a standard course. (WHO 2015, 112; Färkkilä 2014, 1813, 1816.)

New orphan medicinal products are challenging health authorities. Typically, annual acquisition costs for these medicines are 200 000 – 500 000 US$ per patient per year. In the Netherlands, orphan medicine Myozyme, which is used to treat Pompe's disease, the costs ranges between 400 000€ to 700 000€ a year. There is also case of ultra-rare disease treatment which cost about one million $. The medicine was Glybera, heralded as the first gene therapy in the Western world, for lipoprotein lipase deficiency. Only one patient has received this treatment so far. (Kalliokoski et al. 2016, 2042; Regalado 2016; WHO 2015,15.)

5.10.3 Patients access to biological medicines for Rheumatoid Arthritis

Biological medicines have proved effective for the treatment of immune-mediated inflammatory diseases like rheumatoid arthritis (RA). These medicines are used rarely in first-line, because the

European League Against Rheumatism and many national guidelines recommend biological medicines for RA patients who fail to respond adequately to sDMARD (synthetic disease modifying anti-rheumatism drug) treatment alone and partly due to high costs. Even as second-line therapy, all clinically eligible patients do not have access to biological medicines. (Gulácsi el al. 2015; Putrik el al. 2014, 199.)

The access and use of biological medicines varies strongly between countries across World Health Organization European Region and seems to be associated with socio-economic development of the countries (figure 28). Administrative and financial restrictions have been identified as the most important barriers to a treatment with bDMARDs (biologic disease modifying anti-rheumatism drugs). Countries in Eastern and Central Europe have particularly poor access to bDMARDs. Also, limited access to bDMARDs in patients with RA might be associated with poorer health. A study from Putrik et al showed that the cost of annual treatment with sDMARDs never exceeded GDP in WHO European Region (included 46 countries), but cost for 1 year of bDMARD treatment exceeded GDP in 26 countries. (Gulácsi el al. 2015; Putrik el al. 2014, 198, 203.)

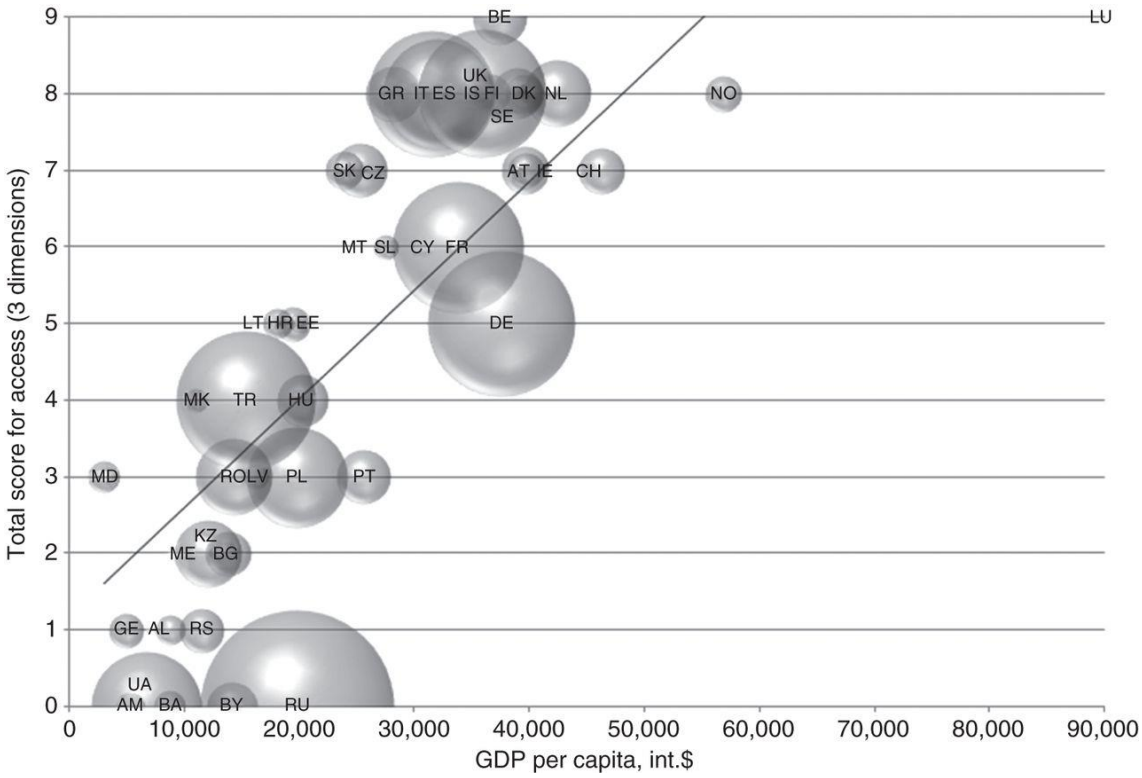


FIGURE 28. Access to treatment with biologic disease modifying antirheumatic drugs and gross domestic product per capita in the European Region. Size of the bubbles is proportional to the

population size of the country. AL, Albania; AM, Armenia; AT, Austria; BA, Bosnia and Herzegovina; BE, Belgium; BG, Bulgaria; BY, Belarus; CH, Switzerland; CY, Cyprus; CZ, Czech Republic, DE, Germany; DK, Denmark; EE, Estonia; ES, Spain; FI, Finland; FR, France; GB, the UK; GE, Georgia; GR, Greece; HR, Croatia; HU, Hungary; IE, Ireland; IS, Iceland; IT, Italy; KZ, Kazakhstan; LT, Lithuania; LU, Luxemburg; LV, Latvia; MD, Moldova; ME, Montenegro; MK, Macedonia; MT, Malta; NL, Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RS, Serbia; RU, Russia; SE, Sweden; SK, Slovakia; SL, Slovenia; TR, Turkey; UA, Ukraine; UK, United Kingdom (adopted from Putrik et al. 2014, 204)

The cost-effectiveness and budget impact of expensive and innovative medications is a major topic of discussion in Western countries, but same time the implications of the unaffordability for low income countries has received limited attention. About 320 million people in the European Region (almost 40 % of the population) have severely restricted access to bDMARDs for the treatment of RA (figure 29). (Putrik el al. 2014, 203 – 204.)

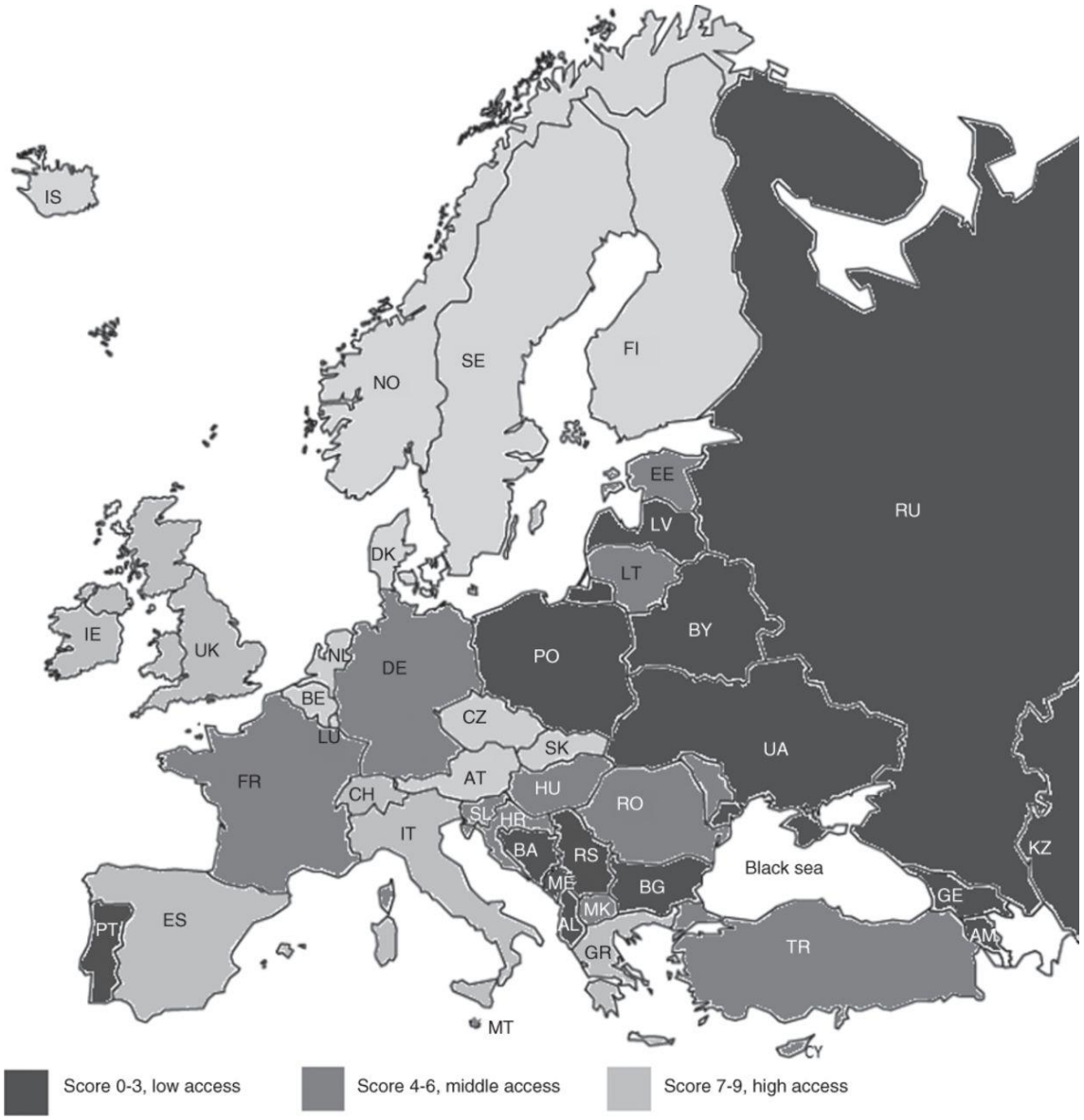


FIGURE 29. Access to treatment with biologic disease modifying antirheumatic drugs in the European Region (adopted from Putrik et al. 2014, 205.)

There is an analyze made of the role of biosimilars in reducing costs and increasing patient access to bDMARDs in rheumatology. The budget impact of switching patients to biosimilar infliximab for RA in the UK, Italy, France and Germany is estimated over 5 years to offer savings of €233 million for 20 percent discount and €433.5 million for 30 percent discount. An additional 7561 patients could be treated across these four countries and the Netherlands with a 30% discount, using medicine cost savings after 1 year of biosimilar infliximab. In Europe, 30 percent price discount for biosimilar infliximab, would represent cost savings of more than 530 million euros every year. With the 50 percent price reduction seen in Nordics could be achieved across the EU, the potential savings to reinvest could exceed 880 million euros annually. (Dörner et al. 2016, 5 – 6.)

European League Against Rheumatism had an update 2013 to its recommendations for use of DMARDs and bDMARDs, highlighting in their overarching principles that when prescribing these therapies, medicinal costs should be considered. Also, American College of Rheumatology 2015 guidelines raised cost as an important issue. Rheumatologists will be at the forefront of the use of biosimilar monoclonal antibodies, in terms of recommendations for use, design and analyses of randomized controlled trials. (Dörner et al. 2016, 6.)

5.11 Finnish hospital districts and University hospital catchment areas

In Finland, health services are divided into primary health care and specialized medical care. Primary health care refers to the municipally arranged monitoring of the health of the population and are provided by some 160 local health centers. Municipalities may organize primary health service alone or form joint municipal authorities or they may also procure services from private service providers. Specialized medical care is performed in hospitals and refers to examinations and treatments provided by medical specialist. (Ministry of social affairs and health (a), (b), (c), accessed 9 January 2017.)

For the organization of specialized medical care, Finland (mainland) is divided into twenty hospital districts (health care services on the autonomous Åland Islands are provided based on the Act on the Autonomy of Åland) and every municipality must belong to one of them. The Hospital District of Helsinki and Uusimaa (HUS) is the largest of the districts, providing specialized medical care for 1,6 million residents and smallest is at Itä-Savo 43 thousand residents. Hospital districts plan and develop the provision of specialized medical care so that primary health care and specialized medical care form an effective entirety. They coordinate and control quality of the municipal laboratory and imaging services, medical rehabilitation and other specialized services, research, development, education and training as well as the harmonization of municipal health care information systems. In the hospital districts, university and central hospitals are responsible for the most demanding medical operations. The five university hospitals locate in Helsinki, Turku, Tampere, Kuopio and Oulu. Some specialized medical care services are centralized on the national level to the university hospitals. For example, Helsinki University Hospital is responsible for organ transplants and children open heart surgeries. (Figure 30; Table 6; Ministry of social affairs and health (h) 2013, 12; Ministry of social affairs and health (c), accessed 9 January 2017.)

All the hospital districts belong to one of the five university hospital catchment areas, HUCH, TUCH, TAUH, KUH or OUH (table 6). Catchment areas coordinate the provision of specialized medical care, information systems, medical rehabilitation and procurement (Ministry of social affairs and health (h) 2013, 12).

TABLE 6. Number of Residents and member municipalities in Finnish Hospital districts and expert responsibility areas (ERA) (Kunnat.net (a), (c), accessed 10 August 2016; Havo 2013, 50)

Abbreviation	Hospital district	Member municipalities	Residents (31.12.2015)	Purchasing period/years
HUS	Helsinki and Uusimaa (Helsinki ja Uusimaa)	24	1 616 321	**2**
EK	South Karelia (Etelä-Karjala)	9	131 155	**4**
KYM	Kymenlaakso (Kymenlaakso)	6	171 778	**2**
	HUCH catchment area, total	**39**	**1 919 254**	**(No common purchasing period)**
P	Pirkanmaa (Pirkanmaa)	23	526 941	
EP	South Ostrobothnia (Etelä-Pohjanmaa)	18	197 371	
KH	Kanta-Häme (Kanta-Häme)	11	174 710	
PH	Päijät-Häme (Päijät-Häme)	12	212 465	
	TAUH catchment area, total	**64**	**1 111 487**	**2**
VS	Varsinais-Suomi (Varsinais-Suomi)	28	477 372	
S	Satakunta (Satakunta)	18	222 957	
V	Vaasa (Vaasa)	13	170 212	
	TUCH catchment area, total	**59**	**870 541**	**2**

PS	Pohjois-Savo (Pohjois-Savo)	19	248 129	
ES	Etelä-Savo (Etelä-Savo)	9	103 278	
IS	Itä-Savo (Itä-Savo)	4	43 453	
KS	Central Finland (Keski-Suomi)	21	251 904	
PK	North Karelia (Pohjois-Karjala)	14	168 329	
	KUH catchment area, total	**67**	**815 093**	**2**
PP	North Ostrobothnia (Pohjois-Pohjanmaa)	29	407 160	
KAI	Kainuu (Kainuu)	8	75 324	
KP	Central Ostrobothnia (Keski-Pohjanmaa)	10	78 608	
L	Lappi (Lappi)	15	117 789	
LP	Länsi-Pohja (Länsi-Pohja)	6	63 069	
	OUH catchment area, total	**68**	**741 950**	**3**
	Mainland Finland	**297**	**5 458 325**	
	Ahvenanmaa (Åland)	16	28 983	
	Total	**313**	**5 487 308**	

FIGURE 30. Hospital districts and university hospital catchment areas. University hospital locations are written in red, central hospital locations in black, hospital districts are abbreviated (table 6) and university hospital catchment areas are in colors (Finnish Medicines Medicines Agency Fimea and Social Insurance Institution 2016, 40; Kunnat.net (b), (d), accessed 10 August 2016)

5.11.1 Health and social service reform

In the next few years' entire system of health and social services will be reformed in Finland. The need for this reform emerged from problems in ensuring equal and adequate social welfare and health care services to citizens in all parts of the county. Currently the organisation of health and social services is entrusted to hundreds of municipalities and joint municipal authorities and small and financially weak municipalities have encountered difficulties in organising and producing services. In the reform, responsibility for providing social welfare and health care services is being

transferred to larger and hence stronger administrative entities and this way, even in remote areas, where a small municipality's own resources would be inadequate, provision of service could be ensured. The Government has decided that in future health and social services will be organised by 18 autonomous counties and these services will be state funded. (Ministry of social affairs and health (h) 2013, 38, 39; National institute for health and welfare 2016.)

Aim of the ongoing reform is to safeguard access to services, ensure regional and social equality across the country, integrate health and social services, and restrain the growth of health and social expenditure. (National institute for health and welfare 2016.)

5.12 Medicines Policy 2020

The main objective of pharmaceutical service is to enable efficient, safe, rational and cost-effective pharmacotherapy for all those in need of it. The core values of medicines policy are responsibility, effectiveness, quality, equality, justice and economy defined as cost-effectiveness. (Ministry of Social Affairs and Health (f) 2011, 5, 10.)

Five main pharmaceutical policy objectives are presented in Medicines Policy 2020 document for coming decade: (Ministry of Social Affairs and Health (f) 2011, 9.)

1. The pharmaceutical service constitutes a part of the social welfare and healthcare service system.
2. The pharmaceutical service is of high quality, efficient and cost-effective.
3. Rational pharmacotherapies and good medication safety promote people's wellbeing and public health, decreasing the healthcare expenditure.
4. Pharmaceutical research has a positive impact on health, wellbeing and employment.
5. Veterinary pharmaceutical services safeguard public health and promote the wellbeing of humans and animals.

These five objectives are joint objectives for the social welfare and healthcare authorities and stakeholders in the field of pharmaceuticals. (Ministry of Social Affairs and Health 2011, 9.)

5.12.1 Rational Pharmacotherapy Action Plan

According to World Health Organization (WHO), medicine use is rational (appropriate, proper, correct) when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community (Holloway et al. 2011, 2).

In Finland, The Rational Pharmacotherapy Action Plan is listed into the Government Programme of Prime Minister Juha Sipilä. The objective is to improve the overall treatment and functional capacity of patients, and to create a framework for using pharmacotherapies that are cost-effective from the perspective of both the patient and society. An interim report will be published at the beginning of 2017. (Ministry of Social Affairs and Health 2016 (d), (e).)

The assessment includes medical treatment processes like, evaluation of the need of medical therapy, the decision of the initiation of medical therapy, the choice of the medicine, delivery of the medicine from pharmacy or implementation of treatment in health care unit, the reimbursement costs of the medicines, patient education and informing, the use of the medicine and monitoring of medicinal treatment, treatment changes and stoppings. Also, structures of pharmaceutical supply in the new social and health system is one of the themes. Rational pharmacotherapy Programme also surveys a range of actions that could lead to medicine cost savings. (Ministry of Social Affairs and Health 2016 (e); Ruskoaho 2016, 20-21.)

One of the subjects in the Governments Rational Pharmacotherapy Action Plan is to promote the adoption of biosimilars in Finland. The purpose is, without compromising the effectiveness of pharmacotherapy for patients, to reduce the costs arising from biological medicinal products. The plan supports the implementation of planned legislative reforms in order to promote the adoption of biosimilars. The implementation of the plan is coordinated by Finnish Medicines Agency Fimea. (Fimea (c) 2016; Ministry of Social Affairs and Health 2016 (d).)

It is possible that the introduction of biosimilars do not lead to the objective decline in the total cost. In this case, money saved could be used to other medicines, including new innovative medicines. If the prescribing of medicine is rational, patients will eventually receive the greatest benefit. (Fimea (g) 2016.)

5.12.2 Rapid Assessment of hospital-only medicinal products

In Finland, a new medicinal product can only be sold after marketing authorisation is granted by the Finnish Medicines Agency Fimea or the European Commission. The efficacy, safety and adequate quality of the medicine must be demonstrated in order to obtain a marketing authorisation. Demonstration of a medicines therapeutic and economic value is not a prerequisite. (Fimea (e), accessed 8 December 2016.)

For adoption of new hospital medicines, Finland has not had so far uniform assessment and decision-making process. Between hospitals, there are considerable differences how the assessments are being carried out. Lack of national coordination has caused regional variation in use of medicines and the adoption speed. Fimea is developing a rapid assessment of hospital medicines in cooperation with stakeholders. The aim is to standardize procedures related to adoption of hospital medicine and to promote the introduction of a regionally equal access to care. Fimea coordinates assessment activities, produces and publishes the assessment reports. The aim is to make outcomes available as soon as the marketing authorization has been granted or receives a new indication. (Härkönen et al. 2015 (b), 46, 47; Fimea (e), accessed 8 December 2016.)

For the pharmacotherapies under evaluation, assessments of the therapeutic and economic value focus on relative effectiveness, safety and economic aspects and when applicable social and ethical aspects are also accounted. With the help of the assessment process, health care total costs can be managed, and resources for new medicines can be targeted appropriately. The assessment takes into account costs related to medicinal products both on hospital's point of view as well as from the perspective of the society. (Fimea (e), accessed 8 December 2016; Härkönen et al. 2015 (b), 47.)

The aim is to consolidate the assessment activities in 2016 - 2017. At that time, as a rule, all new hospital-only medicines are to be evaluated with rapid assessment. That would allow to harmonize guidelines for adopting of a new medicine. 2015 -2016 Fimea has made eleven assessment reports focused on new hospital-only medicines. (Fimea (h), accessed 12 January 2016; Härkönen et al. 2015 (b), 47.)

5.13 Health care expenditures in Finland compared to Nordic and EU countries

Year 2014 total Finland's health care expenditures were about 19,5 billion euros (figure 31). Compared to 2013, health care expenditures increased real 0,6 percent. Pharmaceutical and other medical non-durables expenditures decreased real 0,1 percent compared to previous year. It should be noted that, the relationship between pharmaceutical spending and total health spending can be complex, because increased expenditure on pharmaceuticals to tackle diseases may reduce the need for costly hospitalizations and interventions now or in the future. (OECD 2011, 154; Matveinen et al. 2016, 1.)

In 2014, specialized medical care (6,8 billion euros), primary care (3,8 billion euros), long-term care for the elderly and persons with disabilities (2,8 billion euros), as well as outpatient drugs and other medical consumer goods (2,4 billion euros) accounted for approximately three quarters of health care spending. (Matveinen et al. 2016, 1, 3-4.)

Since 1.1.2016 statistics have been made according System of Health Accounts (SHA) 2011. Health spending measures the final consumption of health care goods and services, including personal health care and collective services, but excludes spending on investments. (OECD (b) 2016.)

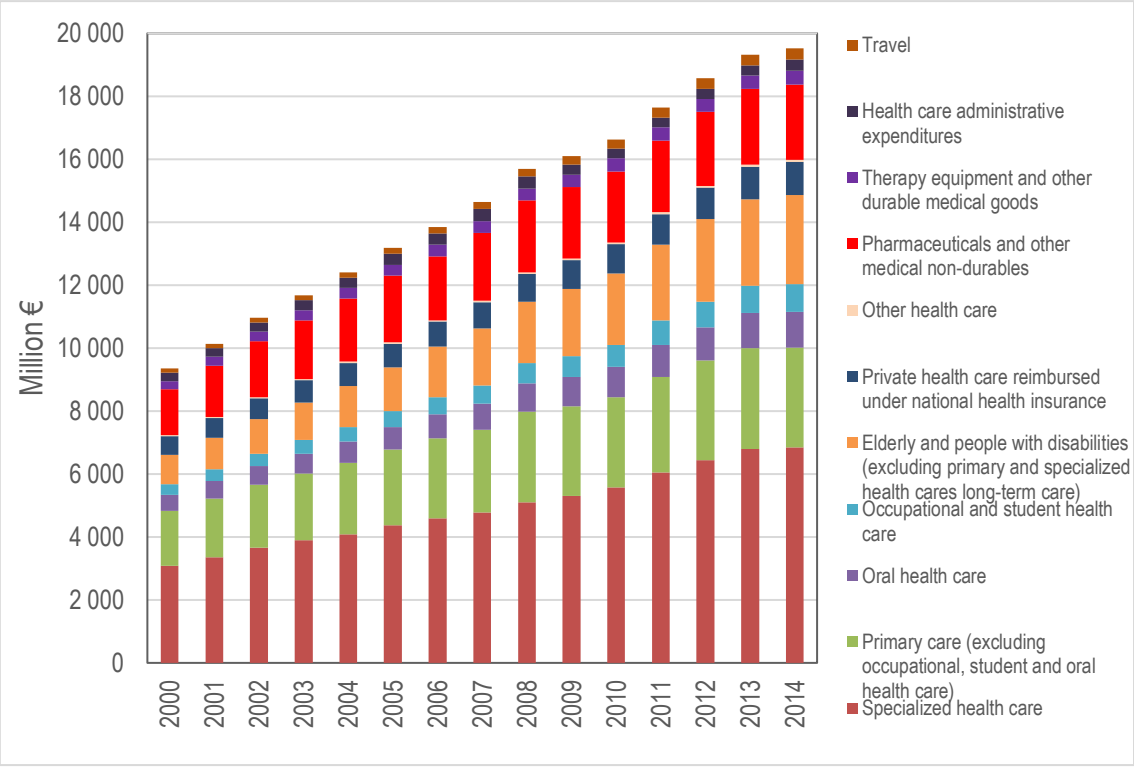


FIGURE 31. Health care expenditures 2000 – 2014, at 2014 prices, million euros (Matveinen et al 2016)

Per capita, health care expenditures in Finland 2015 was 3 984 US$ (figure 32) and health care expenditures share of GDP (Gross Domestic Product) was 9,6 percent (figure 33). Years 2013 and 2014 health care expenditures share of GDP was 9,5 percent (figure 34). In 2015, per capita number was lowest in the Nordic countries but when comparing share of GDP in European union, Finland share was higher (9,6) than average in European Union (8,8 percent). At same year Norway's per capita expenditure was highest in the Nordics, 6 567 US$ (figure 32). 2015 in Nordic's, health care expenditure percent of GDP was lowest in Iceland 8,8 percent and Sweden had highest in whole European Union 11,1 percent (figure 34).

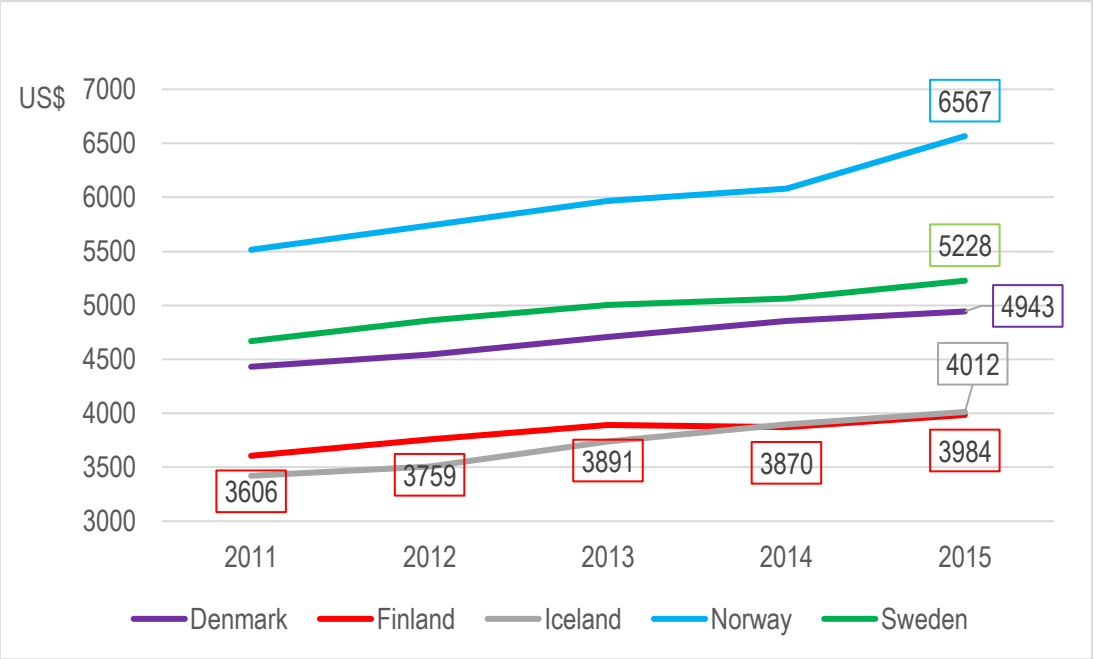


FIGURE 32. Health care expenditures, US dollars/capita 2011 – 2015 (OECD (a) 2016)

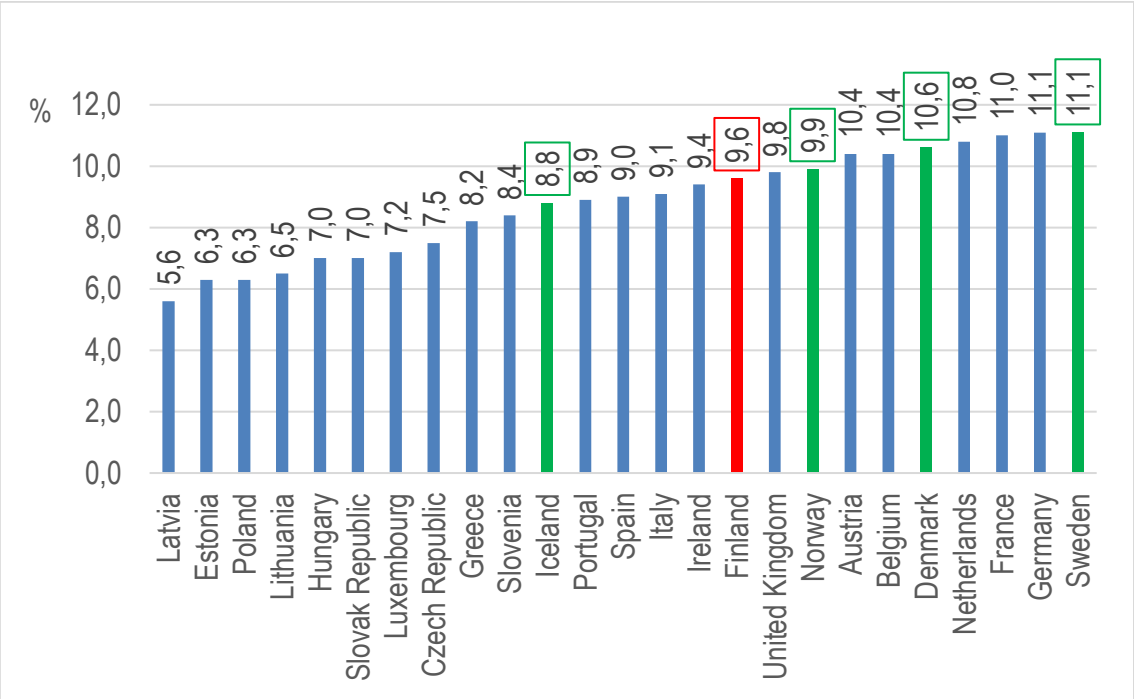


FIGURE 33. Health care expenditures % of GDP in European Union (28) 2015 (OECD (a) 2016)

2015 an important factor behind the increase of Norway's health care spending share of GDP was the fall in oil prices (Statistics Norway 2015). In 2014 health care expenditure share of GDP was 9,26 percent and 2015 it increased to 9,94 percent (figure 34).

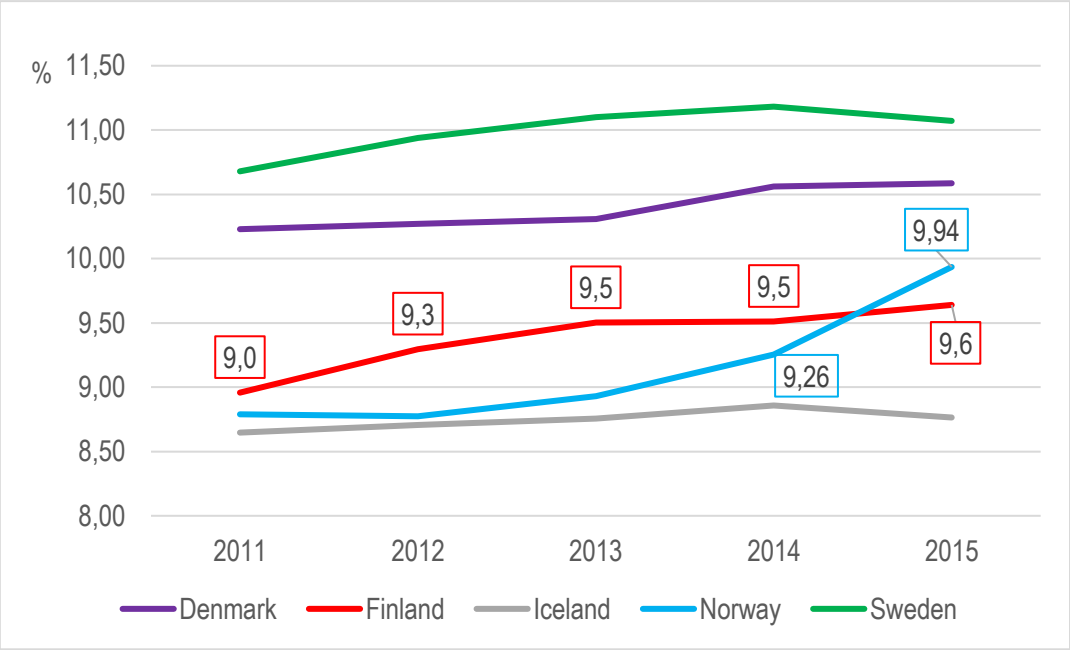


FIGURE 34. Health care expenditures, % of GDP 2011 – 2015 (OECD (a) 2016)

5.14 Pharmaceutical expenditures in Finland

In Finland, 2015, total sales of pharmaceuticals were about 3 billion euros (figure 35) and its change from previous year was 4,5 percent. Total sales include prescription medicines in outpatient care, sales to hospitals and OTC- medicines in outpatient care (Over the Counter medicines).

2015 the best-selling medicine groups were antineoplastic and immunomodulating agents (500 million euros at wholesale prices), medicines affecting the nervous system (360 million euros) and medicines affecting the alimentary tract and metabolism (292 million euros). When measured in terms of consumption, the most commonly used medicinal groups in Finland were cardiovascular system medicines, alimentary tract and metabolism products and medicines affecting the nervous system. The consumption of medicines in the statistics is as defined daily doses (DDD), assumed average maintenance dose per day for a drug used for its main indication in adults). (Appendix 2; Fimea (f) 2016; Finnish medicines agency Fimea and social insurance institution 2016, 31; Metveinen et al. 2016; WHO 2016.)

2014 sale of prescription medicines in outpatient care in Finland was 68 percent of total pharmaceutical sales (figure 36), 1 978 million euros. Sale of medicinal products has increased in recent years, generally 2 – 3 percent each year. Most has increased the cost of higher special rate of

reimbursement categories (100%) medical costs due to new and more expensive drug therapies. In 2015 1 378 million euros was paid as reimbursement payments under the Health Insurance Scheme. Reimbursement payments were up 5,5 percent from previous year, which was more than in the six preceding years. (Finnish medicines agency Fimea and social insurance institution 2015, 31; Ruskoaho 2016, 4; HE 2016, 47.)

In the period 2009 – 2014 the medicine reimbursement costs increased moderately by a maximum of 3,3 percent per annum having also occasional decreases. This was due to retrenchments, of which some were focused on pharmaceutical companies and pharmacies and some increased patient's deductibles. For example, medicine's generic reference price system was introduced on 2009 and at the same time, generic substitution was expanded to include medicines protected by methods patent. However, recently the reference price system's ability to promote price competition between products under the system has faded. Several significant medicine groups prices under reference price system have started to increase, for example groups of statins, other cardiovascular medicines, antacids and antipsychotics. It seems that price competition is no longer functioning as it should and government has made some proposals how reference price system could be intensified. In 2016, basic rate of reimbursement was increased from 35 percent to 40 percent and for pharmaceutical companies were set one-time 6,9 million euro's refund. In 2015 reimbursement payments were increased by the introduction of new, more expensive medicines for example medicines used for treatment of various cancers, diabetes, multiple sclerosis and rheumatoid diseases. The increase can also be partly explained by the fact that purchasers stocked up on medicines in late 2015 in preparation for the new initial deductible limit, adopted in the beginning of 2016. (Finnish medicines agency Fimea and social insurance institution 2015, 31; Ruskoaho 2016, 4, 5, 29-30; HE 2016, 12.)

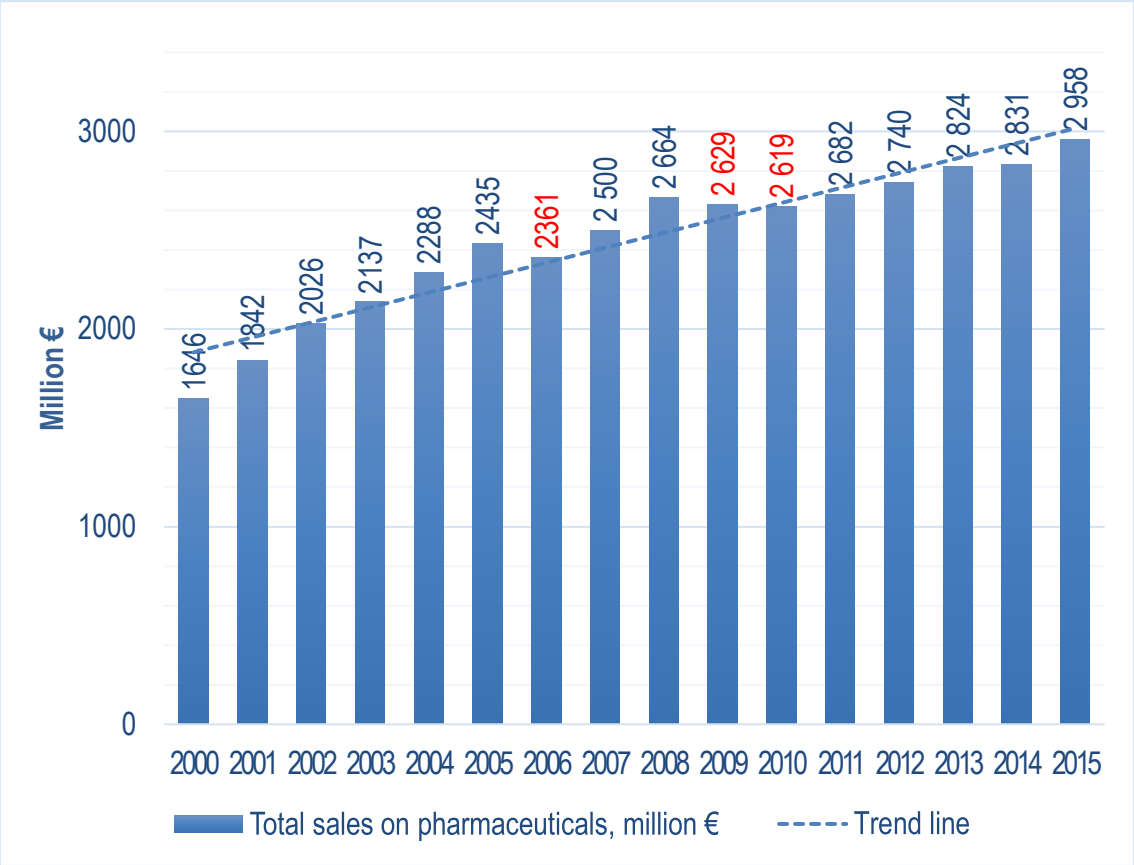


FIGURE 35. Total sales of Pharmaceuticals 2000 – 2014 in million euros. Retail prices (inclusive of tax) were used for calculating sales of medicines in the outpatient selling and wholesale prices were used for sales of medicines sold to hospitals (Appendix 1; Finnish medicines agency Fimea and social insurance institution 2010 – 2016; National Agency for Medicines and Social Insurance Institution 2008 -2009; Matveinen et al 2016)

2014 sales of prescription medicines were 68 percent and other medical durable goods was 2,8 percent of total pharmaceutical sales (figure 36). Compared to previous year, prescription medicine expenditures decreased 0,2 percent. Sales of prescription medicines, self-medication and other medical durable goods correspond 12,3 percent of health care expenditures (Matveinen et al. 2016, 4).

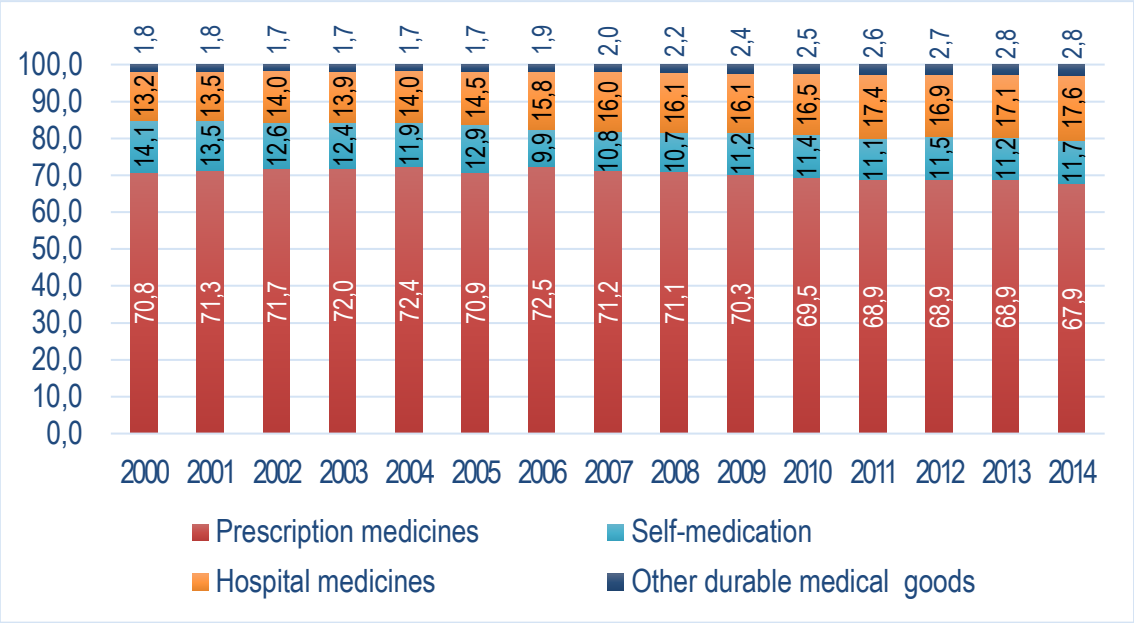


FIGURE 36. Total sales of pharmaceuticals 2000 – 2014, % (Matveinen et al. 2016)

The majority of total medicine sales 2015 are caused by antineoblastic and immunomodulating agents (500 million euros, ATC-code L) (figure 37) and not supprisingly six out of ten best selling medicines in Finland were in these group, Humira, Enbrel, Mabthera, Remicade, Herseptin and Avastin (all biological medicines). The medicines affecting nervous system (313 million euros, ATC-code N, exluding nicotine) and alimentary tract and metabolism medicines (292 million euros, ATC-code A) are also in top three in sales (figure 37). Sales in the group of anti-infectives for systemic use increased most, 36 million euros i.e. 25%. However the consumption of these products increased only by 4%, compared to previous year. In this group, the sales of human normal immunoglobulin increased the most, i.e. by 20 million euros and sales of antivirals for systemic use increased by 11 million euros. Increase of sales in the group of anti-infectives for systemic use was caused by new approved therapeutic indications to immunoglobulins and was seen especially in sales to hospital because immunoglobulins are most often used in hospital setting (84% of sales). Antivirals for systemic use medicine sales increased due the introduction of new medicines indicated for the treatment of HIV infection and hepatitis C. The sales of antineoplastic and immunomodulating agents increased at similar rate compared to last few years, by 9%, i.e. 39 million euros. Under this class of medicines the highest growth was seen in the group of immunosuppressants (includes for example TNF-a inhibitors), 14% i.e. 27 million euros. The second highest growth was in the group of antineoplastic agents, 8% i.e. 15 million euros, in which the costs of monoclonal antibodies increased the most, by almost EUR 9 million euros (Finnish medicines agency Fimea and social insurance institution 2016, 31, 35 - 36.)

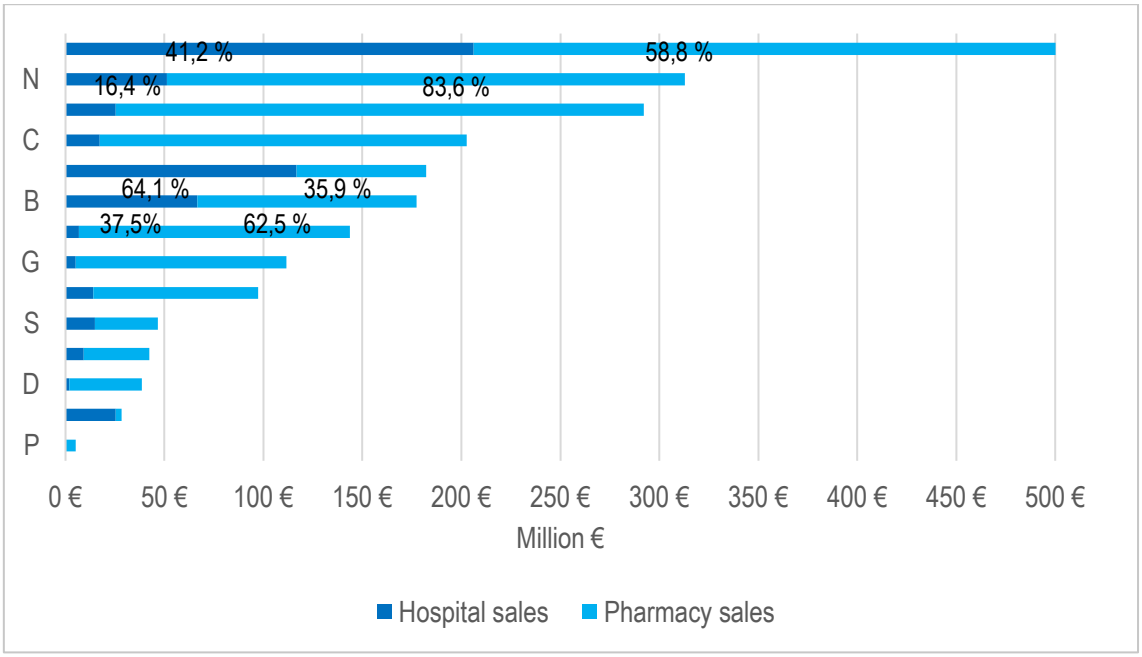


FIGURE 37. In 2015, distribution of medicine sales between pharmacies and to hospitals per the ATC-code, at wholesale prices (million euros). ATC-codes A: Alimentary tract and metabolism, B: Blood and blood forming organs, C: Cardiovascular system, D: Dermatologicals, G: Genito urinary system and sex hormones, H: Systemic hormonal preparations, excl. sex hormones and insulins, J: Antiinfectives for systemic use, L: Antineoplastic and immunomodulating agents, M: Musculo-skeletal system, N: Nervous system, P: Antiparasitic products, insecticides and repellents, R: Respiratory system, S: Sensory organs, V: Various (Appendix 2)

As clearly seen from figure 38, the most commonly used medicine group in previous years has been cardiovascular medicines (ATC-code C) 556,35 DDD/inhabitants/day. The two other commonly used medicine groups in 2015 were medicines affecting the alimentary tract and metabolism (ATC-code A), 296,32 DDD/inhabitants/day and medicines affecting the nervous system (ATC-code N), 259,53 DDD/inhabitants/day (figure 38).

The group of medicines which is biggest in sales, the antineoplastic and immunomodulating agents (ATC-code L), is one of the lesser used medicine groups. In 2015, consumption of this group of

medicines was 18,59 DDD/1000 inhabitants/day and it has increased from 2013, when consumption was 17,16 DDD/1000 inhabitants/day (figure 38).

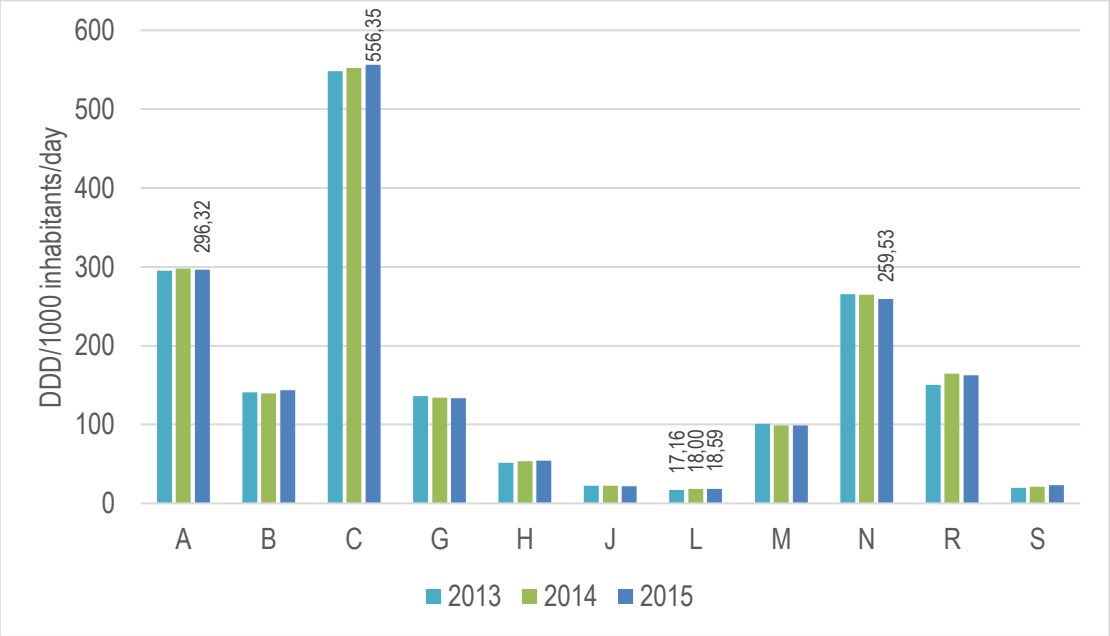


FIGURE 38. 2013 – 2015, consumption of medicines. ATC-codes A: Alimentary tract and metabolism, B: Blood and blood forming organs, C: Cardiovascular system, G: Genito urinary system and sex hormones, H: Systemic hormonal preparations, excl. sex hormones and insulins, J: Anti-infective for systemic use, L: Antineoplastic and immunomodulating agents, M: Musculo-skeletal system, N: Nervous system, R: Respiratory system, S: Sensory organs, V: Various (Fimea (d), 1, 9, 12, 18, 20, 24, 26, 32, 34, 37, 44, 45, 49, 50, accessed 14 November 2016)

5.14.1 Pharmaceutical expenditures in Finland compared to Nordic countries

In relation to the overall economy, 2014 pharmaceutical expenditures accounts for 1,4 percent of GDP on average in European Union countries. However, the dispersion around this average is high: pharmaceutical expenditures accounts for less than 1 percent of GDP in Norway and Denmark, while it reaches over 2 percent of GDP in Greece and Hungary (figure 39). Share of GDP in Finland was little less than average in European Union, 1,2 percent, but highest in Nordic countries (figure 39, figure 40). In most Nordic countries, pharmaceutical expenditures share of GDP has been stable in recent years, except Iceland (figure 40). In Iceland share of GDP have decreased during period 2011 – 2014 (figure 40). Iceland along with Norway and Denmark was among the top three expenditures of health before global financial crisis and the collapse of Iceland's three biggest

banks 2008. After that health expenditure as share of GDP dipped. Pharmaceutical products are mainly imported to Iceland and during the financial crisis prices of pharmaceutical products increased sharply because of a currency collapse. Since 2010 cost-containment strategies have achieved reduction in pharmaceutical costs and prices have come down even consumption of pharmaceutical products have increased. This was achieved partly by prescribing more generics and use of reference pricing and by changing the cost sharing mechanism. (Sigurgeirsdóttir et al 2014, 44, 155.)

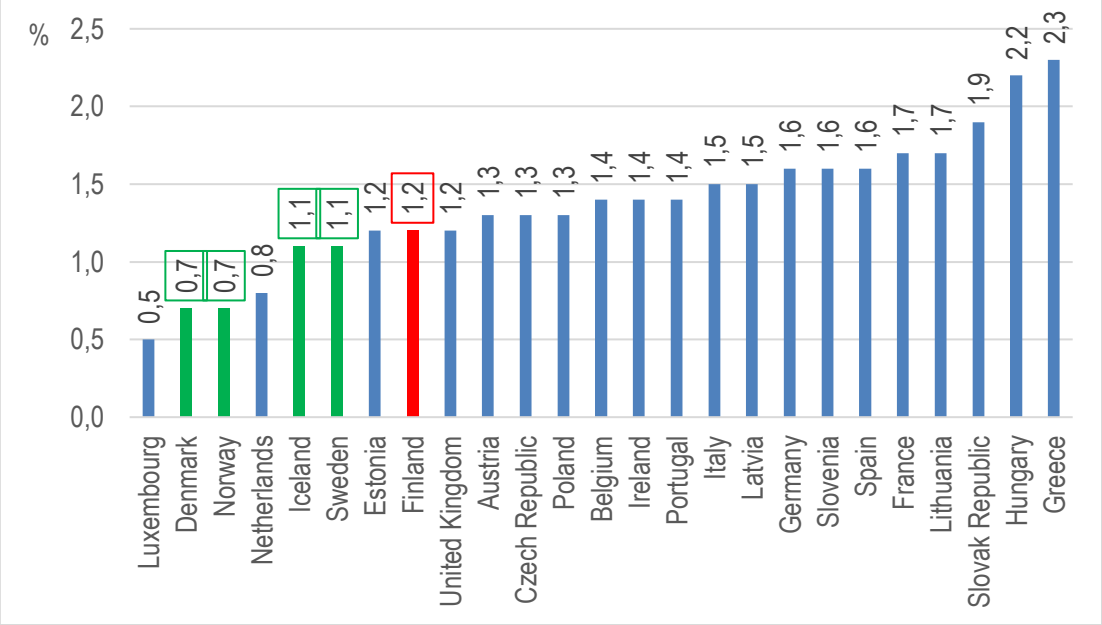


FIGURE 39. Pharmaceutical expenditures in European Union (28), % of GDP 2014 (OECD (b) 2016)

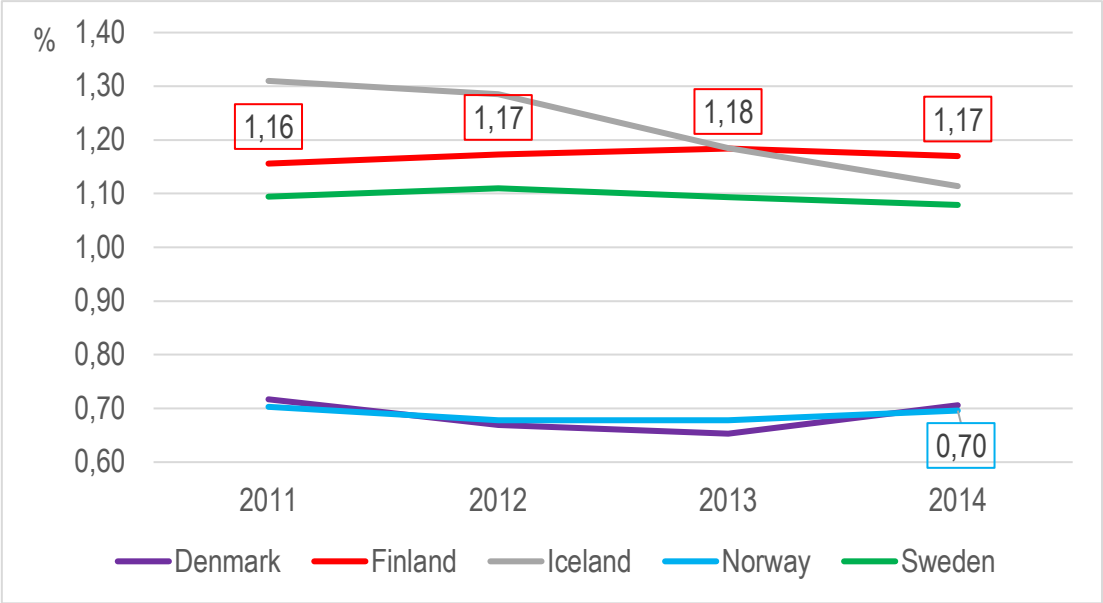


FIGURE 40. Pharmaceutical expenditures in Nordics, % of GDP 2011 - 2014 (OECD (b), 2016)

2014 highest pharmaceutical expenditures share of health care expenditures was in Iceland 12,6 percent, which though last few years has decreased from 15,1 and was 2014 almost same with Finland which was 12,3 percent (figure 41). Lowest share of pharmaceutical expenditures was in Denmark 6,7 percent (figure 41).

In Denmark, pharmaceutical spending decreased in real terms between 2009 and 2012 and was particularly pronounced in 2011 and 2012. Partly this reduction can be explained by the growing market share of generics, related to the patent expiration for some high-volume and high-cost pharmaceuticals, and policies to promote the use of generics. (OECD 2014, 2.)

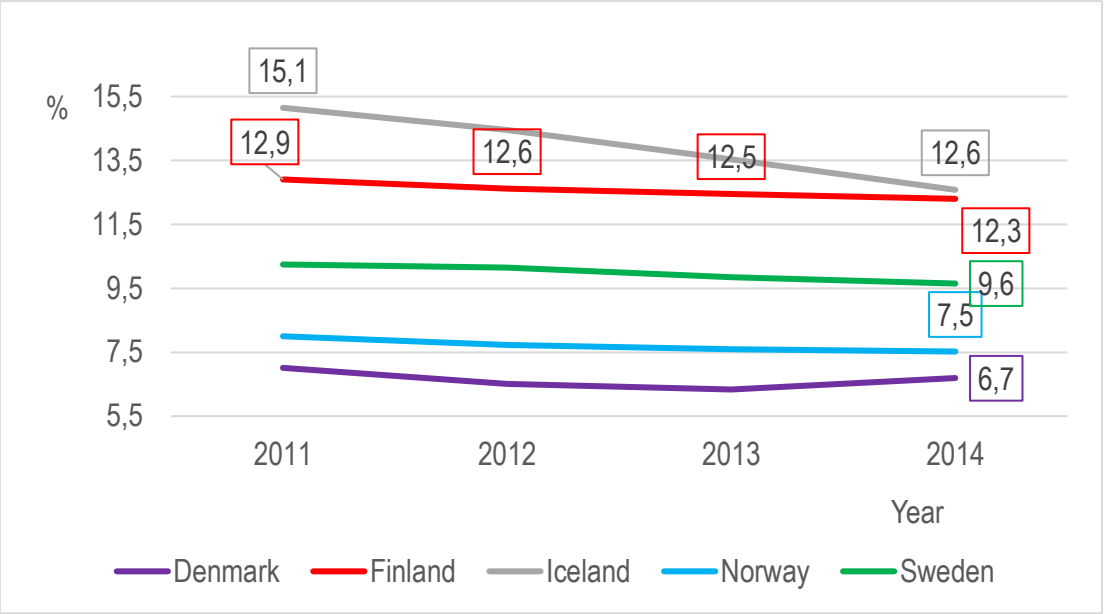


FIGURE 41. Pharmaceutical expenditures, % of health care expenditures 2011 - 2014 (OECD (b) 2016)

Highest pharmaceutical expenditures with US dollars per capita was 2014 in Iceland 490 US$ and lowest in Denmark 325 US$ (figure 42). Denmark has substantially lower per capita expenditures than other Nordic countries, Sweden had 489 US$, Finland 476 US$ and Norway 457 US$ (figure 42).

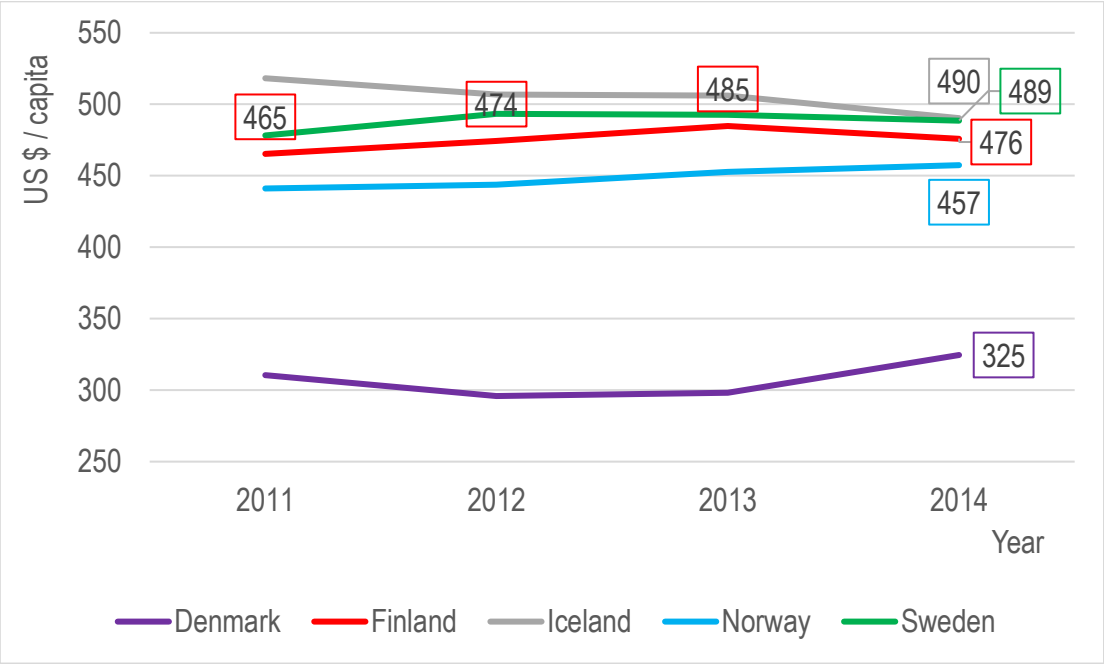


FIGURE 42. Pharmaceutical expenditures in Nordics, US dollars/capita 2011 - 2014 (OECD (b) 2016)

5.14.2 Sales of antineoplastic and immunomodulating agents in Nordic countries

In 2015, ATC-group C medicines (cardiovascular system) were most used in all Nordic countries when measured in DDD/1000 inhabitants/day. Use of ATC-group L agents (antineoplastic and immunomodulating agents) were in similar level in all countries. Iceland 17, Denmark and Norway 18, Sweden and Finland 19 DDD/1000 inhabitants/day. (Figure 43.)

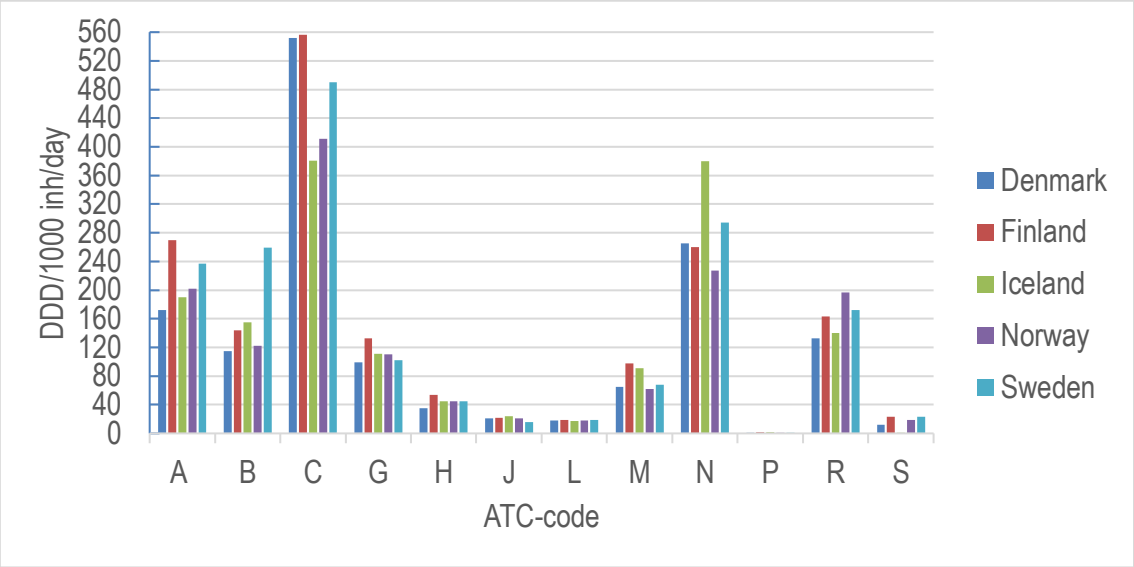


FIGURE 43. Sales of pharmaceutical products in total in Nordic countries by ATC group, 2015. Only ATC groups with WHO DDDs assigned are included (Nomesco 2016, 135)

Sales of antineoplastic agents have been growing in all Nordic countries from 2010 to 2015 (sales statistic from Iceland were not available for 2005). In 2015, highest sales were in Iceland, 107 thousand euros per 1000/inhabitants, and lowest sales in Sweden 32 thousand euros per 1000/inhabitants. Finland had, in 2015, comparable sales to Norway and Sweden (32 thousand euros per 1000/inhabitants), 35 thousand euros per 1000/inhabitants. (Figure 44.)

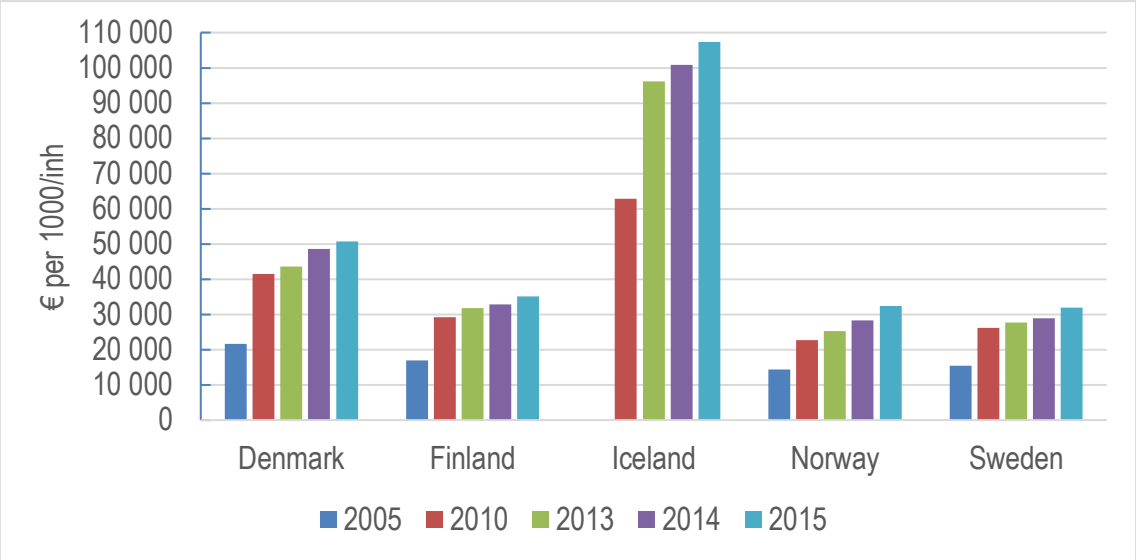


FIGURE 44. Sales of antinoeplastic agents (ATC-group L01) in Nordic countries, Euro per 1000/inhabitants at 2015 prices (Nomesco 2016, 158)

Use of TNF-alpha inhibitors has increase from 2010 to 2015 in all Nordic countries. Iceland and Norway are using TNF-alpha inhibitors most 4,2 and 4,1 DDD/1000 inhabitants/day. In 2015, Finland used the least TNF-alpha inhibitors, 2,4 DDD/1000 inhabitants/day, compared to other Nordic countries but Finland's figure was quite comparable with Sweden and Denmark, 2,8 and 2,7 DDD/1000 inhabitants/day. (Figure 45.)

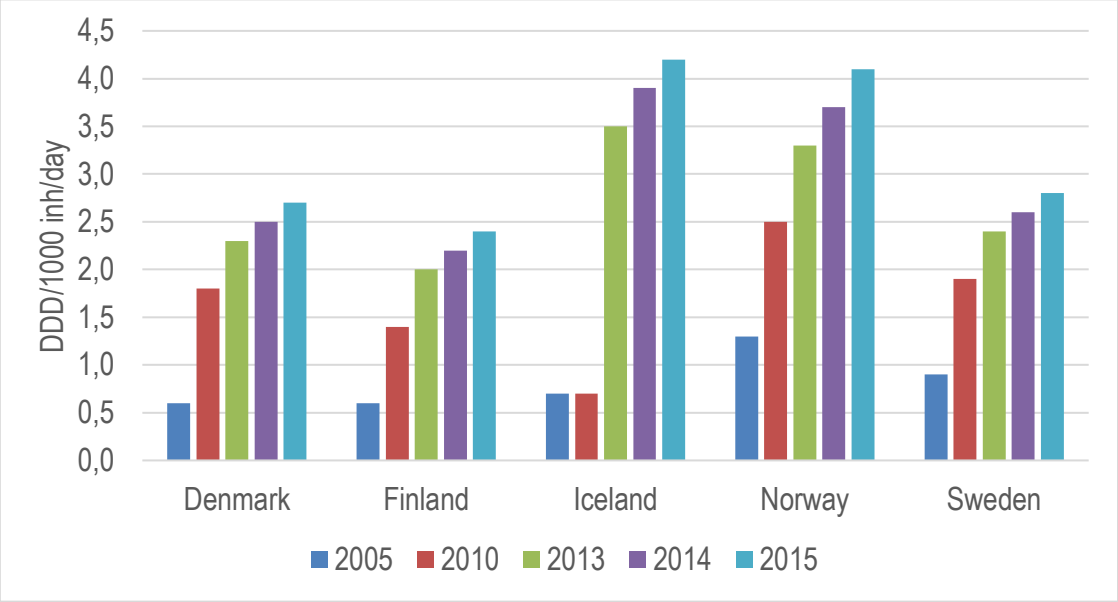


FIGURE 45. Use of tumor necrosis factor alpha inhibitors (L04AB) in Nordic countries, DDD/1000 inhabitants/day (Nomesco 2016, 159)

5.14.3 Country example: pharmaceutical expenditures in Norway

In Norway, graded price model and "preferred medicines" introduced in some medicine groups have limited the cost increase in the period 2010 – 2013. 2014 – 2015 increase was higher due to the approval of new very expensive medicines e.g. for HCV, cancer and multiple sclerosis. (Figure 46.)

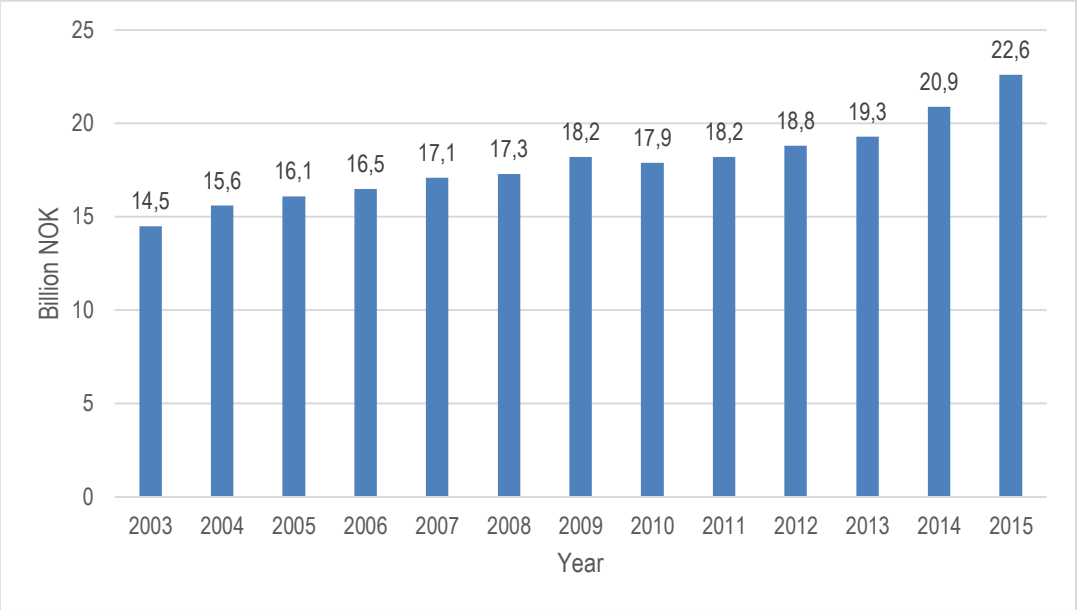


Figure 46. Pharmaceutical expenditures in Norway, billion NOK (Sakshaug 2016,15)

In 2015, antineoplastic and immunomodulating agents (ATC-code L) were the largest group in terms of costs and cost increase was 7 percent. This group has had gradual increase share of total sales due to the increase of use of high cost medicines for treatment of cancer and increased sales of biological medicines (ATC group L04 i.e. immunosuppressant's) for the treatment of e.g. rheumatoid arthritis. (Sakshaug 2016, 11, 13.)

Sales of other antineoplastic agents has increased from 941 million NOK to 1255 million NOK between 2013 to 2015 (figure 47). Same time for example monoclonal antibody rituximab use has increased from 7 696 grams of active ingredient/year to 10 579 grams of active ingredient/year and trastuzumab from 3638 grams of active ingredient/year to 6038 grams of active ingredient/year. (Sakshaug 2016, 63.)

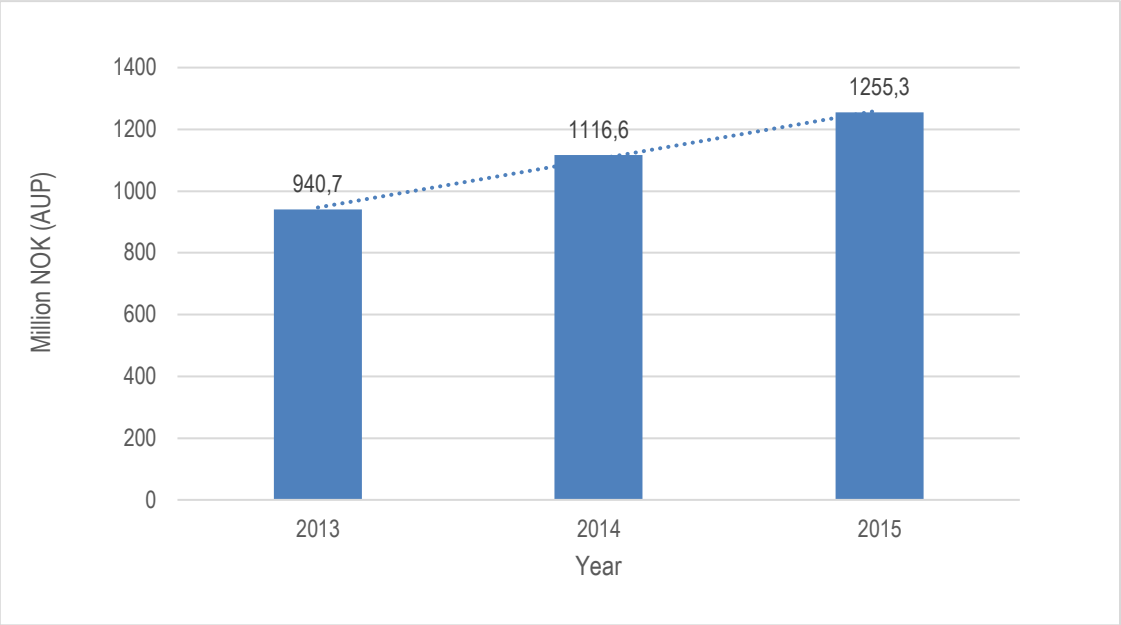


FIGURE 47. Sales of other antineoplastic agents (ATC-code L01X) in Norway 2013 – 2015, million NOK (Sakshaug 2016, 61)

Consumption of TNF-alpha inhibitors has increased in Norway from 3,3 DDD/1000 inhabitants/day to 4,1 DDD/1000 inhabitants/day between 2013 - 2015. Infliximab use has increased at same period from 1,2 to 1,8 DDD/1000 inhabitants/day. (Figure 48.)

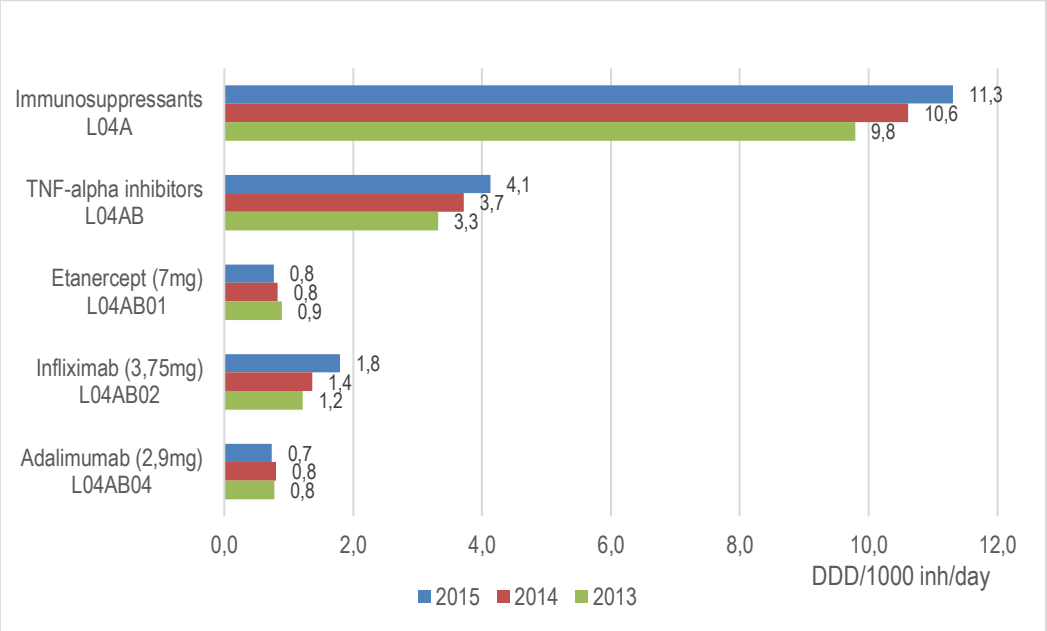


FIGURE 48. Consumption of immunosuppressant's in Norway 2013 - 2015 (Appendix 9)

Biosimilar infliximab was approved in Norway 2013. Biosimilar infliximab (Remsima) became available beginning of 2014 and as of April 2016, the biosimilar infliximab has garnered about 93 percent of market share. Dr. Kvien has said: “if you compare for rheumatoid arthritis, we could treat five patients with Remsima for the same cost as one patient with [Remicade]” (Collins 2016). The total number of infliximab prescriptions (the originator and the biosimilar combined) has leaped between 2014 and end of 2015 from about 7000 to about 13 000. (Collins 2016; Dörner et al. 2016, 5; Welch 2016.)

5.14.4 Hospital pharmaceutical expenditures in Finland

The growth of retail pharmaceutical spending has slowed down in recent years in most OECD countries, while spending on pharmaceuticals in hospital has generally increased (OECD 2015, 9). New hospital medicines are many times significantly expensive and one medicines annual cost can be up to tens of millions of euros. The medicine costs form a significant part of the total expenditures of the hospital districts. (Härkönen et al. (b) 2015, 46; Oksanen et al. 2011, 43.)

In 2015 in Finland, medicine sales to hospitals were 561 million euros at wholesale prices and change from 2014 was 9 percent (figure 49). Medicine sales to hospitals were less than three percent of health care total expenditures in 2014. Although the hospital medicines share of total health expenditure is not substantial, the cost of medicines in hospitals has increased significantly in ten years (figure 49). The multiplication of specialty medicines offers a partial explanation of growth of hospital pharmacy spending, as those are often delivered in hospital setting rather than dispensed via pharmacies and are coming to the market with increasing high prices. (Finnish medicines agency Fimea and social insurance institution 2016, 31; OECD 2015, 32.)

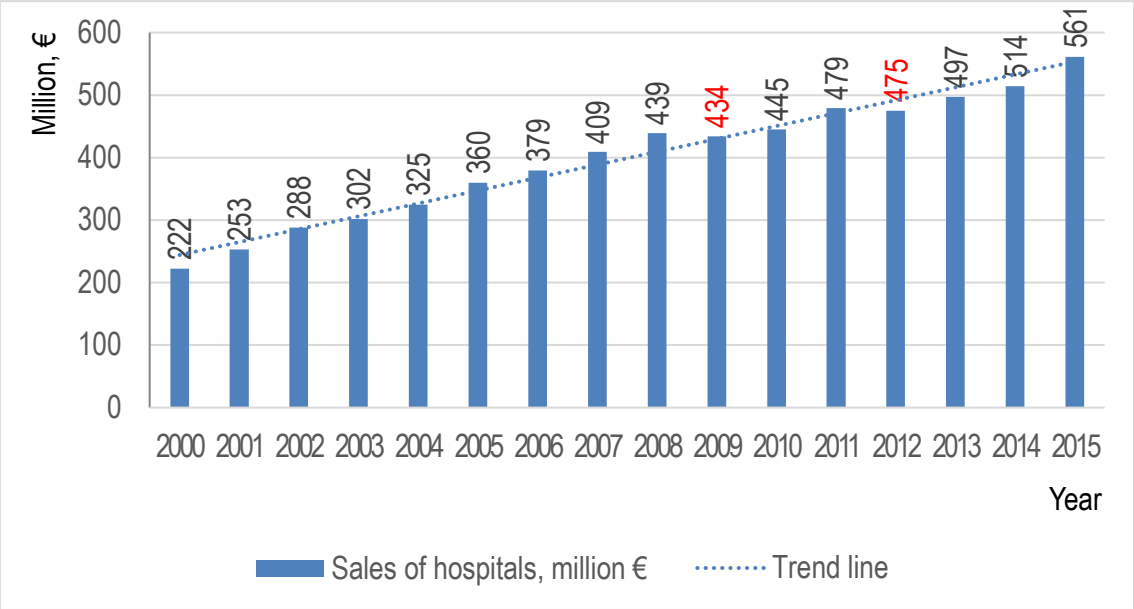


FIGURE 49. Hospital pharmaceutical expenditures 2000 – 2014, million euros at wholesale prices. Possible hospital discounts are not included in the figures presented (Finnish medicines agency Fimea and social insurance institution 2010 – 2016; National Agency for Medicines and Social Insurance Institution 2008 -2009; Matveinen et al. 2016)

In Finland, hospital's sales share of total pharmaceutical sales has increased over the last ten years. 2015 the share of medicine sales to hospital was 19,0 percent, while in 2005 the proportion was 14,8 percent (figure 50).

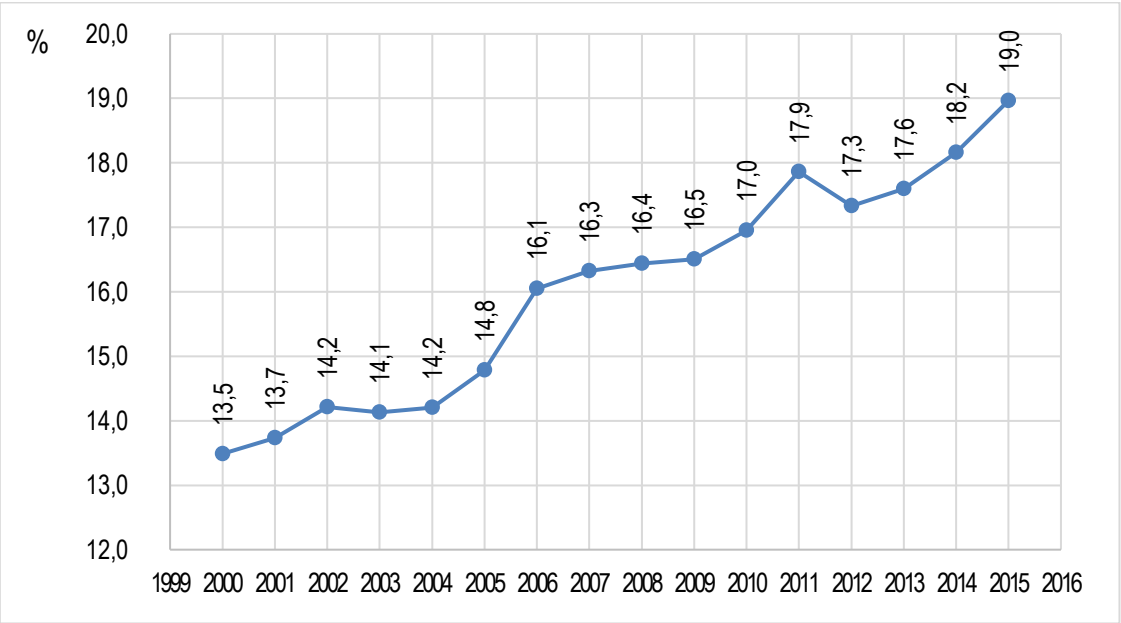


FIGURE 50. Share of hospital sales of total pharmaceutical sales, % (hospital discounts are not taken into account in calculations) (Appendix 1)

The three best-selling medicine groups in hospital setting in wholesale prices were antineoblastic and immunomodulating agents (ATC-code L), anti-infectives for systemic use (ATC-code J) and blood and blood forming organs (ATC-code B) (figure 51). Share of hospital sales of total medicine sales of antineoblastic and immunomodulating agents is 41 percent, representing the largest sales to hospitals in money vise, 206 million euros, of all ATC-groups. Anti-infectives for systemic use medicines hospital sales account 64 percent i.e. 117 million and of blood and blood formig organs 38 percent i.e. 67 million of total sales in groups. (Figure 51, figure 52.)

2015, antineoplastic and immunomodulating agents growth in sales was 8 % i.e. 15 million euros. Bigger growth was seen in the group of anti-infectives for systemic use, 29 % i.e. 26 million euros and in the group of blood and blood forming organs, which growth was 11 % i.e. 6 million euros in wholesale prices. (Appendix 2.)

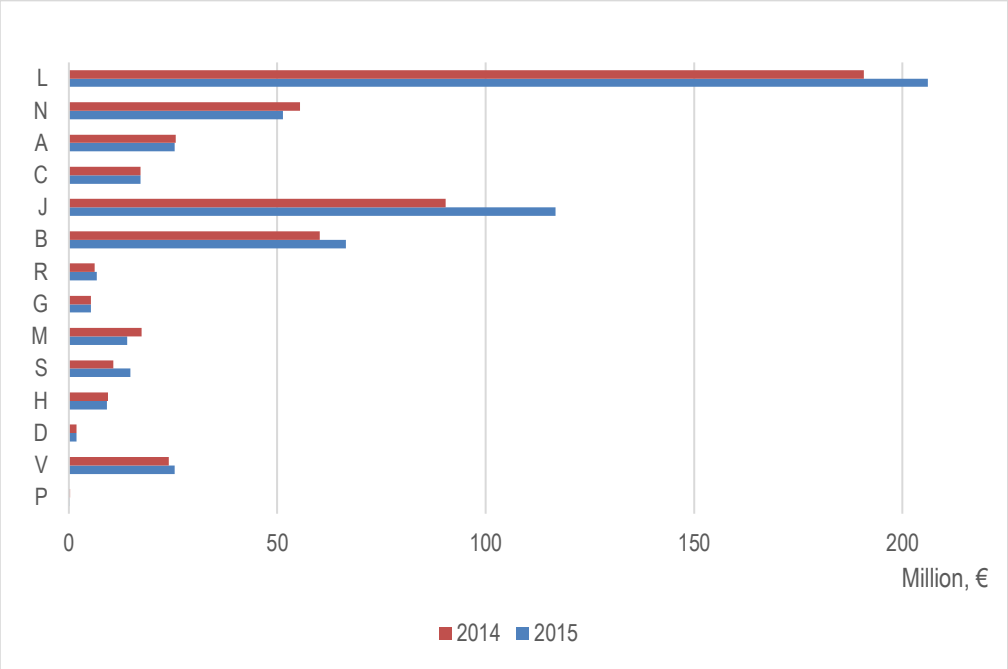


FIGURE 51. 2014 - 2015, distribution of medicine sales to hospitals per the ATC-code, at wholesale prices (million euros). ATC-codes A: Alimentary tract and metabolism, B: Blood and blood forming organs, C: Cardiovascular system, D: Dermatologicals, G: Genito urinary system and sex hormones, H: Systemic hormonal preparations, excl. sex hormones and insulins, J: Antiinfectives for systemic use, L: Antineoplastic and immunomodulating agents, M: Musculoskeletal system, N: Nervous system, P: Antiparasitic products, insecticides and repellents, R: Respiratory system, S: Sensory organs, V: Various (Appendix 2)

Antineoblastic and immunomodulating agents (ATC-code L) are accounting the largest sales to hospitals in ATC classification level 1, as seen in figure 51. Under the ATC-code L, in the classification level 2, largets sales are in group of antineoplastic agents 140 million euros, accounting 73 percent of total antineoplastic agents sales (ATC-code L01). Second largest group in sales is immunosuppressants 58 million euros, accounting 26 percent of total immunosuppressants sales to hospitals (ATC-code L04). (Figure 52.)

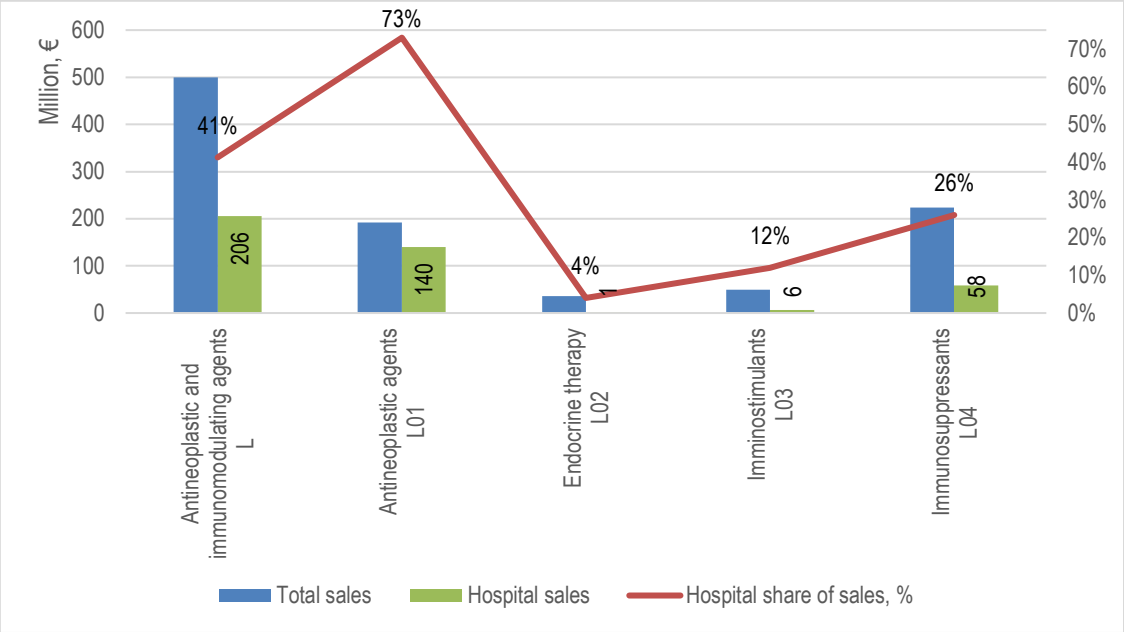


FIGURE 52. Antineoplastic and immunomodulating agent's sales to hospitals, divided to ATC classification level 2. Share of sales to hospital are share of total sales in each ATC-group (Appendix 3)

In the group of antineoplastic agents (ATC-code L01), the group of other antineoplastic agents (ATC-code L01X, classification level 3) have largest sales to hospital, 110 million euros from 140 million euros. Sales in the group of other antineoplastic agents are mostly sales to hospitals, accounting 71 percent of total sales. (Figure 53.) Other antineoplastic agents can be divided to classification level 4 group of medicines. In this group, monoclonal antibodies account clearly largest sales, 90 million euros, and were sold only to hospitals in 2015. (Figure 54.) The costs of monoclonal antibodies increased the most, by almost 9 million euros, in the group of antineoplastic agents (Finnish medicines agency Fimea and social insurance institution 2016, 36).

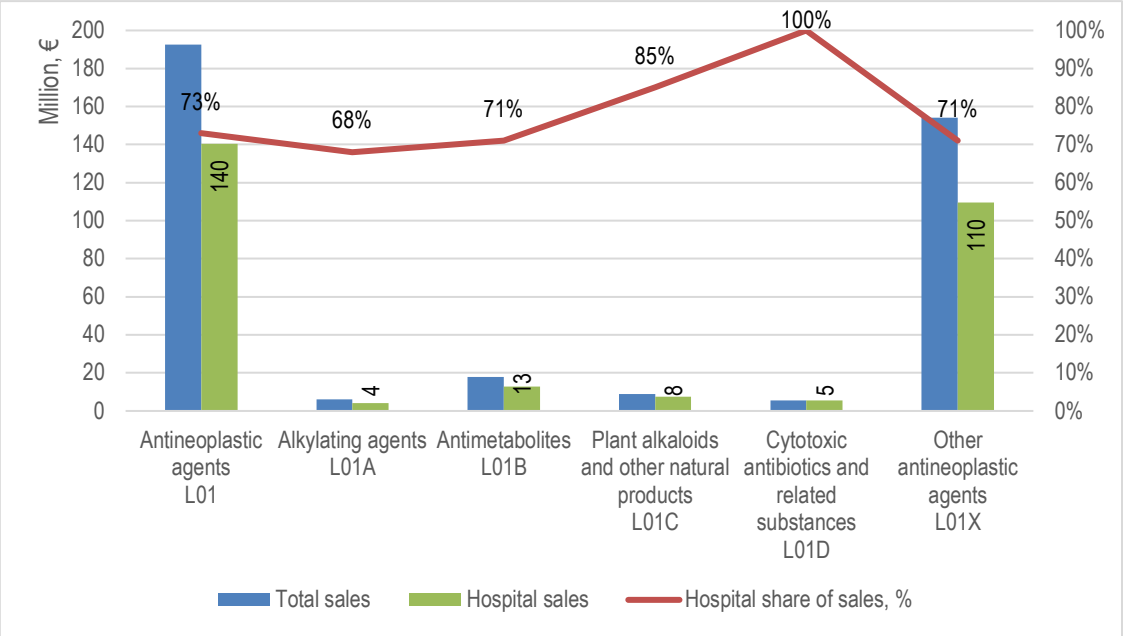


FIGURE 53. Antineoplastic agent's sales to hospitals, divided to ATC classification level 3. Share of sales to hospital are share of total sales in each ATC-group (Appendix 4)

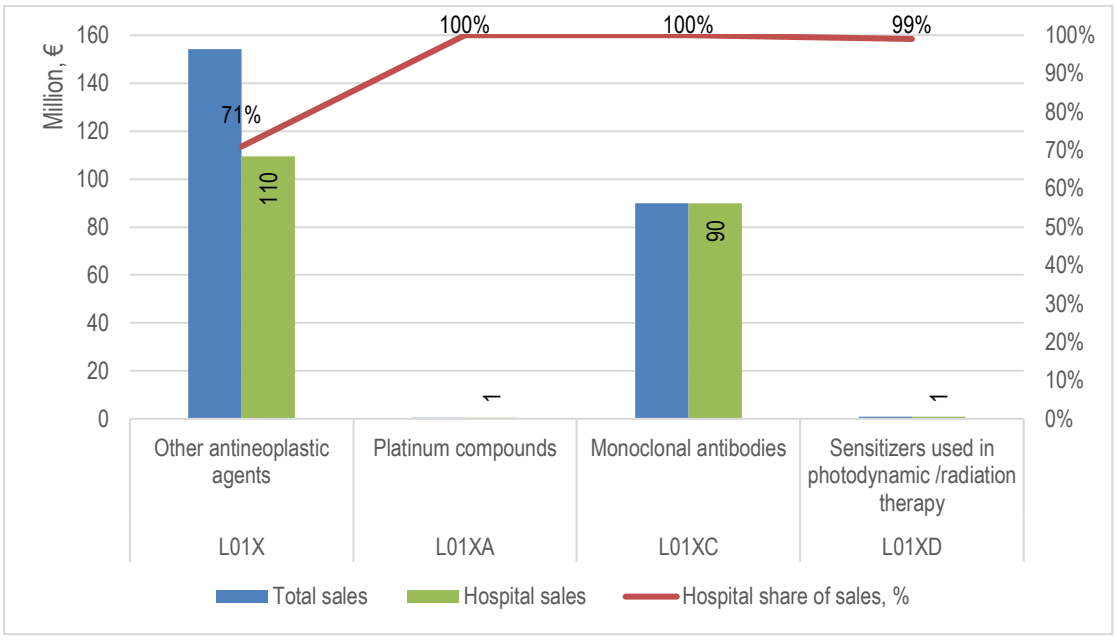


FIGURE 54. Other antineoplastic agent's sales to hospitals, divided to ATC classification level 4. Share of sales to hospital are share of total sales in each ATC-group (Appendix 5)

In the group of immunosuppressant's (ATC-code L04), the group of TNF-alpha inhibitors (ATC-code L04AB, classification level 4) have largest sales to hospitals, 40 million euros from 58 million

euros. Medicine sales in the group of TNF-alphas are mostly prescription medicines in outpatient care, accounting sales to hospitals of 29 percent. (Figure 55.)

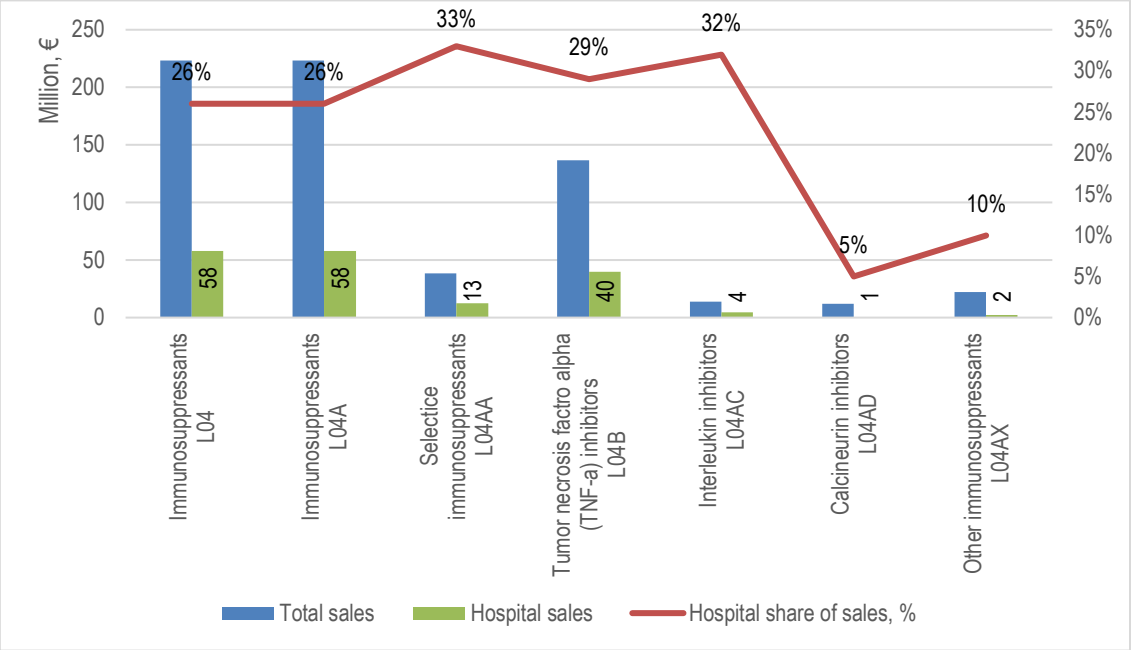


FIGURE 55. Immunosuppressant's sales to hospitals, divided to ATC classification level 4. Share of sales to hospital are share of total sales in each ATC-group (Appendix 6)

5.14.4.1 Cost of monoclonal antibodies in the hospitals in Finland

Expenditures of monoclonal antibodies focused only to hospitals in 2015, i.e. 90 million euros in wholesale prices. Rituximab accounted largest sales 31 million euros and Trastuzumab and Bevacizumab little over 20 million euros. (Figure 56.)

Total monoclonal antibody sales increased 10 percent compared to previous year (Appendix 7). Increase in sales was seen also with Trastuzumab and Bevacizumab, 3 and 13 percent (Rituximab sales 2014 were missing from the data used). Rituximab sales have increased 17 percent when compared to 2013 sales.

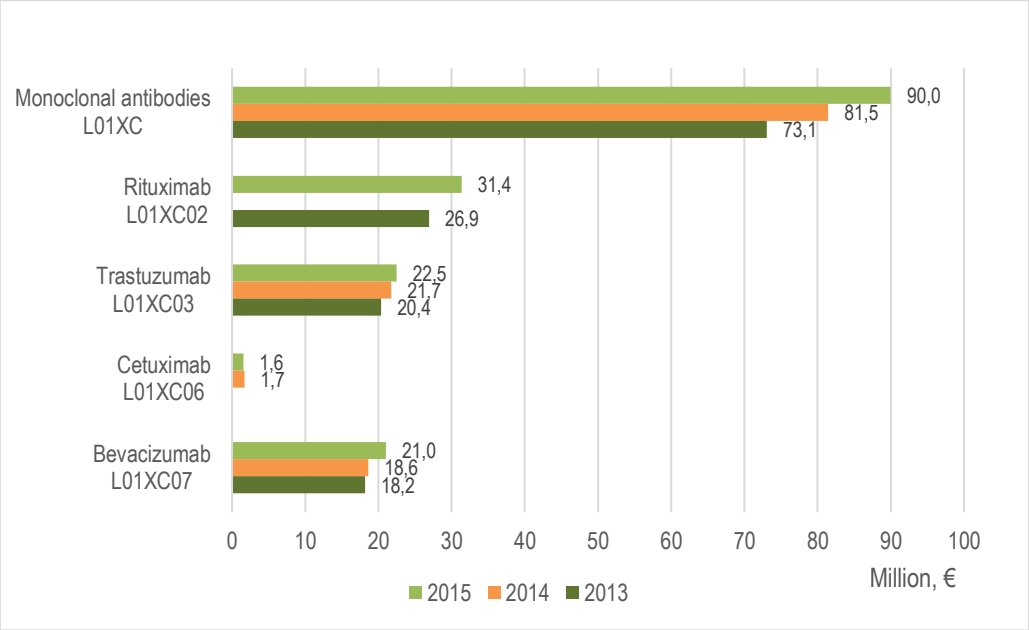


FIGURE 56. Monoclonal antibodies sales to hospitals in wholesale prices 2013 - 2015. Possible hospital discounts are not included in the figures presented (Appendix 7)

At the present time, increase of consumption or prices and introduction of new therapeutic areas and possibly new innovative medicines of monoclonal antibodies, will increase hospitals medicinal costs solely. Though, pharmaceutical industry is focusing to innovate medicines not given in hospital and iv-route, but subcutaneously or orally. This enables patients to take medicines by themselves at home and patient and/or national health insurance pay costs of these medicines, not hospital.

5.14.4.2 Cost of TNF-alphas in the hospitals in Finland

In 2015, TNF-alpha medicines (tumor necrosis factor alpha) total sales (outpatient care and hospital sales) were 137 million euros with wholesale prices, including sales of etanercept, infliximab, adalimumab, certolizumab pegol and golimumab (Appendix 6). Total TNF-alfa sales increased 7 percent compared to 2014. Etanercept, infliximab and adalimumab sales of total TNF-alpha sales account 85 percent i.e. 116 million euros (Appendix 7). TNF-alfa inhibitors adalimumab, infliximab and etanercept are used for the treatment of rheumatoid arthritis, psoriasis, and inflammatory bowel diseases. Adalimumab is most sold TNF-alpha, 47 million euros (figure 59), but second in consumption 0,68 DDD per 1000 inhabitants and per day (figure 58). When measured in terms of

consumption, the most commonly used TNF-alpha is Infliximab 0,89 DDD/1000 inhabitants/day (figure 58), but when compared in sales it is the second biggest, about 38 million euros (figure 59). Infliximab consumption increased from 0,77 to 0,89 DDD/inhabitants/day (figure 58) and sales 5 percent compared to previous year.

Infliximab is provided only in hospitals, while other TNF-alphas (etanercept and adalimumab) are prescription medicines in outpatient care (98 – 100 % of sales and consumption) (figure 57, Appendix 8). As seen in figure 57, etanercept has no hospital sales and adalimumab sales were 0,9 million euros in 2015, and infliximab sales were 39,6 million euros.

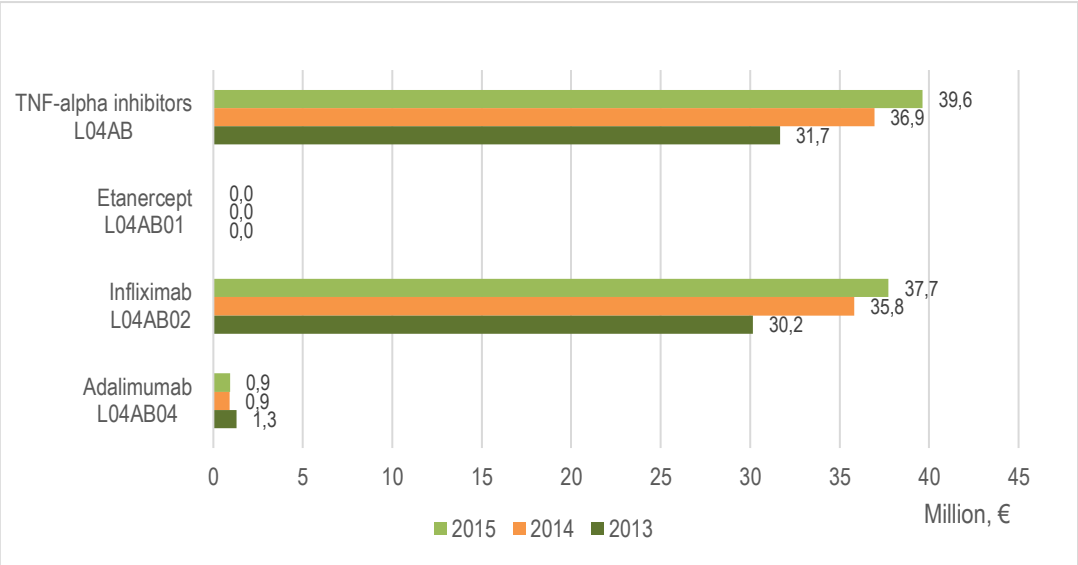


FIGURE 57. Immunosuppressant's sales to hospitals in wholesale prices (million euros) 2014 - 2015 (Appendix 7)

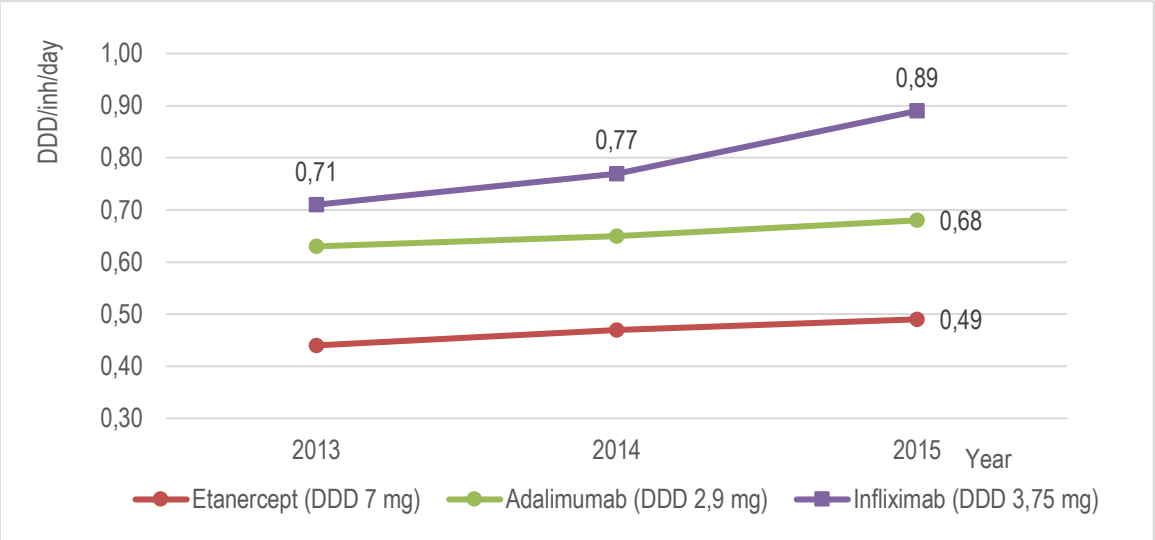


FIGURE 58. Etanercept, adalimumab and infliximab consumptions (outpatient care and hospital), DDD/inhabitants/day, 2013 - 2015 (Appendix 8)

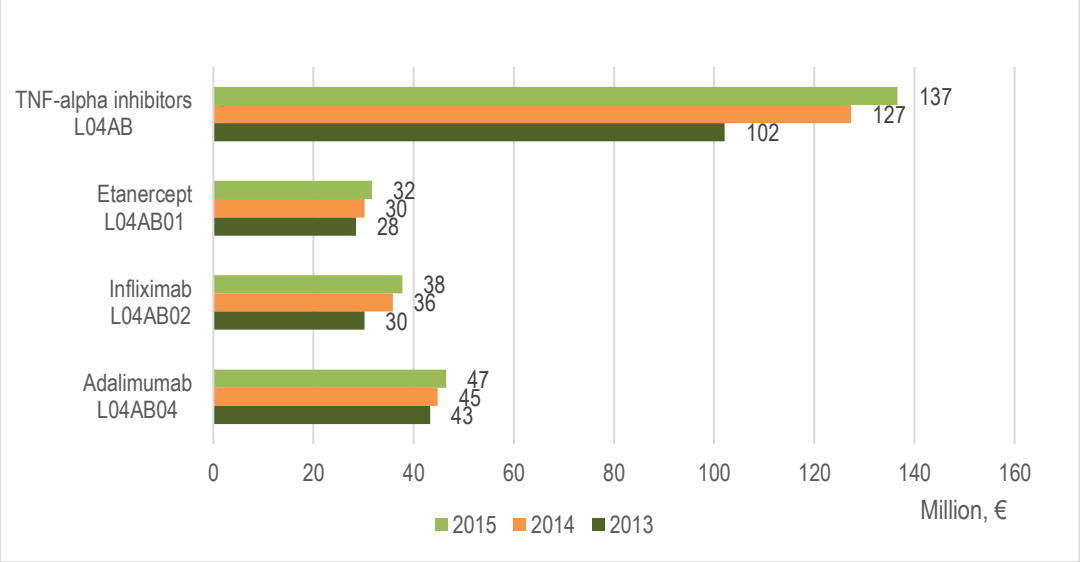


Figure 59. Immunosuppressant's total sales (outpatient care and hospital) in wholesale prices (million euros) 2014 - 2015 (Appendix 7)

In September 2013, biosimilar versions of Remicade (Inflectra and Remsima) were granted marketing authorization (European Medicines Agency (j) 2013; European Medicines Agency (k), 2013) in Finland and it can be speculated that maybe the increase of infliximab consumption seeing in figure 58 was possible after price competition in hospital tenders. 2011 and 2012 the consumption of infliximab was 0,62 and 0,68 DDD/1000 inh/day (Finnish Medicines Agency Fimea and Social Insurance Institution 2013, 230).

6 STUDY EXECUTION

In the sixth chapter, the execution of qualitative study is presented.

6.1 Material

Questionnaire surveys were carried out in autumn 2016 and the target groups were chief gastroenterologists (n = 25), specialist gastroenterologists (11), chief rheumatologists (n = 22), specialist rheumatologists (2), chief oncologists (n = 23), specialist oncologists (3), chief physicians of internal medicine (12) medical directors of health care districts (n = 20), chief assessment physicians (n = 4), heads of departments (n = 28) and chief pharmacists (n = 20) from five university and 16 central hospitals (Table 7). Ahvenanmaa was later excluded because of Swedish language. Two different questionnaire forms were made, one for chief pharmacists and one for other participants (Appendix 11-12.)

TABLE 7. The questionnaires were send to eleven different target groups and for 170 recipients

Target group	**Number of emails sent, N**
Medical director of health care district	20
Head of department Responsible of gastroenterology, rheumatology, oncology, internal medicine	28
Chief assessment physician	4
Chief pharmacist	20
Chief physician, internal medicine	12
Chief physician, gastroenterology	25
Specialists in gastroenterology	11
Chief physician, rheumatology	22
Specialist in rheumatology	2
Chief Physician, oncology	23
Specialists in oncology	3
TOTAL	**170**

Two biosimilar products were included to questionnaire and the respondent were asked to choose a medicine, which is answered. Optional medical products were infliximab and filgrastim. The questionnaires were e-mailed to 170 recipients in total. Filgrastim questionnaire analyses are not included in this thesis due to the low response rate. Only one specialist oncology, two chief pharmacists and two heads of department returned the questionnaire.

6.2 Data collection

Respondents were under no obligation to complete and return the questionnaires if they did not wish to take part in the survey. Respondents could give their contact e-mail in the questionnaires to have link to published thesis. As some of the e-mail addresses of respondents were recorded in completed questionnaires, their anonymity had to be secured. Respondents names and e-mail addresses are not shared in any circumstances and their anonymity will be maintained.

The questionnaires were accompanied by explanation letters (Appendix 10). The questionnaires were send first time 1st of October 2016 and again as remainder 21st – 25th of October 2016. The replies were requested to be sent to the given e-mail address no later than 31st of October 2016.

6.2.1 Drafting of questionnaires

In 2016, two Microsoft Word spreadsheet questionnaires were designed to gather information, opinions and future expectations about biosimilars. The questions used in this study were designed with the help of Professor, Department Head Tuulikki Sokka-Isler, Docent, Ph.D. Pekka Kurki and Hospital Chief Pharmacist.

There were 30 questions to chief pharmacists and 28 to other target groups (Appendix 11 - 12). Both closed and open questions were used. Closed questions had multiple response options (2 – 7) and some included also neutral answers (“I cannot say”). Also, open questions “why” and “other comments” were included to most of the questions, in case respondent wanted to comment the given answer or had alternative which was not given originally as on option. Few open questions were included to gather information when it was not ideal to give prepared response options, but instead to give the respondent an opportunity to express their own opinions on the matter without suggestive options. For example, switching biosimilar to biosimilar becomes relevant in future and

open questions were only possibility not to direct the responses, but to have opinion of the respondent. The questionnaire was piloted by one physician and one chief pharmacist. Following the pilot implementation, some questions were discarded and the wording of others was clarified.

6.2.2 Address list

Questionnaires were send via e-mail to targeted groups. Names and e-mail addresses were gathered from municipal web-pages, including hospital pages, publications, guidelines etc. Also, lot of names I was familiar via my work in medical industry and some were given by respondents, who felt there were not right contacts in their hospitals. Respondents send the questionnaire back to given e-mail. The respondent's names will not be shared outside this thesis and their anonymity is secured. The thesis has not been made for or request of the pharmaceutical companies.

6.3 Data analyzing

Data collection of the survey was conducted by manually transferring answers to Microsoft Excel spreadsheets from word-based questionnaire sheets. The replies were documented according to the different target groups and to University and Central Hospital groups. The questions and answers were translated into English.

University Hospital and Central Hospital responses are not separated in this thesis, so that the respondents' anonymity is maintained. One senior ward physician response is also included to specialist gastroenterologists' group of responses. Chief physician groups do include deputy chief physicians, chief of departments and chief specialists. In table 8, the English job titles are presented in Finnish.

TABLE 8. Professional titles in Finnish

Target group	**Target group in Finnish**
Medical director of health care district	Sairaanhoitopiirin johtajaylilääkäri
Head of department Responsible of gastroenterology, rheumatology, oncology, internal medicine	Toimiala-, palvelualue-, vastuualue-, vastuuyksikkö-, tulosalue-, palveluyksikkö-, toimialuejohtaja

Chief assessment physician	Arviointiylilääkäri
Chief pharmacist	Sairaala-apteekkari
Chief physician, gastroenterology	Gastroenterologian ylilääkäri
Specialists in gastroenterology	Gastroenterologian erikoislääkäri
Chief Physician, rheumatology	Reumatologian ylilääkäri
Specialists in rheumatology	Reumatologian erikoislääkäri
Chief Physician, oncology	Onkologian ylilääkäri
Specialists in oncology	Onkologian erikoislääkäri

The number of recipients from biosimilar infliximab target groups who returned the questionnaire was 30 (18% of 144 recipients). The highest response rate is in the group of rheumatologists, 38 %, and none of chief physicians of internal medicine replied the questionnaire. (Table 9.) It should also be noted that one of the hospitals decided that only chief pharmacist would answer the questionnaire on behalf of everybody. That might lower the response rates of other target groups.

TABLE 9. Response rates of the biosimilar infliximab target groups

Target group	**N**	**Respondents, n**	**Response rate, %**
Medical director of health care district	20	1	5 %
Head of department, responsible of gastroenterology, rheumatology, oncology, internal medicine	28	2	7 %
Chief assessment physician	4	1	25 %
Chief pharmacist	20	6	30 %
Chief physician, internal medicine	12	0	0 %
Chief physician, gastroenterology	25	7	28 %
Specialists in gastroenterology	11	4	36 %
Chief physician, rheumatology	22	9	41 %
Specialist in rheumatology	2	0	0 %
Gastroenterology, total	**36**	**11**	**31 %**
Rheumatology, total	**24**	**9**	**38 %**
TOTAL	**144**	**30**	**21 %**

The response rate of the biosimilar infliximab target groups was really modest, only 5 % and just one specialist oncology returned the questionnaire and thus the analyzes are not included within this thesis. (Table 10.)

TABLE 10. Response rates of the biosimilar filgrastim target groups

Target group	N	Respondents, n	Response rate, %
Medical director of health care district	20	0	0 %
Head of department	28	2	7 %
Chief assessment physician	4	0	0 %
Chief pharmacist	20	2	10 %
Chief Physician, oncology	23	0	0 %
Specialists in oncology	3	1	33 %
TOTAL	**98**	**5**	**5 %**

When analyzing the results, it became clear, that questions should have been further processed and questionnaire should have included only one biosimilar product. Now there was possibilities to misunderstand questions, if the question was not read with proper thought in mind. As a web-based questionnaire, the number of responses could have been greater than by e-mail, and also the processing of responses would have been faster than of Word-based query's. On the other hand, face-to-face interviews could provide more comprehensive answers and clarifying questions could have been asked.

Some of the figures in the replies are not directly comparable and the figures obtained must therefore be considered as indicative. For example, the calculations took a lot of time from the pharmacists and one of the respondents commented that some of the calculations were made with a marginal profit prices, not with purchase prices, as requested in the survey. Also, some figures were asked to give as estimates, because for example future savings cannot be calculated as exact figures.

7 RESULTS

Responses of questionnaire are analyzed by customer groups and central hospital and university hospital replies are not analyzed separately.

7.1 Position of biosimilar product in the hospital's pharmaceutical formulary

Target groups were first asked what is the position of biosimilar product in their hospital's pharmaceutical formulary at the current purchasing period and requested to rationalize why this is the case.

7.1.1 Gastroenterologists

All chief physicians of gastroenterology who responded the questionnaire (n=7), responded biosimilar infliximab to be in pharmaceutical formulary the preferred option. One responded it to be also only infliximab product and other 6 responded that originator infliximab was also available. The same result was also seen in responses of specialists of gastroenterology (n=4). In this group four responded biosimilar infliximab to be the preferred option and one of them responded it to be also the only product and one responded that also originator infliximab was available. (Table 11.)

TABLE 11. Biosimilar infliximab is the preferred option in pharmaceutical formulary

Position of biosimilar infliximab in the hospital's pharmaceutical formulary at the current purchasing period	**Chief Physicians, n = 7**	**Specialist of Gastroenterology, n = 4**
Biosimilar infliximab is the preferred option	7	4
	Price. Main product chosen for the Expert Responsibility Area. Price and efficacy.	Price
Also, originator infliximab is available	6	1
	If patient prohibits switch. In use.	

	Change happens slowly when switching medication, some patients react with worsening of bowel-disease symptoms; possibility to continue treatment with the same product. Some patients want originator product. If biosimilar is inefficient or side effects occur.	
Only biosimilar infliximab in pharmaceutical formulary	1	1
		Was considered that there is no need for other.

The biosimilar infliximab being the preferred option was most of the cases justified with price and one responded biosimilar to be main product chosen for the Expert Responsibility Area. Originator infliximab was available in case if patient prohibits switch, biosimilar proves to be inefficient or side effects occur and respondents saw it also as opportunity to return to originator infliximab if biosimilar infliximab treatment fails. One responded stated that some patients choose originator infliximab instead of biosimilar infliximab.

Two respondents (one chief physician and one specialist) stated biosimilar infliximab to be only product in pharmaceutical formulary (no originator infliximab available), and one justified it with argument that it was considered that there is no need for originator.

7.1.2 Rheumatologists

All chief physicians from rheumatology replied the biosimilar infliximab to be the preferred option in the pharmaceutical formulary at the current purchasing period. Eight respondents told price to be the reason, and three of them also mentioned that biosimilar is demonstrated to be similar to the originator product. One of the respondents also pointed out that he / she had gathered personal experience of biosimilar infliximab. (Table 12.)

Eight out of nine chief physicians replied that also originator infliximab is available, for example, in case if problems occur with the biosimilar product (lack of efficacy, adverse events) and if patient prohibits switch. It makes also possible to continue with originator infliximab if patient's starting

point before switching has been very difficult and is only reasonably under control. In this kind of situation there is no desire to take the risk of switching. In addition, originator product in the pharmaceutical formula makes it possible to return to originator infliximab if biosimilar infliximab treatment fails. Also, one chief physician stated that pediatric rheumatology patients were not “forced” to switch and thus continued with originator infliximab. Remicade was also seen to be more desirable option for some patients, for example for pregnant womens. By keeping originator product in the pharmaceutical formulary, doctors’ autonomy was secured, and they could decide to continue treatments with originator infliximab or to switch to biosimilar one.

TABLE 12. Biosimilar infliximab is the preferred option in pharmaceutical formulary

Position of biosimilar infliximab in the hospital's pharmaceutical formulary at the current purchasing period	**Chief physicians, n = 9**
Biosimilar infliximab is the preferred option	9
	Price, studies have demonstrated biosimilar to be comparable to originator product. Studies and personal experiences have demonstrated that biosimilar is similar to the originator product in terms of efficacy and safety. The most affordable and is assumed to have similar effect as the reference product. Price advantage.
Also, originator infliximab is available	8
	With a few patients in a very difficult situation reasonably under control, there was no desire to take the risk of switching medicine, and the patient did not wish to change the medicine. If problems occur with the biosimilar product. Needed for some patients: 1. laboriously has been found a medicine that affects, Remicade, so treatment continued with the product in question. 2. pregnancy - Remicade has nevertheless two decades of experience. 3. for stable patients whose treatments were switched to biosimilar, but on objective outcome measures efficacy has collapsed, and their treatment was switched back to Remicade. If the biosimilar is not suitable or is not effective enough. No mandatory to switch treatment In case there is exceptional case. Pediatric rheumatology patients are not "forced" to switch. For some, is more suitable.

7.1.3 Medical director of health care district, head of department and chief assessment physician

Two heads of departments answered the questionnaire. Both replied the biosimilar infliximab to be the preferred option in the pharmaceutical formulary at the current purchasing period and both told price to be the reason. The other of the respondents stated that the originator infliximab is also available, because some patients need it.

Medical director of health care district replied that both originator and biosimilar infliximab are in the pharmaceutical formulary. Price was mentioned to be the reason why biosimilar has been chosen and originator infliximab was chosen in order to maintain the doctors' autonomy.

Chief assessment physician replied that the both originator and biosimilar infliximab are in the pharmaceutical formulary. Originator was kept in order to ensure the transitional period and to have as one alternative.

7.1.4 Chief pharmacists

All chief pharmacists replied the biosimilar infliximab to be the primary option in the pharmaceutical formulary at the current purchasing period but also originator infliximab is available for specified patients. (Table 13.)

Biosimilar infliximab is the preferred option because of the price. It has proven to be the most economical choice in accordance with hospital tender criteria's. One replied biosimilar infliximab to be main product chosen for the expert responsibility area. Fimea statement about interchangeability of biosimilars was also mentioned.

Originator infliximab is available for specified patients like pediatric patients or patients who have used originator infliximab for a long period of time and have justified reason which prevents the switch. One chief pharmacist told that originator product can be used on a request for a named patient.

TABLE 13. Biosimilar infliximab is primary option in the pharmaceutical formulary, but also originator infliximab is available if needed

Position of biosimilar infliximab in the hospital's pharmaceutical formulary at the current purchasing period	**Chief pharmacists, n = 6**
Biosimilar infliximab is the preferred option	6
	Per se, Fimea statement notes that it is possible to switch to biosimilar. In accordance with hospital tender criteria's, biosimilar is the most economical choice. Usage costs. Main product chosen for the Expert Responsibility Area. Price.
Also, originator infliximab is available	6
	For those potential long-term users, who have a particular reason that the switch could not be done. On a request for a named patient. Opportunity to continue ongoing treatments with the same product. For pediatric patients, whose treatment has been initiated with the originator infliximab and for patients for whom biosimilar infliximab is not appropriate. For patients, whom originator infliximab has been in long-term use, and switch for biosimilar infliximab cannot be implemented. Pediatric patients.

7.2 Studies of efficacy and safety

Biosimilar application for marketing authorization must demonstrate that potential differences between the biosimilar and the originator product does not affect the efficacy or safety.

7.2.1 Are biosimilar studies sufficiently comprehensive regarding of safety and efficacy

One of the survey objectives was to identify if the biosimilar studies are seen to be sufficiently comprehensive regarding of efficacy and safety.

7.2.1.1 Gastroenterologists

10 out of 11 (6/7 chief physicians and 4/4 specialist) responded biosimilar studies to be sufficiently comprehensive regarding of safety and efficacy. Efficacy and safety results were seen convincing enough, even if those were conducted mainly in rheumatology patients. Also, extrapolation of indications was mentioned in one answer and seen that results obtained from studies in RA and SpA can be extrapolated to IBD. (Table 14.)

Only one respondent did think biosimilar studies are not sufficiently comprehensive regarding of efficacy and stated that for some patients biosimilar is not effective at all, even if biosimilar infliximab is being marketed to have similar efficacy as originator product.

TABLE 14. Gastroenterologists opinion is that biosimilar studies are sufficiently comprehensive regarding the efficacy and safety

Biosimilar studies are	**Chief physicians, n = 6**	**Specialist of gastroenterology, n = 4**
Sufficiently comprehensive	6	4
	Efficacy and safety results are convincing enough, even if conducted mainly in rheumatology patients. Study in rheumatology. Proven safety and efficacy. I have received information about studies, mode of action and safety.	Results obtained from studies in rheumatoid arthritis and SpA can be extrapolated to inflammatory bowel disease. Sufficient number of patients.
Not sufficiently comprehensive	1	
	Marketed to have similar efficacy than originator product, but in reality, to some patients, biosimilar is not effective at all	

7.2.1.2 Rheumatologists

All chief physicians from rheumatology responded the question. Eight out nine answered that studies are sufficiently comprehensive regarding of safety and efficacy, though one hesitates in his /

her answer, that research evidence does not exist to all indications, and only little research evidence and long term follow-up is available. Other reasons were for example, that biosimilar studies meet requirements of the EU, there is confidence to regulatory authorities in this matter and studies are seen to have enough power to demonstrate the biosimilarity. (Table 15.)

One respondent answered studies not to be sufficient enough, because long-term outcomes are not known.

TABLE 15. Head physicians in Rheumatology think, that biosimilar studies are sufficiently comprehensive

Biosimilar studies are	**Chief physicians, n = 9**
Sufficiently comprehensive	8
	Meet the requirements of the EU. I trust the regulatory authorities. In principle, yes, but there is no research evidence for all indications, and only little research evidence, and long term follow-up, is available. In terms of efficacy, studies made for originator product are sufficient; in terms of safety, studies required in the authorization procedure are sufficient. Equality is adequately addressed. If the biosimilar has all the corresponding originator properties and structure, less extensive clinical tests are sufficient.
Not sufficiently comprehensive	1
	Maybe not. The long-term outcomes are not known.

7.2.1.3 Medical director of health care district, head of department and chief assessment physician

Medical director, heads of department and chief assessment physicians replied biosimilar studies to be sufficiently comprehensive regarding of safety and efficacy.

7.2.1.4 Chief pharmacists

All chief pharmacists replied biosimilar studies to be sufficiently comprehensive regarding of safety and efficacy. One chief pharmacist replied that medicinal products will not get authorization unless

the standardized conditions are not met and other one thinks that pharmaceutical regulatory authorities have strict requirements for studies of biosimilars. (Table 16.)

TABLE 16. All chief pharmacists think, that biosimilar studies are sufficiently comprehensive

Biosimilar studies are	**Chief pharmacists, n = 6**
Sufficiently comprehensive	6
	The supervising authority grants the marketing authorization for medicinal products. To obtain the marketing authorization, regulatory authority will assess quality, efficacy and safety, as well as appropriateness in all approved indications. Medicinal product will not get authorization unless the standardized conditions are met. The pharmaceutical regulatory authorities have stringent criteria.

7.2.2 Sources of biosimilar information

The questionnaire surveyed from which sources biosimilar information is obtained.

7.2.2.1 Gastroenterologists

Questionnaire showed that respondents have received information about biosimilars often from many different sources (table 17). The study respondents have all (n=11) received information about biosimilars from pharmaceutical companies. Nine of the eleven respondents have received info also from regulatory authorities (6 of the 7 chief physicians and 3 of the 4 specialists) and eight of all respondents have gotten information also from colleagues (chief physicians 5/7 and specialists 3/4).

TABLE 17. Information about biosimilars is received mostly from pharmaceutical companies and regulatory authorities

Where have you received information about biosimilar products	**Chief Physicians, n = 7**	**Specialist of gastroenterology, n = 4**
Pharmaceutical companies	7	4
Regulatory authorities	6	3
From colleagues	5	3

From elsewhere?	5 FROM: Scientific publications. Congresses. Meetings Training sessions	3 FROM: Medical journals and congresses. EMEA, journals, the literature of the field.

Other sources of information have been publications (was mentioned most frequently), congresses, meetings and training sessions. Also, one mentioned EMEA as information source.

7.2.2.2 Rheumatologists

Questionnaire showed that respondents received information about biosimilars from multiple sources (table 18). The study respondents have all received information about biosimilars from pharmaceutical companies and almost as many, eight out of nine, has received information also from regulatory authorities. Seven respondents have received info also from colleagues and same number has gotten information from other sources. Other sources of biosimilar information have been journals and literature, congresses, and presentations. One also mentioned that he/she has had biosimilar in trial use and one has been involved in some way in EU's development work.

TABLE 18. Information about biosimilars is received from mostly from pharmaceutical companies and regulatory authorities

Where have you received information about biosimilar products	**Chief Physicians, n = 9**
Pharmaceutical companies	9
Regulatory authorities	8
From colleagues	7
From elsewhere?	7
	Been involved in EU's development work. Literature. From published studies. Biosimilar has been in trial use. The congresses lectures. Congresses, journals, presentations. Rheumatology journals.

7.2.2.3 Medical director of health care district, head of department and chief assessment physician

Questionnaire showed that also respondents in this group have received information about biosimilars from multiple sources (table 19). Just one of the head of department replied source to be only regulatory authorities. The other head of department has received information from regulatory authorities, pharmaceutical companies, and educational meetings. Both medical director and chief assessment physician mentioned regulatory authorities, colleagues, and pharmaceutical companies as information sources. Chief assessment physician has gathered information also from scientific publications and educational meetings.

TABLE 19. Biosimilar information has been obtained mostly from the regulatory authorities

Where have you received information about biosimilar products	**Number of answers, n = 4**
Pharmaceutical companies	3
Regulatory authorities	4
From colleagues	2
From elsewhere?	2
	Scientific publications. Educational meetings.

7.2.2.4 Chief pharmacists

Questionnaire showed that chief pharmacists have received information about biosimilars from multiple sources, usually at least from pharmaceutical companies, regulatory authorities, and colleagues (table 20). Just one chief pharmacists replied source to be only regulatory authorities. Three chief pharmacists have gathered information also from professional publications, literature and pharmaceutical databases.

TABLE 20. Biosimilar information has been obtained mostly from the regulatory authorities and pharmaceutical companies

Where have you received information about biosimilar products	**Chief pharmacists, n = 6**
Pharmaceutical companies	5
Regulatory authorities	6
From colleagues	4
From elsewhere?	3
	Pharmaceutical databases. Professional publications. Literature.

7.2.3 Need for additional information about biosimilars

The survey was intended to identify the need for information of the biosimilar products, and the topics on which additional information is required.

7.2.3.1 Gastroenterologists

All chief physicians had the opinion that they do not need additional information about biosimilars. One specialist (1/4) felt she/he needs information about long-term outcomes and comparison such as Nor-Switch. All other specialists (3/4) had same opinion as chief physicians, no need for more information. (Table 21.)

TABLE 21. Most of the respondents do not see a need for additional information about biosimilars

Do you need more information about biosimilars	**Chief Physicians, n = 7**	**Specialist of gastroenterology, n = 4**
Yes		1
		Long-term outcomes, comparison such as Nor-Switch.
No	7	3

7.2.3.2 Rheumatologists

Three out of nine respondents would like to have information of new upcoming biosimilars and when those are coming. One requires also long-term results of switches and stated, that she/he is already been longing for more details on how switches have succeeded in practice. (Table 22.)

However, the majority of respondents did not feel they need more information about the biosimilars.

Table 22. Some of the respondents are interested of upcoming biosimilars

Do you need more information about biosimilars	**Need information for, n = 9**
Yes	3
	When will there be new biosimilar products introduced. Long-term results, and at the beginning I would have liked more information on how the switches have succeeded in practice. Of the many upcoming biosimilar products.
No	6

7.2.3.3 Medical director of health care district, head of department and chief assessment physician

Medical director, heads of department and chief assessment physicians did not feel they need more information of the biosimilars.

7.2.3.4 Chief pharmacists

Two out of six respondents would like to have information about biosimilars, one for safety and another one whenever new information is published or regulatory authorities inform of the biosimilars. However, most respondents did not feel they need more information of the matter. (Table 23.)

TABLE 23. Some would like to have more information about biosimilars, for example, about safety

Do you need more information about biosimilars	**Need information for, n = 6**

Yes	2
	Safety. Always, if new information is published or regulatory authorities inform on the matter.
No	4

7.3 Switching from infliximab originator to its biosimilar

In some hospitals, patients treated with originator infliximab were switched to its biosimilars.

7.3.1 Preparations before switching originator infliximab to biosimilar

Questionnaire aimed to determine whether the hospital made preparations before switching originator infliximab to biosimilar infliximab. For example, in the Statement of The Finnish Society for Rheumatology is recommended to measure drug trough concentration and anti-drug antibodies before switching.

7.3.1.1 Gastroenterologists

Most of the respondents (nine out of eleven) stated that switching did cause separate arrangements (table 24) and the reported arrangements have been either “guiding the patient what biosimilar is” or “educating personnel about what biosimilar is”. Six out of eleven respondents indicated that both arrangements were implemented in their hospitals.

Only three out of eleven reported that switching did not cause separate arrangements. However, one of these three respondents did nevertheless also inform that drug trough concentration and antibodies were determined before switching and patient and personnel education was given and other one informed that personnel were educated.

TABLE 24. Only few felt that switching did not cause separate arrangements

	Chief Physicians, n = 7	**Specialist of gastroenterology, n = 4**
How switches were prepared?	**Number of answers**	**Number of answers**
Switches did not cause separate arrangements	2	1
Determining drug trough concentration and antibodies before switching	2	2
By guiding the patient about what biosimilar is	4	4
By educating personnel about what biosimilar is	4	4

Four respondents (2 chief physicians and 2 specialists) informed determination of drug trough concentration and antibodies before switching. None of the responses did not inform determination of antibody and drug concertation was made solely, but also education for patient and/or personnel was given.

7.3.1.2 Rheumatologists

Most chief physicians (seven out of nine) stated, that certain arrangements were made before patients who have been treated with originator infliximab were switched to its biosimilar. Seven out of nine of the respondents reported that both arrangements "guiding the patient what biosimilar is" and "educating personnel about what biosimilar is" were implemented in their hospitals. Only two out of nine reported that switching did not cause separate arrangements. However, one of those two respondents did nevertheless also inform that personnel education was given and other one informed that treatments of all patients were switched from originator infliximab to its biosimilar. (Table 25.)

Four respondents informed determination of drug trough concentration and antibodies before switching. None of the responses did not inform determination of antibody and drug concertation was made solely, but also personnel had been educated and patients had been informed about biosimilars.

Two chief rheumatologists had identified more precisely patients, whose treatments are to be switched from originator infliximab to biosimilar infliximab. One chief rheumatology defined, that patients had to be stable with the originator infliximab and they should have patient's approval. Another had set an age limit of at least 18 years.

Two chief physicians told that the all patients treated with originator infliximab, were systematically switched to its biosimilar. In these cases, one clinic had educated personnel and patients about biosimilars and one told that there were no special arrangements made.

TABLE 25. Before switching, personnel and patients were educated and informed about biosimilars

How switches were prepared?	**Number of answers, n = 9**
Switches did not cause separate arrangements	2
Determining drug trough concentration and antibodies before switching	4
By guiding the patient about what biosimilar is	7
By educating personnel about what biosimilar is	8
By identifying patients who can be switched	3
	Basically, treatment of all patients was switched if situation was stable with the treatment of originator product and the patient did not refuse. Not less than 18 years of age. Switches were made systematically for all patients on originator infliximab treatment.
Otherwise, how?	1
	All patients treated with originator infliximab were switched.

7.3.1.3 Medical director of health care district, head of department and chief assessment physician

Both heads of department reported that switching did not cause separate arrangements. However, one of these two respondents did also inform that both arrangements "guiding the patient what biosimilar is" and "educating personnel about what biosimilar is", were made. The other mentioned,

in addition what is mentioned above, that clinic had identified more precisely patients,' whose treatments were going to be switched from originator infliximab to biosimilar infliximab. Though, he did not specify precisely which types of patients were selected. (Table 26.)

Medical director of health care district informed that several arrangements were made prior the treatments were switched from originator infliximab to biosimilar infliximab. Both, patients and personnel were educated about biosimilars, and drug trough concentration and antibodies were determined before switching.

Chief assessment physician replied that switching did not cause separate arrangements. However, she/he also informed that both arrangements, guiding the patients what biosimilar is and educating personnel, were made and drug trough concentration and antibodies were determined.

None of the responses did not inform determination of antibody and drug concertation was made solely, but also personnel had been educated and patients had been informed about biosimilars.

TABLE 26. Prior the switching of treatments, personnel and patients received information about biosimilars

How switches were prepared?	**Number of answers**
Switches did not cause separate arrangements	3
Determining antibody and drug concentrations before switching	2
By directing the patient about what biosimilar is	4
By educating personnel about what biosimilar is	4
By identifying patients who can be switched	1

7.3.1.4 Chief pharmacists

Most chief pharmacists (four out of six) reported that switching did not cause separate arrangements. However, three of them replied that personnel were educated about biosimilars, and one of them told that also patients were informed and one replied that also antibody and drug concertation were determined. One respondent notified biosimilar infliximab was reviewed in the man-

agement teams and the other told that medical expert and pharmaceutical advisory board handling was made, as part of hospital tendering. Only one chief pharmacist argued that any separate arrangements were made. (Table 27.)

One chief pharmacist replied that both arrangements "guiding the patient what biosimilar is" and "educating personnel about what biosimilar is" were implemented in their hospital. Also, drug trough concentration and antibodies prior the switching were determined, to be able to identify patients which could be switched.

One stated that he/she has no information, because switches were done in polyclinics.

TABLE 27. Most chief pharmacists replied that, prior the switching of treatments, personnel received educated about biosimilars

How switches were prepared?	**Number of answers, n = 6**
Switches did not cause separate arrangements	4
Determining antibody and drug concentrations before switching	2
By directing the patient about what biosimilar is	2
By educating personnel about what biosimilar is	4
By identifying patients who can be switched	1
	Antibody and drug concentrations
Otherwise, how?	3
	Biosimilar infliximab was reviewed in the management teams. Medical expert and pharmaceutical advisory board handling, as part of hospital tendering. There is no information: switches are done in polyclinics.

7.3.2 Has the switching the treatment from originator infliximab to its biosimilar, affected the safety and/or efficacy?

The concern has been, that switching of the treatment form originator infliximab to its biosimilar could affect the safety and/or efficacy of the treatment. The aim of the questionnaire was to investigate, if the switching of the treatment from originator infliximab to its biosimilar has affected the efficacy and/or safety, and to find out what these effects have been.

7.3.2.1 Gastroenterologists

All specialist gastroenterologists answered that switching of the treatment did not affect the efficacy or safety and one commented that there have not been so far problems related to switching. One chief physician out of seven had observed allergic reactions in some patients and intestinal symptoms had returned for some patients. Two chief physicians could not say, if the switching had affected the treatment, however one of them commented that there is research on going but the impression is that it has not impact. Other chief physicians (four out of seven) commented that they had not observed switching to affect safety and efficacy. (Table 28.)

TABLE 28. The switching had not impact on safety and/or efficacy, according to most chief gastroenterologists

	Chief Physicians, n = 7	**Specialist of gastroenterology, n = 4**
Has the switching of the treatment affected the efficacy and/or safety of the treatment?	**Number of answers**	**Number of answers**
Yes	1 Some patients have had allergic reactions, for some patients' intestinal symptoms have returned	
No	4	4
Cannot say	2	
Other comments	Research on going, but the impression is that there is no impact on the efficacy or safety	No problems so far related to the switching

7.3.2.2 Rheumatologists

Most chief rheumatologists (seven out of nine) answered that they had not observed that the switching the treatment would have affected the efficacy or safety, though one had observed an individual patient to have poor response to biosimilar infliximab treatment. One chief physician experienced, that for some patients, the switching the treatment has possibly affect the efficacy and safety, because when treated with biosimilar infliximab, for some patients' subjective efficacy had worsened, and also antibodies were detected. However, the physician pointed out that samples were not taken

from all patients before switching and as a result of this, it is not possible to draw definite conclusions that switching patients from originator infliximab to biosimilar infliximab has actually affected their treatment. (Table 29.)

One chief physician could not say, if the switching had affected the treatments, however he/she commented that they have research on going.

TABLE 29. Most chief rheumatologists felt that the switching of the treatment did not have effect safety and the efficacy

Has the switching of the treatment affected the efficacy and/or safety of the treatment?	**Number of answers, n = 9**
Yes	1
	Possibly in some patients, subjective efficacy was worsened, and some of them, also antibodies were detected. Unfortunately, samples had not been taken from all before switching of treatment, so some questions were left open.
No	7
Cannot say	1
Other comments	Research on going. A single patient with poorer efficacy.

7.3.2.3 Medical director of health care district, head of department and chief assessment physician

Medical director, chief assessment physician and one of the heads of department answered that the switching of the treatment from originator infliximab to its biosimilar had no effect on the efficacy or safety. One head of department could not say if the switches have affected the treatment, but did not specify the answer.

7.3.2.4 Chief pharmacists

Half of chief pharmacist, could not say if the switching of the treatment from originator infliximab to its biosimilar has affected the safety and/or efficacy, even though one replied that side effects related to biosimilar infliximab has not occurred. One of them commented that the switching did mainly not affect the treatment, but some individual cases the antibodies were detected and patients' treatments were switched back to the originator infliximab. There was also another chief pharmacist, who commented that the switching the treatments affected safety in some patients, because adverse events occurred when treated with biosimilar infliximab. Those patients' treatments were switched back to originator infliximab. (Table 30.)

Two out of six respondents did not think the switching the treatments affected the safety and/or efficacy.

TABLE 30. The treatment of some patients has been switched back to originator infliximab

Has the switching of the treatment affected the efficacy and/or safety of the treatment?	**Number of answers, n = 6**
Yes	1
	The treatment of some patients has been switched back to the originator infliximab because of side effects.
No	2
Cannot say	3
Other comments	Biosimilar-related adverse events have not occurred. Mainly did not affect. Some individual cases in which the antibodies were detected, patients' treatments were switched back to the originator infliximab.

7.3.3 Follow-up, after the switching from originator infliximab to its biosimilar

Efficacy and safety of biologics medicines are monitored many ways routinely, for example via assessments by clinicians, self-assessments by patients, and laboratory tests.

Because all biological medicinal products are immunogenic, it is recommended for example in the Statement of The Finnish Society for Rheumatology, that "drug trough concentration and anti-drug antibodies are measured at time, especially in patients who experience adverse effects or secondary treatment failure". (The Finnish Society for Rheumatology, 2015.)

One aim of the questionnaire was to determine whether some follow-up was made after the treatments were switched from originator infliximab to its biosimilar, and what issues were monitored.

7.3.3.1 Gastroenterologists

Majority, seven out of eleven, of gastroenterologists answered that there has not been any special follow-up made of the switches. One specialist out of four told that follow-up after switching was made by determining drug trough concentration and antibodies in certain intervals. (Table 31.)

Of chief physicians, four out of seven answered that there was no special follow-up made. However, one these respondents did also comment that drug trough concentration and antibodies were determined when necessary. Also, one commented that some patients have been switched back to originator infliximab. One chief physician determined drug trough concentration and antibodies, but did now specify it in more detail. He/she also made follow-up via symptom queries. Two out of seven chief physicians answer that follow-up is made by determining a drug trough concentration and antibodies when necessary. (Table 31.)

TABLE 31. Follow-up of the switches is made in some clinics

Is follow-up made of the switches?	**Chief Physicians, n = 7**	**Specialist of gastroenterology, n = 4**
No special follow-up	4	3
Drug trough concentration and antibodies determined in certain interval		1
Drug trough concentration and antibodies determined when necessary	3	
Otherwise, how?	2	
	Symptom queries.	

	Switched back to originator product.	

7.3.3.2 Rheumatologists

Most chief rheumatologists (seven out of nine) measured drug trough concentration and antibodies, to follow-up of the switches. Usually measurements were not done in certain intervals. Five out of nine respondents made measurements only when necessary, one respondent did measurements in certain intervals and also if considered necessary and one has done follow-up measurements in certain intervals. In addition to what the above-mentioned, one monitors also clinically the efficacy of the treatment, and the tolerability of the medicine. One chief physician pointed out that follow-up of efficacy and safety of medicines are part of routines. (Table 32.)

Four of the respondents tracked the causes of the treatment interruptions, and one told that there is an intention to prepare a summary of the results.

Only three respondents out of nine told, that there is no special follow-up done, however one of them had answered that also drug trough concentration and antibodies were measured if seen necessary and one chief physician also pointed out, that even though there is no special follow-up done, the switched patients have the same follow-up than patients treated with any biological medicine.

TABLE 32. Most chief rheumatologists have done some follow-up

Is follow-up made of the switches?	**Number of answers, n = 9**
No special follow-up	3
Drug trough concentration and antibodies determined in certain interval	2
Drug trough concentration and antibodies determined when necessary	6
By tracking the causes of treatment interruption	4
Otherwise, how?	2
	Follow-up of efficacy and safety of medicines are part of routine.

	By monitoring clinically the efficacy of the treatment, and the tolerability of the medicine.
Other comments?	The normal follow-up, as when patient is treated with any biological medicine. Summary of the results has not yet been made.

7.3.3.3 Medical director of health care district, head of department and chief assessment physician

Medical director replied that follow-up is done of the switches by measuring the drug trough concentration and antibodies in certain intervals and by following the causes of the treatment interruptions.

Only one of the heads of department replied that there is no special follow-up done. The other head of department and chief assessment physician both answered that drug trough concentration and antibodies were measured if seen necessary. (Table 33.)

TABLE 33. Usually drug trough concentration and antibodies were determined

Is follow-up made of the switches?	**Number of answers**
No special follow-up	1
Drug trough concentration and antibodies determined in certain interval	1
Drug trough concentration and antibodies determined when necessary	2
By tracking the causes of treatment interruption	1

7.3.3.4 Chief pharmacists

Most chief pharmacists replied that no special follow-up was done. Two of them commented that patients treated with biosimilar infliximab have the normal monitoring related to biological medicines and biosimilar does not change this comprehensive follow-up. One chief pharmacists had no information if any special follow-up was made and another one reported that it should be queried from the treating physicians. (Table 34.)

One chief pharmacists replied that, in one hospitals, pharmaceutical advisory board has done the cost monitoring.

TABLE 34. Biosimilar infliximab patients are followed as any other patient treated with biological medicines

Is follow-up made of the switches?	**Number of answers, n = 6**
No special follow-up	4
Otherwise, how?	2
	The normal monitoring of drug therapy. No information.
Other comments?	All patients receiving Infliximab are patients, whose disease and its progression/healing are monitored quite comprehensively in any case. Biosimilar does not bring any changes to this comprehensive follow-up. Pharmaceutical advisory board has done cost monitoring. Should be asked from physicians who treats the patients.

7.4 Switching biosimilar to biosimilar (same active substance)

Biosimilar competition is increasing due to fact that, in future, originator biosimilar will have several biosimilar versions in the market. Thus, switching between biosimilars (same active substance) might be reality in near future.

It should be noted, that biosimilar product might be marketed with different trade names even if the same manufacturer. For example, biosimilar infliximab is being marketed in Europe as Remsima and Inflectra, both manufactured and developed by Celltrion. In EU, third biosimilar infliximab Flixabi, manufactured by Biogen, has received marketing authorization in May 2016, and thus is changing the switching situation between infliximabs.

7.4.1 Are biosimilars interchangeable (switching biosimilar to biosimilar)?

Target groups were asked, do they think biosimilars are interchangeable (same active substance and originator product) in hospital.

7.4.1.1 Gastroenterologists

Most of the respondents (nine out of eleven) do think that biosimilars with same active substance are interchangeable in hospital, but some stated that only in under certain conditions. One chief physician stated that there must be sufficient evidence obtained on the equivalence, and other that efficacy and safety must be demonstrated. When there were doubts (two out of eleven replies), the thoughts were that not enough is known yet and much depends on the structural and functional similarity of molecules, the quality of the production technological processes and possible changes in those. (Table 35.)

One chief physicians answered both yes and know. In option "yes", he justified the switching with the same quality requirements, but saw that it might be that all patients should be evaluated in case there are obstacles against the switching, for example patients who have developed antibodies, allergic patients, patients who use other immunosuppressive medicines. In option "no" he argued against the switching by saying, that in practice, biosimilars are not as similar as promised compared to originator products.

TABLE 35. Most of the gastroenterologists think that, in hospitals, biosimilars are interchangeable under certain conditions

	Chief Physicians, n = 7	**Specialist of gastroenterology, n = 4**
Are biosimilar products (with same active substance) interchangeable in hospitals?	**Number of answers**	**Number of answers**
Yes	7	2
	After the sufficient evidence has been obtained on the equivalence. Quality requirements are same, it might be that all patients should be evaluated if barriers to switch; patients who developed antibodies, allergic patients, patients who use other immunosuppressive medicines etc. If proven efficacy and safety. Have the same efficacy.	Efficacy appears to be similar to originator product. The results can be extrapolated from other indications.

No	1	
	In practice are not as similar as promised compared to originator product	
Cannot say		2
		I'm not sure, switching from biosimilar to other is not necessarily good thing. However, we do not know enough yet. Probably are, but much depends on the structural and functional similarity of molecules, the quality of the production technological processes and possible changes in those.

7.4.1.2 Rheumatologists

Five out of nine respondents did not see problems when switching between biosimilars with same active substance in hospitals. They justified their answers of the switches by saying that biosimilars are approved by the pharmaceutical regulatory authorities, those are adequately studied and there are safety requirements which biosimilars must fulfill. (Table 36.)

Still almost half of the respondents (four out of nine) were not sure if biosimilars with same active substance are interchangeable. One chief physician was concerned about, if biosimilars come from a large number of different manufacturers, whether differences occur in the quality, and thus also in the efficacy of the biosimilars. One respondent did not recommend repeated switches of the medicines, because it makes more difficult to follow-up the treatment and also the documentation would be more difficult. Though, the switches were not expected to affect the treatment otherwise.

One chief physician could not say, whether biosimilars are interchangeable and asks if there are comparability studies made between biosimilars.

TABLE 36. Almost half of the respondents have concerns when switching between biosimilars

Are biosimilar products (with same active substance) interchangeable in hospitals?	**Number of answers, n = 9**
Yes	5
	Are approved by the regulatory authorities. Are been adequately studied. If studied, such as the authorization procedure requires. The safety requirements.
Cannot say	4
	If the same manufacturer, then should be the same product, but if a large number of different manufacturers, then suspicion, whether differences occur in quality of the products, and thus also in the efficacy. Each of the biosimilar product and its related studies must be evaluated separately. The constant back and forth or repeated switching of the treatment should probably try to be avoided. It makes difficult to follow-up the treatment. Will not likely otherwise affect treatment. Documentation is going to be more difficult. Is there a comparison between the biosimilars?

7.4.1.3 Medical director of health care district, head of department and chief assessment physician

Chief assessment physician and medical director did not see problems of switching between biosimilars with same active substance in hospital care. (Table 37.)

One head of department was not sure if all biosimilars with same active substance are interchangeable. She/he argued that some biosimilars, like filgrastims, which are used for a short period of time, are interchangeable, but with medicines used for long time, respondent was more cautious.

Another head of department considers that clinicians cannot know if biosimilar can be switched to biosimilar, and in his/her opinion, this should be the responsibility of the pharmaceutical regulatory authorities.

TABLE 37. Regulatory authorities should be responsible of determining if biosimilars with same active substance are interchangeable

Are biosimilar products (with same active substance) interchangeable in hospitals?	**Number of answers**
Yes	2
No	1
	Some of them are, for example, filgrastim, which is used for a short period of time. Those, which are used for a long time, should be contemplated.
Cannot say	1
	Practical operator cannot know, this must be the responsibility of the pharmaceutical regulatory authorities.

7.4.1.4 Chief pharmacists

All chief pharmacist think that biosimilar products, which have same active substance, are interchangeable in hospitals. There seems to be trust to the regulatory authorities and one commented that the Finnish supervising authority has taken a favorable position about the switching. Though, some thought that possibly there should be similar approach to the matter that was implemented with infliximab. (Table 38.)

TABLE 38. Biosimilar products with same active substance are seen to be interchangeable in hospitals

Are biosimilar products (with same active substance) interchangeable in hospitals?	**Number of answers, n = 6**
Yes	6
	In Finland, supervising authority has taken a favorable position about the switching. The biosimilar is similar enough and the experiences about infliximab are positive. With certain restrictions, like was done with Infliximab. The quality requirements are the same, each patient will probably need to be individually assessed whether there are special groups of patients, who have barriers to the switching.

	Meets the requirements of the regulatory authorities.

7.4.2 Thinks to consider when switching between biosimilars with same active substance

"Because each new batch of a biologic is a different product, switching a patient between biosimilars for the same reference product is "no more risky" than switching a patient from the reference product to one of the biosimilars" (Brennan (b) 2017).

One interest of the questionnaire was to find out what should be considered when switching a patient between biosimilars with same active substance.

7.4.2.1 Gastroenterologists

Eight out of the eleven respondents answered the question concerning what should be taken in to the consideration when switching between biosimilars. (Table 39.)

Three specialist gastroenterologists responded the question and one of them had opinion that possible allergic reactions and formation of antibodies should be monitored, other would possibly measure drug concentrations and monitor immunization and third pointed out that there has to be sufficient documentations about the products.

Five chief physicians answered the question and one pointed out that switching should not be done during the induction phase, though later switching would be ok. Other chief physician pondered if switching should be done blinded to be able to remove the subjective knowledge experienced by patients. Third chief physician thinks that price should be taken in to consideration and two of the chief pharmacists thought that patients should be informed about the switching. One pointed out the research-based information about the products.

TABLE 39. Different issues were raised when considering the switching biosimilar to biosimilar with same active substance

	Chief Physicians, n=5	**Specialist of gastroenterology, n=3**
What should be taken in to consideration when switching between biosimilars (same active substance)?	No switching during the induction phase, later switching is ok. Possibly should be done blinded, to be able to remove the subjective knowledge experienced by a patient. On the other hand, whether it is ethically right not to tell the patient if the medicine is changing? I do not know! Price. Inform patient. There is a research-based information about the product (efficacy/safety).	To monitor possible allergic reactions and the formation of antibodies, in particular if as a result of switch treatment is interrupted or the break is prolonged for one reason or another. Possibly measure concentrations and monitor immunization. There is sufficient documentation about the product.

7.4.2.2 Rheumatologists

Seven chief rheumatologists out of the nine responding the questionnaire answered the question about what should be taken in to the consideration when switching biosimilar to biosimilar with same active substance. (Table 40.)

One chief pharmacist answered that there is really not anything what should be taken in to consideration and one could not say what it could be.

One chief physician saw that information activities are important and other one thought that indications and co-medications are important to take into account. Also, the Finnish Society of Rheumatology has made position paper about biosimilar use and this was mentioned in one of the answer.

Two of the respondents wanted to follow and document the switches more specifically, and one of them replied that the results of the monitoring should also be reported for example to the register of biological treatment.

TABLE 40. Switching biosimilar to biosimilar with same active substance should be closely monitored

	Chief physicians, n=7
What should be taken in to consideration when switching between biosimilars (same active substance)?	Not really anything. Careful monitoring, the efficacy before and after, systematically to follow-up before and after the switch the possible side effects, drug trough concentration and antibodies, to report the results for example to the register of biological treatment. I agree to what the Finnish Society for Rheumatology is saying in its position paper about use of biosimilars. Indications and co-medication. To document the switch and to monitor possible changes in efficacy and tolerability. Information activities. Could not say what it could be.

7.4.2.3 Medical director of health care district, head of department and chief assessment physician

Only chief assessment physician answered the question about what should be taken in to the consideration when switching biosimilar to biosimilar with same active substance. Respondent's opinion is that acquisition periods should be long enough, so that switches do not occur too frequent and drug safety has to be taken into account.

7.4.2.4 Chief pharmacists

The question about what should be taken in to the consideration when switching biosimilar to biosimilar which has same active substance gave various answers from chief pharmacists. One thinks that patients treated with biological medicines are monitored comprehensively anyway and biosimilars do not bring any extra following to group of patients treated with infliximab's. When using biological medicines, humans are administered a foreign protein, whether it be the originator or biosimilar product. Whenever a foreign protein is administered to humans, the risk to develop antibodies increases. This risk is not in itself higher between various biological medicinal products. (Table 41.)

Also, product trainings and information about biosimilars as well as closer monitoring of antibodies at the beginning and safety should be taken in to account when switching between biosimilars. One good remark was that sharing of the information should be objective.

TABLE 41. When switching biosimilar to biosimilar with same active substance, sharing of the information should be objective

	Number of answers, n = 6
What should be taken in to consideration when switching between biosimilars (same active substance)?	Patients treated with biological medicines are monitored comprehensively anyway. Biosimilars do not cause anything special extra to the group treated with infliximab. When using biological medicines, humans are administered a foreign protein, whether it be the originator or biosimilar product. Whenever a foreign protein is administered to humans, the risk to develop antibodies increases. This risk is not in itself higher between various biological medicinal products. Biologic drugs are produced in living cells, and purified through a variety of processes. There may have differences in the purification residues, because the production plants are the living cells and proteins are result of their metabolism. In the biological world, nothing is exactly the identical, not even the monoclonal cell culture metabolism. Normal practice when changing one medicine for another. Sharing information should be objective. Product trainings, information. Safety. At the beginning, the formation of antibodies should be monitored more closely.

7.4.3 Obstacles which slow down the wider usage of biosimilar products

Questionnaire participants were asked which are the obstacles slowing down the wider usage of the biosimilar products.

7.4.3.1 Gastroenterologists

Two respondents of specialist gastroenterologists answered question about obstacles slowing down the wider usage of the biosimilar products and two did not. One answered that there are

necessarily any obstacles and another thought that there are no obstacles at the moment as biosimilar infliximab has dominance in the market. (Table 42.)

Six out of seven chief physicians answered question and two of them saw attitude as an obstacle and another mentioned also prejudices. As an obstacle were also seen the too rarely performed tendering's of the medicines, the long term patents and evidence of the efficacy. One mentioned that indications of biosimilar products should be kept sufficiently tight.

TABLE 42. Gastroenterologists think that there is several obstacles influencing to the greater use of biosimilar products

	Chief Physicians, n = 6	**Specialist of gastroenterology, n = 2**
What are the obstacles for the greater use of biosimilars?	Indications must be kept sufficiently tight (price, benefits, disadvantages). Too rarely performed tendering of medicines. Evidence of efficacy. Long term patents. Attitude. The attitudes and prejudices.	Biosimilar infliximab has dominance, so I think there is no obstacles at the moment. Not necessarily have any.

7.4.3.2 Rheumatologists

Eight of the nine respondents answered the question, that aimed to find out, which things slow down the wider usage of biosimilars. (Table 43.)

Most of the respondents (six out of eight) saw multiple obstacles slowing down the wider usage of biosimilars. Patients and doctors have still prejudices of the biosimilar products, some might not have experience with biosimilars and one reason is also the pressure from the company that has manufactured the original product. There is also speculation, whether the quality of the products can be guaranteed, if biosimilars are manufactured in many different countries where cultural practices differ. This puts lot of pressure to the pharmaceutical regulatory authorities, which have to be able to ensure quality of the products. The repeated switches are also seen as a potential threat to

achieve the best possible care. Access to information of the new biosimilars must also be guaranteed. Each physician prescribing biological medicinal products, needs a lot of information of each new biosimilar coming to the market. In addition, it is a challenge to get the prescriber to change the practice, because it is easier to stick to the original product, which physician already knows

Two chief physicians out of eight think that at the moment, there are not so many known obstacles for wider use of the biosimilars.

TABLE 43. Rheumatologists see many obstacles which slow down the wider usage of biosimilars

	Arguments, n = 8
What are the obstacles for the greater use of biosimilars?	Prejudices and uncertainties, the pressure from company which has developed the drug. Patients and doctors have prejudices. The quality must be guaranteed. Probably the biosimilars are manufactured and will be manufactured in many different countries, having different sorts of cultural practices. The pharmaceutical regulatory authorities (such as the EMEA) have a great responsibility on what kind of products will be approved. Each physician prescribing biological medicinal products, needs a lot of information of each biosimilar he/she is using. It is easier to stick to the originator medicine, which physician knows. Inexperience. Treatment should be clear, documented and reliably implemented. Repeated switches can complicate this. There are not many known obstacles. There are still so few.

7.4.3.3 Medical director of health care district, head of department and chief assessment physician

One of the heads of department, medical director and chief assessment physician replied the question about obstacles for wider usage of biosimilars. One reason which has slowed down the use of biosimilars is pharmaceutical industry's strong anti-marketing. Also, prescribers might have fears, misconceptions, and insufficient biosimilar knowledge Some of the originator products have now "improved" versions of themselves on the market and as a result of that, those versions might be seen as better options than the biosimilars. (Table 44.)

TABLE 44. One obstacle slowing down the wider usage of the biosimilars, is the pharmaceutical industry's strong anti-marketing against biosimilars

	Number of answers, n = 3
What are the obstacles for the greater use of biosimilars?	Prescriber's fears and misconceptions, insufficient knowledge of biosimilar. From the originator product has come an option, that is better than the biosimilar. The pharmaceutical industry's strong anti-marketing.

7.4.3.4 Chief pharmacists

Five of the six respondents answered the question, that aimed to find out, which things slow down the wider usage of biosimilars. (Table 45.)

The reasons slowing down the use of biosimilars are insufficient biosimilar knowledge, originator companies' product development and prejudices, as well as originator companies' effective marketing systems. Clinicians have been reluctant to use biosimilars, however, the resistance of physicians is not so intense than it used to be. Also, safety was seen to be one of the reasons slowing down the wider use of biosimilars.

TABLE 45. Lack of knowledge and prejudices, for example, are obstacles for wider usage of biosimilars

	Number of answers, n = 5
What are the obstacles for the greater use of biosimilars?	Attitudes, originator companies' product development. If there are barriers, lack of information. Prejudices. Safety, clinicians' resistance (is no longer so intense than before). Originator companies' effective marketing system.

7.5 Price competition

When biosimilar product enters to the market, it is assumed to cause price competition. The first biosimilar filgrastim received a marketing authorization in Europe in September 2008 and Infliximab in September 2013.

7.5.1 Estimated price differences

The questionnaire participants were asked, what they estimated price difference to be between biosimilar and originator infliximab, before the first biosimilar infliximab entered to the market.

7.5.1.1 Gastroenterologists

Nine out of eleven (6/7 chief physicians and 3/4 specialists) respondents answered the question what were their estimates of price difference between biosimilar infliximab and originator infliximab, before the first biosimilar infliximab entered to the market. (Table 46.)

The estimated price differences varied quite a lot, between 25 – 80 %. Chief gastroenterologists had estimated that the price difference could have been 30 - 60%, and they had based their presumptions of the price difference mostly purely to the guesses. One justified his/her estimate by previous experience in competitive tendering, other one told that the originator research is expensive and one based his/her estimate to what he/she had heard. One specialist's estimated price difference was based on to the information received from pharmaceutical companies.

TABLE 46. The estimated price difference varied between 25 to 80 %

	Chief Physicians, n = 6		**Specialist of gastroenterology, n= 3**	
	Estimated price difference	**Arguments**	**Estimated price difference**	**Arguments**

Before the biosimilar infliximab entered to market, you estimated price difference between biosimilar infliximab and its originator infliximab to be	50% 35% 60% 40% 30%	Guess. Previous experience in competitive tendering. The originator research is expensive; research information. On the basis of I have heard and memory. Estimate Assumption.	50 - 80% 30% 25%	Based on information received from pharmaceutical companies. Guess

7.5.1.2 Rheumatologists

The estimated price differences of originator infliximab and its biosimilar varied only little, between 30 – 50 %. Most chief physicians (six out of nine) had estimated that the price difference could have been 30 %, and one of them had purely speculated the price difference and another had thought that 30 % is a significant enough and had not expect it to be more radical. One chief physician had based his/her estimate to what was general supposition and one physician had had expert evaluations in use and had assumed that the price difference could have been 30% and pointed out that challenging manufacturing processes do affect the pricing. One had trusted the competition and had assumed the price difference could have been little more, 40 %. Also, 50 % price difference was mentioned twice, and one told it to be a speculative. (Table 47.)

TABLE 47. The price difference was estimated to be 30 – 50 %

	Estimated price difference	**Arguments, n = 9**
Before the biosimilar infliximab entered to market, you estimated price difference between biosimilar infliximab and its originator infliximab to be	50% 40% 30%	Competition. Estimate. General supposition. Guess. Expert evaluations, challenging manufacturing process. Thought that it would be significant, but assumed that the price difference would not be more radical. To the best of my recollection.

7.5.1.3 Medical director of health care district, head of department and chief assessment physician

Chief assessment physician and two heads of department replied the question about estimated price difference between biosimilar infliximab and originator infliximab (before biosimilar infliximab came on the market). The other head of department had estimated the price difference to be 30 %, and another 50 %. Chief assessment physician had speculated, that the price difference could have been 50 %.

7.5.1.4 Chief pharmacists

Five of the six respondents answered the question. The estimated price differences of originator infliximab and its biosimilar varied between 30 – 60 %. One chief pharmacist based his/her the presumption of 40% price difference to the speculations of how much the new entrants wanted to penetrate the market. Two of the respondents did estimate the price difference could have been 30%, and one of them based his/her estimate to the discussions in professional journals. Two chief pharmacists had assumed the price difference could have been as high as 60%. One replied that when more options of same product enters the market, the competition will start, as in the any market area. Chief pharmacist commented that there is no possibility to ponder beforehand what will happen to one individual product's price, since hospital has in use several thousands of different medicinal products, when taking into account the different dosages, pack sizes and forms of medicines. (Table 48.)

TABLE 48. The estimated price difference was estimated to be 30 – 60 %

	Estimated price difference	**Arguments, n = 5**
Before the biosimilar infliximab entered to market, you estimated price difference between biosimilar infliximab and its originator infliximab to be	60% 40% 30%	Does not possibility to think about the possible changes in prices, when the market of an individual product changes. When more options of the same product enter the market, the competition will start, as in any market area. Discussions in professional journals. On research information.

		To a feeling, how much the new entrants wanted to penetrate the market

7.5.2 Price difference when biosimilar product was selected to pharmaceutical formulary

The questionnaire participants were asked to reveal the price difference between the biosimilar and originator infliximab, when biosimilar infliximab was selected to the pharmaceutical formulary at the first time. Also, the year when this happened was requested to give.

7.5.2.1 Gastroenterologists

Not all respondents answered this question. Six out of seven chief gastroenterologists and three out of four specialists answered. One chief physician advised to inquire from the pharmacy, and one specialist did not know the answer. (Table 49.)

In the answers given, the price difference (calculated on the purchase prices) between originator and biosimilar infliximab varied quite much, between 20 – 70%. The first time when biosimilar infliximab was selected to the pharmaceutical formulary, varied from 2014 to 2016.

TABLE 49. The year when biosimilar was selected to the pharmaceutical formulary varied from 2014 to 2016, and the price difference between originator and biosimilar infliximab varied between 20 – 70 %

	Chief Physicians, n = 6		**Specialist of gastroenterology, n = 3**	
	Price difference, %	**Biosimilar was selected to pharmaceutical formulary (year)**	**Price difference, %**	**Biosimilar was selected to pharmaceutical formulary (year)**
Price difference (calculated on the purchase price) between biosimilar infliximab and its originator infliximab, after biosimilar was selected	65% 57% 20% 70% 40%	2016 2015 2015 2014 2015 Advised to inquire from the pharmacy.	65% 70% as far as could recollect	2016 2015 Did not know

to pharmaceutical formulary				

7.5.2.2 Rheumatologists

The price difference (calculated on the purchase price) between originator and biosimilar infliximab, when biosimilar was selected to pharmaceutical formulary for the first time, varied quite much, between 30 – 80 %. In four responses, price difference varied between 70 – 80%, and in five responses the difference was 30 – 50 %. Two of the respondents mentioned that also the originator infliximab had lowered the price and one of them had used the "original price" of the originator product in calculations. One chief rheumatology commented, that essential is the price difference to the originator product before biosimilar came on the market. In the tenders, the price difference is not that important. (Table 50.)

Biosimilar infliximab has been selected to the hospitals' pharmaceutical formulary between 2014 – 2016.

TABLE 50. The year when biosimilar was selected to pharmaceutical formulary varied from 2014 to 2016, and the price difference between originator and biosimilar infliximab varied between 30 – 80 %

	Price difference, % **n = 9**	**Biosimilar was selected to pharmaceutical formulary (year)**
Price difference (calculated on the purchase price) between biosimilar infliximab and its originator infliximab, after biosimilar was selected to pharmaceutical formulary	50% 80% 40% 70% 70 % of the original price of the originator product 30%	2016 2014 2015

Other comments	I understood, that 80% of the price of the originator, although the originator dropped the price also X %. The originator dropped the price also due to the competition. In my view, essential is the price difference to the originator product before biosimilar came on the market. In the tenders, the price difference is not that important.	

7.5.2.3 Medical director of health care district, head of department and chief assessment physician

Medical director and one of the head of the department replied the question about the price difference (calculated on the purchase price) between originator and biosimilar infliximab, when biosimilar was selected to pharmaceutical formulary for the first time. Head of the department replied that the price difference is 60 % and medical director 43 %.

7.5.2.4 Chief pharmacists

The price difference (calculated on the purchase price) between originator and biosimilar infliximab, when biosimilar was selected to pharmaceutical formulary for the first time, varied between 50 to 57% in the four replies and in two responses difference was 40 – 43 %. (Table 51.)

The year when biosimilar infliximab was selected to the hospital's pharmaceutical formulary varied from 2014 to 2016.

TABLE 51.The year when biosimilar was selected to the pharmaceutical formulary varied from 2014 to 2016, and the price difference between originator and biosimilar infliximab varied between 40 – 57 %

	Price difference, % n = 6	**Biosimilar was selected to pharmaceutical formulary (year)**
Price difference (calculated on the purchase price) between biosimilar infliximab and its	57% 50%	2016 2015

originator infliximab, after biosimilar was selected to pharmaceutical formulary	43% 40%	2014

7.5.3 Has biosimilar infliximab affected the price of the originator infliximab?

The survey participants were asked to reveal if the purchase price of originator infliximab was changed after the biosimilar infliximab for first time participated in the hospital tendering, compared to the purchase price of the originator infliximab offered in the previous hospital tendering.

7.5.3.1 Gastroenterologists

Six out of seven chief gastroenterologists and three out of four specialist gastroenterologists answered the question. Of these responses, one chief physician refused to answer, one gave an estimate and one specialist did not know the answer. (Table 52.)

Four chief physicians told that purchase price of the originator product was reduced when biosimilar infliximab participated the hospital tendering for the first time and the price was compared to previous hospital tendering purchase price. The price decrease varied from 20 % to 30 % (35% was told to be an estimate). One answered that the originator Infliximab purchase price was not change.

Two specialists (2/4) told that the originator infliximab price was reduced, but one did not know how much of the purchase price of originator infliximab has changed and other one answered 50 %.

TABLE 52. The originator infliximab purchase price decreased, when biosimilar infliximab participated hospital tendering first time

	Chief Physicians, n = 6		**Specialist of gastroenterology, n = 3**	
When biosimilar entered the hospital tendering for the first time, did the originator product's purchase price change, when compared to the previous purchase price?	**Number of answers**	**Price change, %**	**Number of answers**	**Price change, %**
Reduced	4	30%	2	50%

		20% 35%, estimate		Did not remember how much
Did not change	1			
Other comments?	1	Did not want to comment	1	Did not know

7.5.3.2 Rheumatologists

All chief rheumatologists replied to the question. Of these respondents one did not know if the price of the originator infliximab has changed. (Table 53.)

Six chief physicians told, that the purchase price of the originator product was reduced, when biosimilar infliximab participated hospital tendering for the first time and the price was compared to the previous hospital tendering purchase price. Two responded the price reduction be 30 % and 40 %, one did not know the exact price reduction, and two of the respondents did not give figures. One chief physician replied that the originator infliximab purchase price was not changed.

TABLE 53. When the biosimilar infliximab participated hospital tendering for the first time, also the originator infliximab purchase price decreased

When biosimilar entered the hospital tendering for the first time, did the originator product's purchase price change, when compared to the previous purchase price?	**Number of answers, n = 9**	**Price change, %**
Reduced	6	40% 30%
Did not change	1	
Other comments?	2	Did not know Did not know the exact difference.

7.5.3.3 Medical director of health care district, head of department and chief assessment physician

Medical director and one head of department replied the question. Head of department told that the purchase price of the originator product was reduced when biosimilar infliximab participated hospital tendering for the first time and the price was compared to the previous hospital tendering purchase price. Medical director answered that the originator product price had lowered during the previous acquisition period and the same price was offered to the current procurement season. However, none of the respondents did not reveal the exact price reduction of the originator product.

7.5.3.4 Chief pharmacists

Two chief pharmacists replied that the purchase price of the originator product was lowered by 30% when biosimilar infliximab participated hospital tendering for the first time and the price was compared to the previous hospital tendering purchase price. (Table 54.)

Three replied that originator infliximab purchase price had not changed and one of them commented that the price had decreased already during the previous acquisition period after the new competitive tendering had been opened during the procurement period. Another commented that new competitive tendering was opened during the procurement period 2014 – 2015, but originator infliximab had lowered the price already in 2013. When competitive tendering was opened for 2014-2015 period, company having the originator product offered the same price again and also two companies with biosimilar product participated.

TABLE 54. At least in one hospital, originator infliximab price was lowered before biosimilar infliximab participated tender process for the first time

When biosimilar entered the competitive tendering for the first time, did the originator product's purchase price change, when compared to the previous purchase price?	**Number of answers, n = 5**	**Price change, %**
Reduced	2	30%
No	3	

Other comments?	A new competitive tendering was made between the procurement period 2014 - 2015 (the possibility is recognized in the invitation to tender). Already in 2013, for the period 2014 to 2015, the originator company gave a discount. Originator company gave the same price again when competitive tendering was opened in between 2014-2015 period and also two biosimilar providers participated. The other biosimilar's offer was overall more economical and was chosen for 2015. Price decreased during the previous acquisition period, after new competitive tendering was made during the current procurement period.	

7.6 Cost savings

The introduction of biosimilars is expected to reduce prices and to generate medicinal cost savings for the hospitals.

7.6.1 For which patients' biosimilar infliximab treatments were initiated?

One aim of the questionnaire was to find out, how medicinal cost savings were attempted to be achieved by using biosimilar infliximab.

7.6.1.1 Gastroenterologists

All chief physicians, and three out of four specialists, replied the question. (Table 55.)

One specialist gastroenterology replied, that the medicinal cost savings were attempted to be achieved by initiating biosimilar infliximab for new patients and by switching chosen patient groups, treated with infliximab originator, to biosimilar infliximab. Another two respondents told that all patients treated with originator infliximab were switched to its biosimilar.

Two out of seven chief physicians replied, that the medicinal cost savings were attempted to be achieved by switching all patients treated with originator infliximab to biosimilar infliximab. One chief physician who had switched the treatment only for the chosen patient groups commented, that skeptical patients were not switched. One replied that the savings were attempted to be achieved by initiating biosimilar infliximab to new patients and also by switching the treatment for chosen patient groups. The patients whom were not switched, were highly allergic patients and for whom had been difficulties to find the suitable medicines. Three out of seven chief gastroenterologists had all initiated biosimilar infliximab for the new patients and also all the patients treated with originator infliximab were switched to its biosimilar.

No one answered that the savings would have been attempted to be achieved only by initiating biosimilar infliximab for the new patients.

TABLE 55. Most often, the medicinal cost savings were attempted to be achieved by switching all patients treated with the originator infliximab to its biosimilar and also by initiating biosimilar infliximab for the new patients

	Chief Physicians, n = 7	**Specialist of gastroenterology, n = 3**
How drug cost savings were attempted to be achieved by using biosimilars?	**Number of answers**	**Number of answers**
By initiating biosimilar for new patients	4	1
By switching all patients from originator product to biosimilar product	5	2
By switching chosen patient groups from originator product to biosimilar product	2	1
	Highly allergic patients who also otherwise have been difficult to find suitable medicines. Skeptical patients.	Specific patients.

7.6.1.2 Rheumatologists

Four chief rheumatologists replied that drug cost savings were attempted to be achieved by initiating biosimilar infliximab for new patients and by switching all patients treated with the originator infliximab to its biosimilar. (Table 56.)

Three replied that savings were attempted to be achieved by initiating biosimilar infliximab for new patients and by switching chosen patient groups treated with the originator infliximab to the biosimilar infliximab. In all cases, pediatric patients were excluded from the switches and in another case, also patients who had refused of the switch despite given information, were excluded. At least in one hospital, pediatricians have initiated the infliximab treatments with biosimilar infliximab instead of the originator infliximab.

Two of the respondents told that all patients treated with originator infliximab were switched to the biosimilar infliximab.

No one answered that savings would have been attempted to achieved only by initiating biosimilar infliximab treatments for new patients.

TABLE 56. Pediatric patients were not switched, but at least in one hospital, pediatricians initiated the infliximab treatments with biosimilar infliximab

How cost-savings were attempted to be achieved by using biosimilars?	**Number of answers, n= 9**
By initiating for new patients	7
By switching all patients from originator product to biosimilar product	6
By switching chosen patient groups from originator product to biosimilar product	3
	Pediatric patients were apparently not switched, and also if the patient refused, despite the information given. Young patients. Pediatricians decided not to switch the originator products of pediatric patients, but the new treatments were initiated with biosimilar.

7.6.1.3 Medical director of health care district, head of department and chief assessment physician

Both, medical director, and chief assessment physician replied that medicinal cost savings were attempted to be achieved by initiating biosimilar infliximab for new patients and by switching the chosen patient groups treated with the originator infliximab to the biosimilar infliximab. Pediatric patients and reluctant patients were not switched.

Two heads of department replied that savings was attempted to be achieved by switching chosen patients treated with originator infliximab to the biosimilar infliximab. One respondent did not specify patients which were not switched and other one told the most difficult patients were excluded of the switches.

7.6.1.4 Chief pharmacists

Three chief pharmacists replied that medicinal cost savings were attempted to be achieved by initiating biosimilar infliximab for new patients and by switching chosen patient groups treated with originator infliximab to the biosimilar infliximab. One of them commented that pediatric patients were not switched and another commented that rheuma, psoriasis and IBD-patients were excluded and one did not specify. (Table 59.)

Only one respondent told that treatments of all patients were switched to biosimilar infliximab and one commented that medicinal cost savings were attempted to be achieved by switching chosen patient groups, treated with originator infliximab, to its biosimilar. The pediatric patients were excluded of the switches.

No one answered that savings would have been attempted to achieved only by initiating biosimilar infliximab for new patients.

There was also commented that beforehand there cannot be set any certain saving targets or discount percentage goals. The Health Care Act and the Act on Specialized Medical Care stipulates that the hospital concerned must provide to patients the known effective treatment. By initiating the usage of the selected biosimilar, it was possible to lower the growth pressure of the medicine costs.

Encouraged by the hospital's medical director, the target was set to switch, as widely as possible, to the use of biosimilar infliximab. The same target was set for the period 2016-2017.

TABLE 57. Most often, medicinal cost savings were attempted to be achieved by switching chosen patient groups treated with originator infliximab to its biosimilar and also by initiating biosimilar infliximab for new patients

How cost-savings were attempted to be achieved by using biosimilars?	**Number of answers, n = 6**
By initiating for new patients	3
By switching all patients from originator product to biosimilar product	1
By switching chosen patient groups from originator product to biosimilar product	4
	Pediatrics. Rheuma, Psoriasis, IBD.
Other comments?	By starting to use the selected biosimilar, it was possible to reduce the growth pressure of medicine costs. Encouraged by the hospital's medical director, the target was set to shift, as widely as possible, for the use of biosimilar. The same target was set for the period 2016-2017.

7.6.2 Were the medicinal cost savings achieved?

If the drug cost savings were attempted to be achieved by using biosimilar infliximab, were the medicinal cost saving goals achieved?

7.6.2.1 Gastroenterologists

All chief gastroenterologists, and two out of four specialist gastroenterologists responded the question. Most respondents (seven out of nine) felt, that cost savings were achieved by using biosimilar infliximab, and the factors which helped the realization of cost savings were that infusions were cheaper than before and originator infliximab treatments of all patients from were switched to biosimilar infliximab. (Table 60.)

Two chief physicians felt that the cost savings were achieved only partly. One explained that for some patients' the higher doses had to be used, for some patients more frequent doses were given

because of exacerbations, and exacerbations of intestinal inflammatory disease appeared to increase despite of all medications. Other one stated that the usage of infliximab has increased compared to the past.

No one answered that the drug cost savings were not achieved by using a biosimilar infliximab.

TABLE 58. Most of the respondents felt, that the cost savings were achieved by using biosimilar infliximab

	Chief Physicians, n = 7	**Specialist of gastroenterology, n = 2**
Are the cost savings realized?	**Number of answers**	**Number of answers**
Yes	5	2
	All patients switched from originator product biosimilar. Each infusion is cheaper than before.	
Partly	2	
	Some of the patients use higher doses, more frequent doses are given because of exacerbations, and exacerbations of intestinal inflammatory disease appears to increase despite of all medications. Increased use of infliximab compared to the past.	

7.6.2.2 Rheumatologists

All but one chief rheumatology felt, that cost savings were achieved by using biosimilar infliximab. The factors which helped the realization of cost savings were, that biosimilar infliximab was used with same indications that originator infliximab was used, all adult patients treated with originator infliximab were switched to biosimilar infliximab, and new infliximab treatments were initiated with lower price biosimilar infliximab. (Table 61.)

All but one chief physicians felt, that cost savings were achieved by using biosimilar infliximab. The factors that helped to achieve the cost savings were, that biosimilar infliximab was used with same

indications that originator infliximab was used, all adult patients treated with the originator infliximab were switched to the biosimilar infliximab, and new infliximab treatments were initiated with the more affordable biosimilar infliximab.

No one answered that the drug cost savings were not achieved by using a biosimilar Infliximab.

TABLE 59. Most chief rheumatologists felt, that cost savings were achieved by using a biosimilar infliximab

Are the cost savings realized?	**Number of answers, n = 9**
Yes	8
	Same indications. Principally, the treatment of all patients was switched to biosimilar infliximab. Lower price made possible to achieve savings, because adult patients were switched to biosimilar infliximab and all new infliximab treatments were initiated with biosimilar.
Partly	1
	All patients were not switched, some patients had to be switched back to originator infliximab. Though, cost savings were achieved by initiating biosimilar infliximab for new patients.

7.6.2.3 Medical director of health care district, head of department and chief assessment physician

Medical director, chief assessment physician and both heads of department estimated that cost savings were achieved. The factors helping in the realization of cost savings were, new infliximab treatments were initiated with lower price biosimilar infliximab, the switching was done actively and biosimilar infliximab is considerably cheaper compared to originator infliximab.

7.6.2.4 Chief pharmacists

Four chief pharmacists commented, that cost savings were achieved by using biosimilar infliximab. The factors that helped to achieve the cost savings were, that after hesitation, also originator infliximab treatments were switched to biosimilar, and not only initiated biosimilar infliximab treatments

for new patients. In one hospital, it is recommended that originator product may only be used in exceptional cases. (Table 62.)

One chief pharmacist felt that cost savings were achieved only partly, but did not explain what was the reason.

There was also one comment in which was explained why total medicinal costs will not reduce. It said that even if through tendering is achieved more favorable net price level the new innovations are usually more costly than previous ones and for this reason, usually as a whole, medicinal costs do not reduce. Competition and competitive tendering restrain the growth of medicinal costs, but do not eliminate it.

TABLE 60. Most chief pharmacists commented that cost savings were achieved by using biosimilar infliximab

Are the cost savings realized?	**Number of answers, n = 6**
Yes	4
	Originator product may only be used in exceptional cases. After hesitation, also originator infliximab treatments switched to biosimilar.
Partly	1
Other comments?	Through competitive tendering is achieved as a whole more favorable net price. New innovations are usually more costly than previous ones. For this reason, usually as a whole, drug costs are not reduced. Competition and competitive tendering in itself restrain the growth of medical costs, but do not eliminate it.

7.6.3 How much was saved by using biosimilar infliximab?

If the drug cost savings were achieved by using the biosimilar infliximab, how much were the cost savings?

7.6.3.1 Gastroenterologists

Only one out of four specialist gastroenterologists answered the question and he/she told that there was no drug cost savings achieved 2015, but this could be explained by the fact that biosimilar infliximab was chosen to hospital's pharmaceutical formulary for the first time one year later, 2016. (Table 63.)

Five out of seven chief gastroenterologists, answered the question. One chief physician answered that there was no drug cost savings achieved 2015, but as with specialist, this could be explained by the fact that the biosimilar infliximab was chosen to hospital's pharmaceutical formula first time 2016. Other estimates of the savings varied from 40 000€ to 700 000€.

TABLE 61. Estimated drug cost savings achieved by using biosimilar infliximab were up to 700 000€

	Chief Physicians, n = 5	**Specialist of gastroenterology, n = 1**
Your estimate of the cost savings, that were achieved with use of bio-similar product in 2015. (€)	0€ 40 000€ 50 000€ 300 000€ 700 000€	0€

7.6.3.2 Rheumatologists

Only six out of nine chief rheumatologists replied the question. The five chief physicians' estimated cost savings varied from 50 000€ to over 500 000€. One chief rheumatology answered that there was no drug cost savings achieved 2015, but as with specialist of gastroenterology, this could be explained by the fact that biosimilar infliximab was chosen to the hospital's pharmaceutical formulary first time in 2016. (Table 64.)

TABLE 62. Estimated drug cost savings achieved by using biosimilar infliximab were up to 500 000€

	Estimated cost savings, € **n = 6**
Your estimate of the cost savings, that were achieved with use of biosimilar product.	As far as I have understood over 500 000€. 300 000€ 200 000€ 50 000€ 0€ (switching started beginning of 2016)

7.6.3.3 Medical director of health care district, head of department and chief assessment physician

Medical director estimated the cost savings be 1,8 million euros and head of department 50 000€. Chief assessment physician and other head of department did not answer the question.

7.6.3.4 Chief pharmacists

five out of six chief pharmacists replied the question and estimated cost savings varied from 140 000 € to 950 000 €. One chief pharmacist did not reply to the question, but this could be ex-plained by the fact that biosimilar infliximab was chosen to hospital's pharmaceutical formulary first time in 2016. (Table 65.)

TABLE 63. Estimated drug cost savings achieved by using biosimilar infliximab were up to 950 000€

	Estimated cost savings, € **n = 5**
Your estimate of the cost savings, that were achieved with use of biosimilar product.	950 000 335 000 313 000 300 000 140 000

7.6.4 How the released funds, which were achieved by using a biosimilar infliximab, were spent?

If the drug cost savings were achieved by using the biosimilar infliximab, how the money saved was spent?

7.6.4.1 Gastroenterologists

All chief physicians and three out of four specialists responded the question. (Table 66.)

The majority of chief physicians (six out of seven) commented that the medicinal cost savings, which were achieved by using biosimilar infliximab, were used hospital's cost of medicines management. One told in addition, that the cost savings did enable commissioning of new medicinal products to the pharmaceutical formulary and it made also possible to treat more patients with the biosimilar infliximab. In one hospital, drug cost savings were used to treat more patients with biosimilar infliximab.

One specialist did not know how money saved was spent. One answered that drug cost savings were used to the hepatitis C medications and also to the management of cost of medicines. One told that savings was used to the operating area and hospital budgets in generally.

TABLE 64. Drug cost savings, achieved by using biosimilar infliximab, were used to manage the cost of medicines

	Number of answers	
If medicine cost savings were achieved for the hospital with use of biosimilar product, where the released funds were used?	**Chief Physicians, n = 7**	**Specialist of gastroenterology, n = 3**
Made possible to treat more patients with the product in question	2	
Enabled commissioning of new medicinal products to the pharmaceutical formulary.	1	
To manage the cost of medicines	6	1
Other, what?		3

		I do not know. For hepatitis C medications. To the operating area and hospital budget generally.

7.6.4.2 Rheumatologists

Most chief rheumatologists (eight out of nine) told that cost savings achieved by using biosimilar infliximab, were used to manage the cost of medicines. Only three replied that the management of drug costs was the only target. Five answered also, that the cost savings enabled commissioning of the new medicinal products to the pharmaceutical formulary and/or made possible to treat more patients with the infliximab. In one hospital, addition the above mentioned, the money saved was used to hiring personnel and for equipment procurement. (Table 67.)

Only one chief physician replied, that no substitute was received.

TABLE 65. Cost savings, achieved by using biosimilar infliximab, were used to manage the cost of medicines

If medicine cost savings were achieved for the hospital with use of biosimilar product, where the released funds were used?	**Number of answers, n = 9**
Made possible to treat more patients with the product in question	3
Enabled commissioning of new medicinal products to the pharma-ceutical formulary	4
To manage the cost of medicines	8
To hire personnel	1
Other, what?	2
	For equipment procurement. We did not get any substitute.

7.6.4.3 Medical director of health care district, head of department and chief assessment physician

Medical director and one head of department replied that cost savings, achieved by using biosimilar infliximab, were used to manage the hospital's cost of medicines. Chief assessment physician and other head of department mentioned also, that the cost savings enabled commissioning of new medicinal products to the pharmaceutical formulary.

7.6.4.4 Chief pharmacists

Most chief pharmacists (four out of six) told that cost savings, which were achieved by using biosimilar infliximab, were used to manage the hospital's cost of medicines. Only one responded that the management of drug costs was the only focus. Three of them mentioned also, that the cost savings enabled commissioning of the new medicinal products to the pharmaceutical formulary and made possible to treat more patients with infliximab. In one hospital, the cost savings enabled commissioning of new medicinal products to the pharmaceutical formulary and was also used to manage the hospital's cost of medicines. (Table 68.)

One chief pharmacist pointed out that in the budget, the euros earmarked for medicines, cannot be used to recruit staff, or vice versa.

TABLE 66. Cost savings, achieved by using biosimilar infliximab, were used to manage the cost of medicines

If medicine cost savings were achieved for the hospital with use of biosimilar product, where the released funds were used?	**Number of answers, n = 6**
Made possible to treat more patients with the product in question	3
Enabled commissioning of new medicinal products to the pharmaceutical formulary	4
In order to manage the cost of medicines	5
Other, what?	1

	In the budget, the euros earmarked for medicines, cannot be used to recruit staff, or vice versa.

7.6.5 Biosimilar infliximab share of the total use of infliximab

The aim was to survey, how much was biosimilar infliximab usage share of the total use of infliximab products (ATC -code L04AB02), in 2015. Infliximab was counted in milligrams.

7.6.5.1 Gastroenterologists

One specialist gastroenterology answered the question. He/she told that the share of biosimilar infliximab was 30% of the total usage of infliximab products. (Table 69.)

Almost all chief gastroenterologists, who had returned the questionnaire, answered the question (six out of seven). The lowest biosimilar share was 40 %, and highest 100%. Four out of seven told that the biosimilar infliximab share was 95 % - 100 %. One chief physician did not answer the question, but this hospital had no biosimilar infliximab in hospital's pharmaceutical formulary in 2015.

TABLE 67. Biosimilar infliximab share (%) varied quite much, from 30 to 100 %

	Chief Physicians, n = 6	**Specialist of gastroenterology, n = 1**
	Percentage of, %	
Biosimilar infliximab share of the total use of infliximab products, ATC-code L04AB02 (infliximab mg).	100% 95% 98% 50% 40%	30 %

7.6.5.2 Rheumatologists

Four chief rheumatologists replied that the share of the biosimilar infliximab of the total use of infliximab products was 90% (one answer was probably 2016 year's figure) and two told it to be 95%,

in 2015. The lowest biosimilar share was 80 % and it might be also 2016 year's figure, since in this hospital, biosimilar infliximab was chosen to the pharmaceutical formulary in the beginning of 2016. Actually, one chief physician mentioned this in his/her reply, by saying that infliximab share was 90% but not until 2016. In that hospital, pediatric patients continued using originator infliximab. One chief rheumatology did not know the answer. (Table 70.)

TABLE 68. Biosimilar infliximab share (%) varied from 80 to 95 %

	Percentage of, % **n = 9**
Biosimilar infliximab share of the total use of infliximab products, ATC-code L04AB02 (infliximab mg).	95% 90% 80% Do not know 90% (I think not until 2016, only the pediatric patients continued with the originator infliximab)

7.6.5.3 Medical director of health care district, head of department and chief assessment physician

One head of department did not answer the question. One head of department and chief assessment physician replied the biosimilar infliximab share of the total use of infliximab products be 90% and medical director, told it to be 73% in 2015.

7.6.5.4 Chief pharmacists

Five chief pharmacists answered the question. One did not answer, due the fact that biosimilar infliximab was chosen to pharmaceutical formulary in 2016 for the first time. (Table 71.)

The highest biosimilar infliximab share in 2015 was in hospital where it was chosen to pharmaceutical formulary already 2014, 71 %. Others had chosen biosimilar in 2015 for the first time and the biosimilar infliximab share of the total use of infliximab varied between 4 – 48 %.

TABLE 69. Biosimilar infliximab share (%) varied from 4 to 71 %

	Percentage of, % **n = 5**
Biosimilar infliximab share of the total use of infliximab products, ATC-code L04AB02 (infliximab mg).	71% 48% 40% 30% 4%
Other comments?	The product was switched middle of the year.

7.7 Future biosimilars

Several biological products are expected to be exposed to biosimilar competition over the next years. Competition in the market is also growing, because new biosimilar products will enter the market for biological products already facing biosimilar competition.

7.7.1 Pricing of biosimilars in hospitals in the future

The survey examines what the biosimilar products' prices are expected be in hospitals in the future.

7.7.1.1 Gastroenterologists

Three out of four specialist gastroenterologists responded the question, and two of them answered that in hospitals biosimilars are going to be cheaper than the originator products. One specialist gastroenterology expects that originator products do participate price competition and will be as affordable as biosimilar products. One specialist expects biosimilar to be 20 – 30 % cheaper than originator product, and the other assumes that in the beginning the price difference is bigger and in long term the biosimilar will be 20 – 50% cheaper. (Table 72.)

All chief gastroenterologists answered this question and they all expect the biosimilars be cheaper than the originator products. In future, most chief physicians (five out of seven) do expect biosimilars to be at least 50% cheaper, and the answers varied in range of 20 - 65 %. However, two answered not only that biosimilars are going to be cheaper, but after the biosimilars have received

marketing authorization, the originator products will also participate the price competition and will be as affordable as the biosimilars.

No one expects the originator products be cheaper than the biosimilars.

TABLE 70. In hospitals, biosimilars are expected to be cheaper than originator products

	Chief Physicians, n = 7		**Specialist of gastroenterology, n = 3**	
What you expect biosimilar product's pricing in hospitals to be in the future	**Number of answers**	**Price difference, %**	**Number of answers**	**Price difference, %**
Biosimilar products are cheaper than the originator products	7	65% 60% 50% 30% 20%	2	20 - 30% At the beginning the difference is greater, in the long term 20 - 50%
After the biosimilar product has received marketing authorization, the originator product participates price competition and is as affordable as biosimilar products	2		1	

7.7.1.2 Rheumatologists

In hospital, all chief rheumatologists expect biosimilars to be cheaper than the originator products, and the answers varied in range of 30 - 60 %. Three chief physicians expect the price difference to be 50 %, three 30 %, two 40 % and one between 30 – 60% (biosimilar cheaper option). However, five answered not only that biosimilar are going to be cheaper, but also, after biosimilar receives marketing authorization, originator products will participate price competition and are going to be as affordable as biosimilars. One commented that the originator product tends in price competition to remain on the same level than the biosimilar, but biosimilars generally might be a little cheaper than the originator products. He thinks competition is going to be steady and the originator products will learn to cope in this competitive situation. (Table 73.)

One respondent thinks biosimilars are going to be the cheapest option and originator products' prices will not lower their prices. Other chief physician expects that the products are included to the price band.

In future in hospitals, no one expects originator products be cheaper than biosimilars.

TABLE 71. In hospitals, biosimilars are expected to be cheaper than originator products, but also originator products are expected to participate price competition

What you expect biosimilar products pricing to be in the future (hospital)	**Number of answers, n = 9**	**Price difference, %**
Biosimilar products are cheaper than the originator products	9	50% 40% 30% 30-60%
After the biosimilar product has received marketing authorization, the originator product participates price competition and is as affordable as biosimilar products	5	
Originator product's price does not decrease	1	
Other comments?	Is going to be included to the price band. The originator product tends in price competition to remain on the same level than the biosimilar, but it is probably difficult, so biosimilars generally might be a little cheaper than the originator products. The competition is steady and the originator products will learn to cope in competition.	

7.7.1.3 Medical director of health care district, head of department and chief assessment physician

Both heads of department, chief assessment physician and medical director expect biosimilars to be cheaper than the originator products in hospitals, and the answers varied between 30 - 40 %. One head of department also anticipates that after biosimilar has received marketing authorization, originator products will participate price competition and are going to be as affordable as biosimilars.

The other head of department answered, somewhat inconsistently, that biosimilars will be cheaper than originator products, but also originator products are going to be cheaper than biosimilars, and price difference would be 25 %.

7.7.1.4 Chief pharmacists

In hospitals, five chief pharmacists expect biosimilars to be cheaper than the originator products, and the price difference varied in range of 20 - 60 %. One commented that it may be that the originator products gives small discounts and the effort to direct the use to the dosage forms which have longer patents is very active. Also, one answered not only that biosimilar are going to be cheaper, but also, after biosimilar receives marketing authorization, originator products will participate price competition and are going to be as affordable as biosimilars. (Table 74.)

One chief pharmacist commented that all alternatives provided are in principle possible. It depends on the market situation in the EU and whether the biosimilar will enter Finnish market among the first EU countries or has it already been marketed in other EU countries. Often, but not always, the biosimilar offers a cheaper price than the originator product. The first round of the competition the discounts are often from 10 to 30%, in the longer run sometimes up to 70% can be achieved.

TABLE 72. In hospitals, biosimilars are expected to be cheaper than originator products

What you expect biosimilar products pricing to be in the future (hospital)	**Number of answers, n = 6**	**Price difference, %**
Biosimilar products are cheaper than the originator products	5	60 50 40 20-30
After the biosimilar product has received marketing authorization, the originator product participates price competition and is as affordable as biosimilar products	1	
Other comments?	2	

	All alternatives provided are in principle possible. Depends on the market situation in the EU and whether the biosimilar will enter Finnish market among the first EU countries or has it already been marketed in other EU countries. Often, but not always, the biosimilar offers a cheaper price than the originator product. The first round of the competition the discounts are often from 10 to 30%, in the longer run sometimes up to 70% can be achieved. It may be that the originator products give small discounts. The effort to direct the use to the dosage forms which have longer patents is very active.	

7.7.2 Biosimilar competition induced drug cost saving in future

In the questionnaire was asked to assess how much during the next five years, biosimilars price competition would help to achieve cost saving in hospitals for drug purchases.

7.7.2.1 Gastroenterologists

Of specialist gastroenterologists, one out of four answered to question about cost savings for drug purchases. He/she guessed that biosimilars caused price competition can help to achieve 10 million euros' savings to the hospital during the next five years. (Table 75.)

Six out of seven chief gastroenterologists answered the question and their estimated cost savings varied from 100 000 to 5 million euros during the next five years. Their estimates were based on consumption knowledge, current price trend and that more biosimilar products are coming available.

TABLE 73. Biosimilars are expected to cause significant drug cost savings for hospitals during next five years

	Chief Physicians, n = 6		**Specialist of gastroenterology, n = 1**	
	Cost savings, €	**Arguments**	**Cost savings, €**	**Arguments**
How much, within the next five years, you estimate biosimilar products price competition to cause medicinal cost savings for drug purchases in your hospital?	5 million 2 million 1,5 million 700 000 500 000 100 000	We know the consumption. The current price trend. More biosimilar products coming in to use.	10 million	Guess

7.7.2.2 Rheumatologists

Seven out of nine chief physicians replied the question about how much biosimilar price competition could cause medicinal cost savings for hospital drug purchases within the next five years and estimated cost savings varied from 100 00 to 10 million euros. Their estimates were based on expected price advantage and know number of patients and the knowledge what has been saved previously. One commented that estimate is difficult to assess, because a large part of the biological medicines in Rheumatology are already outpatient care products, and not administered or funded by the hospital. He/she thinks that probably in five years even more drugs will be administered subcutaneously in outpatient care (part originator products, part biosimilars) and hospital costs are reduced for this reason also. (Table 76.)

One chief physician estimates savings in hospital to be 1 million euros/year, including savings about 0,5 million euros from rheumatology and 0,5 million euros form other specialties.

TABLE 74. Biosimilars are estimated to cause several millions cost savings for hospitals during next five years

	Cost savings, €	**Arguments, n = 7**
How much, within the next five years, you estimate biosimilar products price competition to	10 million 5 million 1,5 million	A rough estimate. In rheumatology 0,5 million/year and other specialties could have the same amount/year.

cause medicinal cost savings for drug purchases in your hospital?	1,2 million 1 million 250000 100 000	Previous savings Price advantage and number of patients. Very difficult to assess. A large part of the biological medicines in Rheumatology are already outpatient care products, and not administered or funded by the hospital. Probably in five years more drugs will be administered in subcutaneous in outpatient care (part originator products, part biosimilars) and hospital costs are reducing for this reason also.

7.7.2.3 Medical director of health care district, head of department and chief assessment physician

One head of department and medical director commented that biosimilar price competition could cause medicinal cost savings in hospital for drug purchases within the next five years and estimated cost savings varied from 500 000 to 7,5 million euros. Medical director based the estimated saving to the price difference which he/she mentioned earlier in the questionnaire.

Chief assessment physician and the other head of department did not reply the question.

7.7.2.4 Chief pharmacists

Five out of six chief pharmacists replied the question about how much biosimilar price competition could cause medicinal cost savings in hospital for drug purchases within the next five years and estimated cost savings varied from 490 000 to 5 million euros. One estimate was based on what has happened with mAb already existing. (Table 77.)

One commented that several monoclonal antibody product patents are going to expire within the next five years and savings, which could be achieved, are dependent on how quickly biosimilar products get marketing authorizations after patents have expired and competition is possible. In their hospital, the medical budget for the next five years is a few hundred million euros. In this perspective, the decrease in the net price caused by a single biosimilar is small in percentages, even though millions in euros.

TABLE 75. Biosimilars are estimated to cause several millions cost savings per hospital during next five years

	Cost savings, €	Arguments, n = 5
How much, within the next five years, you estimate biosimilar products price competition to cause medicinal cost savings for drug purchases in your hospital?	3-5 million 3,0 million 2-3 million 1,5 million 490 000€	Several monoclonal antibody product patents are going to expire within the next five years. It depends on how quickly biosimilar products get marketing authorizations after the patents expire, after which the competition begins. The budget for the next five years is a few hundred million euros. In this perspective, the decrease in the net price caused by a single biosimilar is small in percentages, even though millions of euros. Based on what has happened with mab already existing.

7.7.3 Next biosimilar product which will impact hospital medicinal costs

Respondents were asked to indicate, which biosimilar products will next significantly impact the drug costs in their hospital and how much hospital's cost savings could be per year.

7.7.3.1 Gastroenterologists

None of the specialist gastroenterologists answered the question. Six out of seven chief physicians answered and most of them (four out of seven) did comment that the next biosimilar in gastroenterology will be adalimumab, but they also commented, that it will not affect to hospital's drug costs (patients inject themselves at home). One estimated that adalimumab biosimilar could help to achieve cost savings 20 000€ per year in his/her hospital and based his/her estimate on experience gained on infliximab and for adalimumab use. (Table 78.)

One chief physician expects Remsima to be the next biosimilar, which affects most to hospital's drug costs, about 22 000 € per year. He/she comments that the amount is only guess, but savings will be more than at the moment.

Trastuzumab was mentioned once and estimated cost savings, what hospital could achieve, is 200 000 € per year.

TABLE 76. Chief physicians expect next biosimilar in gastroenterology to be adalimumab, but it will not affect hospital's drug costs

	Product, n = 6	**Estimated cost savings, €**	**Cost saving estimate is based on**
Biosimilar product, which you expect to affect significantly your hospital's medicine costs?	Trastuzumab Adalimumab Remsima	200 000 20 000 22 000	The experience with infliximab, and the use of adalimumab. Only guessing, but more than now (Remsima).
Other comments?	In gastroenterology, adalimumab, but it does not cause costs to hospital. Do not know, Humira is self-inject medication and not paid by hospital.		

7.7.3.2 Rheumatologists

Eight out of nine chief physicians expect the next biosimilar, affecting significantly hospital's medicine costs, be rituximab. One commented that etanercept and adalimumab are outpatient care products and biosimilars of those products will not directly affect hospital's cost of medicines. Estimated costs saving for hospital varied between 20 000 € to 300 000 €/year and estimates were based on prior use of the product and to number of users. (Table 79.)

One chief physician expects next biosimilar, which affects most to hospital's drug costs, be possibly some medicine for cancer.

TABLE 77. Chief physicians in rheumatology expect next biosimilar affecting significantly hospital's medicine costs to be rituximab

	Product, n = 9	**Estimated cost savings, €**	**Cost saving estimate is based on**
Biosimilar product, which you expect to affect significantly your hospital's medicine costs?	Rituximab	300 000 150 000 100 000 20 000	On prior use. Number of users. About 100 treatments x X€.

Other comments?	Some cancer drug? Etanercept and adalimumab are outpatient care products and biosimilars of those products will not directly affect hospital's cost of medicines.

7.7.3.3 Medical director of health care district, head of department and chief assessment physician

Both heads of department expect the next biosimilar, affecting significantly hospital's medicine costs, be rituximab. One of them assumes cost savings to be 50 000 euros per year (in purchase price). The head of department based the answer to the current use of medicine.

Chief assessment physician commented the next biosimilar will be trastuzumab and medical director thinks that iv-forms of trastuzumab and rituximab biosimilars have significant affect to hospital's medicine costs. Medical director estimated that the biosimilars mentioned could provide 30 % savings based on the current consumption (last 12 months). This would mean savings of 430 000 euros per year (in purchase price).

7.7.3.4 Chief pharmacists

Four out of six chief pharmacists replied the question about next biosimilar, affecting significantly hospital's medicinal costs. This biosimilar is expected to be either rituximab or trastuzumab. (Table 80.)

One commented that if both, rituximab and trastuzumab will have biosimilar or even several per molecule in the market in 2017 and will come before the submission of tenders, the discounts may be at best 30 to 50 %. Unless authorized biosimilars come to market, price changes are not expected.

Estimated costs saving for hospital varied between 200 000 € to 1-2 million € per year and one based the estimate on current consumption of the product and to estimated discount.

TABLE 78. Chief pharmacists expect next biosimilar affecting significantly hospital's medicine costs to be rituximab or trastuzumab

	Product, n = 4	**Estimated cost savings, €**	**Cost saving estimate is based on**
Biosimilar product, which you expect to affect significantly your hospital's medicine costs?	Rituximab Trastuzumab	1-2 million 300 000 200 000	If both will have biosimilar or even several per molecule in 2017 in the market and come before the submission of tenders, the discounts may be at best 30 to 50%. Unless authorized biosimilars come to market, price changes are not expected. Consumption, estimated discount.

7.8 Costs of medicines in hospitals

Spending on pharmaceuticals in hospitals have generally increased and are challenging hospital budgets. The medicine costs form a significant part of the total expenditures of the hospital districts.

7.8.1 Total hospital's medical costs

The questionnaire aimed to find out, how much the total medicinal costs were in hospitals (in purchase prices) in 2015. This question was only targeted for chief pharmacists.

7.8.1.1 Chief pharmacists

The total hospital medicinal costs in 2015, when calculated in purchase prices, were between 9,5 to 44,2 million euros. One chief pharmacists pointed out that there might be some differences, what are calculated in to medicinal costs. There might be for example, blood and blood products, radioactive medicines and/or medicinal gases included. Therefore, the given amounts are not necessarily directly comparable to each other. (Table 81.)

TABLE 79. In 2015, the total hospital's medicinal costs were between 9,5 to 44,2 million euros, calculated in purchase prices

	Costs at purchase prices, million € **n = 6**
In 2015, the total hospital's medical costs at purchase prices.	44,2 23,1 13 11,6 10,3 9,5

7.8.2 How the costs of medicines have changed in hospitals

The survey aimed to find out how the last five years the cost of medicines has changed in hospital.

7.8.2.1 Gastroenterologists

Two out for four specialist gastroenterologists and six out of seven chief physicians answered the question. All responded that cost of medicines has increased the past five years. One specialist gastroenterology answered that drug costs have increased by 18 % and three chief gastroenterologists think it has increased by 13 - 40 %. (Table 82.)

All chief physicians told the cause of increased drug costs are the new expensive medicines, which have entered the market.

TABLE 80. Hospital drug costs have increased the past five years

	Chief Physicians, n = 6		**Specialist of gastroenterology, n = 2**
	Increased, %	**Arguments**	**Increased, %**
During the past five years, the hospital medicine costs have	13 % 20 % 40 %	New expensive highly selective drugs have entered the market. A lot of new, expensive medicines. New drugs.	18 %

		Expensive new treatments enter continuously.	

7.8.2.2 Rheumatologists

All chief rheumatologists responded, that the cost of medicines has increased the past five years and in five replies cost increase has been between 20 to 35 %. Four chief physicians did not give percentage. (Table 83.)

All replied the cause of increased drug costs to be the new expensive medicines. Two specified medicines to be biological medicines and one pointed out that also the use of existing biological drugs has increased.

TABLE 81. Hospital drug costs have increased the past five years

	Increased, %	**Arguments, n = 9**
During the past five years, the hospital medicine costs have	20% 25% 30% 35%	Consumption and prices have increased. Biological medicines. Likely, because for example for the treatment of infectious diseases and oncology, is coming new, expensive, and more effective drugs. New medicines (biologic). New treatment options, new drugs are expensive. Expensive new drugs have been introduced. The use of existing biological drugs has increased. New expensive drugs.

7.8.2.3 Medical director of health care district, head of department and chief assessment physician

Chief assessment physician and medical director responded the cost of medicines has increased the past five years. The cause of increased drug costs is seen to be the new expensive medicines for example for cancer, mAbs and medicines for rare diseases. They replied that the increase has been 2,3 % and 2 %.

One head of department did not reply the question about change of the cost of medicines and the other one answered that the cost of medicine have not changed. The head of department stated that new medicines are entering the market, but at same time prices of older medicines are decreasing.

7.8.2.4 Chief pharmacists

All chief pharmacists replied, that the cost of medicines has increased the past five years and increase varied between 9,6 to 27,7 %. One commented that increase has been about 5 percent per year. (Table 84.)

All replied the cause to increased medicinal costs to be the new expensive medicines. One specified medicines to be for cancer and hepatitis C. Also in university hospital medicines for life-threatening infections and for complications of bone marrow transplants have increased the costs.

TABLE 82. Hospital drug costs have increased the past five years between 9,6 to 27,7 %

	Increased %	**Arguments, n = 6**
During the past five years, the hospital medicine costs have	27,7% 20% 15% 12% 9,6%	New cancer treatments as well as new medicines for hepatitis C and in university hospitals treatments for life-threatening infections and treatments for complications of bone marrow transplants. New expensive treatments. About 5% per year.

7.8.3 Hospital medicine costs share of total hospital expenditure

In the questionnaire was asked, how much the hospital medicine costs accounted of total hospital expenditure in 2015.

7.8.3.1 Gastroenterologists

Only three out of seven chief gastroenterologists answered the question and none of the specialists replied. Two out of the three respondents told the hospital medicine costs accounted of total hospital expenditure, in 2015, 20 %. One of them told he/she estimated the percentage. One replied hospital medicine costs accounted for 4,8 % of total hospital expenditure. (Table 85.)

TABLE 83. Hospital medicine costs were estimated to account up to 20 % of total hospital expenditure in 2015

	Percentage, %
The hospital medicine costs as a percentage of total hospital expenditure in 2015? The total costs are the operating costs, that is, they do not take into account the investment costs.	Estimate 20% 20%, 4,8%

7.8.3.2 Rheumatologists

Only six out of nine chief rheumatologists answered the question. Two respondents told the hospital medicine costs accounted for 5% of total hospital expenditure, in 2015. One told he/she guessed the percentage to be about 10% and highest share mentioned was 30%. (Table 86.)

TABLE 84. Hospital medicine costs were estimated to account up to 30 % of total hospital expenditure in 2015

	Percentage, %
The hospital medicine costs as a percentage of total hospital expenditure in 2015? The total costs are the operating costs, that is, they do not take into account the investment costs.	5% Maybe 10% 15% 30% Do not know

7.8.3.3 Medical director of health care district, head of department and chief assessment physician

Chief assessment physician and both heads of department did not reply the question of how much the hospital medicine costs accounted of the total hospital expenditure in 2015. Medical director had calculated, that the hospital medicine costs accounted for 4,7 % of the total hospital expenditure.

7.8.3.4 Chief pharmacists

Four out of six chief pharmacists answered the question. The hospital medicinal costs as a percentage of total hospital expenditure in 2015 varied between 4,5 to 12,8 percent. The total costs are the operating costs, that is, they do not take into account the investment costs. One chief pharmacist pointed out that external service purchases are not taken into account. There might be differences what external service there are in each hospital. (Table 87.)

TABLE 85. Hospital medicine costs accounted up to 12,8 % of total hospital expenditure in 2015

	Percentage, %
The hospital medicine costs as a percentage of total hospital expenditure in 2015? The total costs are the operating costs, that is, they do not take into account the investment costs.	12,8% 9,8% 6% 4,5%

7.8.4 Share of hospital's biological medicinal costs of the total medicinal expenditures

In the questionnaire were asked, how much the hospital's biological medicinal costs accounted of the total medicinal expenditures in 2015 and has the share of biological medicinal products increased in past five years. These questions were only presented to chief pharmacists. The calculation supposed to include products that are included under the ATC codes: A10A (insulins), B03XA (anemia), H01AC (somatropins), J06 (immunoglobulins), L03AA (cytokines), L03AB (interferons), L04AA (immunosuppressants, excluding -06, -10, -13, -27, -29, -31, -32), L04AB (tumor necrosis factor alpha inhibitors), L04AC (interleukin inhibitors), L01XC (Monoclonal antibodies).

7.8.4.1 Chief pharmacists

Five out of six chief pharmacists replied the question about how much the hospital's biological medicinal costs accounted of the total medicinal expenditures in 2015. In table 90 is presented which ATC-codes were included to calculations. The highest calculated share of biological medicinal products was 42 percent and lowest 27 percent. (Table 88.)

TABLE 86. The hospital's biological medicinal costs accounted 27 to 42 percent of the total medicinal expenditure in 2015

	Percentage, %
Percentage of biological medicinal products of the total cost of hospital medicines in 2015. The calculation should include products that are included under the following ATC codes: A10A (insulins), B03XA (anemia), H01AC (somatropins), J06 (immunoglobulins), L03AA (cytokines), L03AB (interferons), L04AA (immunosuppressants, excluding -06, -10, -13, -27, -29, -31, -32), L04AB (tumor necrosis factor alpha inhibitors), L04AC (interleukin inhibitors), L01XC (Monoclonal antibodies).	42% 37%, 34,6% 31,3% 27 %

Three out of five chief pharmacists replied that the share of biological medicinal products has grown of the total cost of hospital medicines in past five years. One calculated that the share of biologics mentioned in question has grown 1,4 percent, another 38 percent and one did not give any percentage. One of them commented, that the new indications are the reason for this. One chief pharmacists told that share of biological medicines mentioned was exactly same in 2015 than it was 2011. Another chief pharmacist commented that biological medicine share of the total cost of hospital medicines has not increased meaningfully, being 2011 27,6 % compared to 27 % in 2015. This was explained with the fact, that also, the costs of other ATC-groups' medicines have increased. In euros, the cost of biological medicines has increased about 2 million euros. (Table 89.)

TABLE 87. The share of biological medicinal products of the total cost of hospital medicines has not necessarily grown, because costs of other medicine-groups have increased same time

Has the share of biological medicinal products grown of the total cost of hospital medicines in past five years? ATC codes: A10A (insulins), B03XA (anemia), H01AC (somatropins), J06 (immunoglobulins), L03AA (cytokines), L03AB (interferons), L04AA (immunosuppressants, excluding -06, -10, -13, -27, -29, -31, -32), L04AB (tumor necrosis factor alpha inhibitors), L04AC (interleukin inhibitors), L01XC (Monoclonal antibodies)	**Number of answers, n = 5**	**Percentage, %**
Yes	3	38 % 1,4%
	New indications.	
No	2	
	Biological medicine share of the total cost of hospital medicines has not increased meaningfully. Was 2011 27,6 % compared to 27 % in 2015. New expensive medicines have been introduced to the treatment of cancer, as well as new medicines in the B-, M- and N-groups and the macular degeneration medicines in S-group. These have raised the cost in terms of other ATC groups. C The cost of medicines in the ATC groups mentioned in question, have increased by 2 million euros, when comparing year 2011 to year 2015. Biological medicinal products share of the total medication costs in 2011 and 2015 is the same.	

7.9 Biosimilars for patients in outpatient care

Biosimilar infliximab is a hospital product and was first biosimilar monoclonal antibody approved by the EMA. The first biosimilar monoclonal antibody among other things raised questions on the immunogenicity and efficacy of the product compared to originator infliximab. The questionnaire explored the respondents' biosimilar readiness in outpatient care.

7.9.1 Willingness to prescribe biosimilars for patients in outpatient care?

The questionnaire explored the willingness to prescribe upcoming biosimilars (authorized for use) for patients in outpatient care.

7.9.1.1 Gastroenterologists

Three out of four specialist gastroenterologists answered the question about their willingness to prescribe up-coming biosimilars (authorized for use) for patients in outpatient care. They all were ready to prescribe, and one justified it to be economically sensible. (Table 90.)

All chief gastroenterologists gave response and six of them were ready to prescribe biosimilar products for outpatient care patients and one was reluctant. The justifications for prescribing were reduction of costs, cost savings, and expectations that biosimilars are going to be more affordable. One chief physician not willing to prescribe biosimilars for outpatient care patient justified his/her decision by telling that patients should be monitored in hospitals.

None of the respondents were not using biosimilars in outpatient care at the time.

TABLE 88. Most of the gastroenterologist were willing to prescribe biosimilars for outpatient care patient

If you treat patients in an outpatient setting, would you prescribe up-coming (authorized for use) biosimilar products for patients in outpatient care?	**Chief Physicians, n = 7**	**Specialist of gastroenterology, n = 3**
Yes	6	3
	To reduce costs. Cost savings. Finland economize. Price. More affordable.	Economic sense
No	1	-

	Patients should be monitored in the hospital	-

7.9.1.2 Rheumatologists

Eight chief rheumatologists gave response and seven of them were ready to prescribe biosimilar products for outpatient care patients, and one could not provide response at the moment, because she/he need more information about future biosimilars. The justifications for prescribing biosimilars were cost savings (for society), right price-quality ratio, biosimilars are inexpensive and more patients could be treated with the same amount of money. One chief physician stated that the costs do not play a large role only for the society, but also for patients. (Table 91.)

None of the respondents were not using biosimilars in outpatient care at the time.

TABLE 89. Most chief rheumatologists were willing to prescribe biosimilars for outpatient care patient

If you treat patients in an outpatient setting, would you prescribe new (marketing authorized) biosimilar products for patients in outpatient care?	**Arguments, n = 8**
Yes	7
	Right price-quality ratio. Are inexpensive. Ok, if efficacy and safety has been demonstrated, costs have a big role in both the patient and to society. Cost savings. The cost savings for society, or more patients can be treated with the same amount of money. The nation's advantage.
Other comments?	1
	Do not know yet.

7.9.1.3 Medical director of health care district, head of department and chief assessment physician

Chief assessment physician did not reply the question of willingness prescribing biosimilars for patients in outpatient care. Both heads of department and medical director were willing to prescribe biosimilar products for outpatient care patients. The justifications for prescribing biosimilars were cost savings and price of the biosimilar medicines.

One of the heads of department is using biosimilar epoetin and filgrastim in outpatient care.

7.10 Hospital's the three most expensive biological medicines in 2015

The questionnaire aimed to find out which were the hospital's three most expensive biological medicines in 2015. Amounts were calculated at purchasing prices. This question was only presented to chief pharmacists.

7.10.1 Chief pharmacists

Five out of six chief pharmacists replied the question and three of them commented that the hospital's most expensive biological medicine at purchase price was rituximab, varying from 0,8 to 1,4 million euros. Second most expensive biological medicine was usually trastuzumab, accounting 0,5 to 1,9 million euros. Infliximab was mentioned in three replies as third position, accounting 0,5 to 0,8 million at purchase price. Only one chief pharmacist did not mentioned infliximab in the list of three most expensive biological medicines and only one had listed it as most expensive. (Table 92.)

Rituximab was mentioned in all answers, infliximab and trastuzumab in four answers and bevacizumab in two answers.

TABLE 90. The most expensive biological medicine was usually rituximab (at a purchase price). The amounts have been rounded to the nearest hundred thousand

The hospital's three most expensive (at a purchase price) biological medicines in 2015.	**Biological medicine**	**Amount, million €**
1.	Rituximab Infliximab Bevacizumab	0,8; 0,8; 1,4 2,2 1
2.	Trastuzumab Rituximab	0,5; 0,6; 0,9; 1,9 1
3.	Infliximab Rituximab Bevacizumab	0,5; 0,8; 0,8 1,8 0,5

The cost share of infliximab of total cost of medicines in different hospitals varied between 4 to 6 percent, being 5 percent in hospital where it was mentioned as the most expensive biological medicine. Also cost share of trastuzumab was between 4 to 6 percent, rituximab accounted between 4 to 8 percent and bevasizumab 5 to 8 percent in hospitals. (Table 95.)

TABLE 91. The cost share of most expensive biological medicines of total cost of medicines (at purchase price) in hospitals. Calculated from figures obtained from replies of chief pharmacists

Biological medicinal product	**Share, %**
Infliximab	4 - 6
Trastuzumab	4 - 6
Rituximab	4 - 8
Bevasizumab	5 - 8

The cost share of three most expensive biological medicines accounted in the highest 22 percent and in lowest 13 percent of total cost of medicines in hospitals. (Table 96.)

TABLE 92. Cost share of three most expensive biological medicines in hospitals varied between 13 to 22 % of total cost of medicines. Calculated from figures obtained from replies of chief pharmacists

Hospital	Cost share of three most expensive biological medicines in different hospitals, %
A	13
B	14
C	22
D	19
E	18

8 SUMMARY OF THE RESULTS

The author's own assumption was that the biosimilars have already established their position amongst specialists in question, although the user experience has not yet accumulated from a long period of time. The maximum experience with biosimilar infliximab has accumulated in Finland since September 2013, when biosimilar infliximab received its marketing authorization.

In the case of biosimilar infliximab, hardly anyone expected the price competition to be so aggressive as what it turned out. Hospitals' tendering periods influenced the introduction of biosimilar infliximab, because infliximab is fully a hospital product. After the biosimilar infliximab received a marketing authorization, some of the hospitals opened a new tendering during the valid acquisition period. The responses also indicate, that company having originator infliximab started the price competition even before biosimilar infliximab was able to participate tendering competition for the first time, by decreasing its price during the previous acquisition period.

When the respondents compared the originator infliximab purchase price after the biosimilar first time participated in the hospital tendering, to the purchase price offered in the previous tendering, they reported that price of originator product had decreased by 20 - 40 %. Biosimilars responded to price competition, and based on the results obtained from chief pharmacists' questionnaires, the price difference between originator and biosimilar infliximab was 40 to 57%. In other responses, the price difference varied between 20% and 80%. Biosimilar infliximab has been selected to hospitals' pharmaceutical formulary between 2014 - 2016, depending on whether the tendering process was re-opened during the valid acquisition period, or whether was the tendering made in according the normal tendering. Hospitals can re-open tenders if the market situation changes substantially (the possibility is recognized in the invitation to tender) and in this case, biosimilar infliximab fulfilled the criteria. Before the biosimilar infliximab entered the market, chief gastroenterologist estimated the price difference between originator and biosimilar infliximab to be 30 – 60 %. The estimates from chief rheumatologists and hospital chief pharmacists were very much in line with gastroenterologists.

Biosimilar infliximab is, at the current acquisition period, the preferred option in the hospitals' pharmaceutical formulary and only one responded that biosimilar infliximab is solely selected to hospital's pharmaceutical formulary. The price was most commonly the reason, why biosimilar infliximab

was chosen as a primary option, but also studies in which similarity was demonstrated and Fimea's statement on biosimilars, came up in the responses. One rheumatology had also gained personal experience of biosimilar infliximab. Some replied that also originator infliximab is chosen, because of various reasons. Originator was available to be able to continue treatment with pediatric patients, with patients who prohibited the switch and with patients whose treatment was poorly controlled. Also, respondents wanted to have originator infliximab in pharmaceutical formulary, in case biosimilar proves to be inefficient or side effects occur. Medical director pointed out, that originator infliximab was chosen to formulary in order to maintain the doctor's autonomy.

Biosimilar application for marketing authorization must demonstrate that potential differences between the biosimilar and the originator product does not affect the efficacy or safety. In most replies, biosimilar studies were seen to be comprehensive enough regarding of safety and efficacy. The comments of gastroenterologists revealed, that the studies demanded for marketing authorization were conducted with rheumatology patients, but this was not considered a problem. There was some hesitation among rheumatologists about lack of long term follow-up. One of the gastroenterologists stated that biosimilar infliximab is being marketed to have similar efficacy as originator, but in reality, for some patients biosimilar is not effective at all.

Respondents have received information about biosimilars often from many different sources, and most of them felt, that there is no need for additional information. In general, information is received at least from pharmaceutical companies and from regulatory authorities, and this did not vary between groups. Almost the same number had received information also from colleagues and other sources. Other sources mentioned were congresses, professional journals and meetings. One respondent had also been involved in EU's development work. Those who would like to have more information, would like to have information of the long-term outcomes, the switches and new upcoming biosimilars. In the answers of the hospital chief pharmacists, information is wanted about the safety of biosimilars and whenever new information is published or the regulatory authorities inform of the biosimilars. It would have been interesting to separate pharmaceutical companies to biosimilar marketers and originator product-focused companies and to find out whether or not the biosimilar marketers were also actively sharing information and in what format compared to originator-focused companies.

In hospitals, treatments are switched from originator infliximab to its biosimilar. Based on the survey, hospitals prepared for switches usually by educating personnel and by guiding the patients

about biosimilars. Some of the respondents who informed that special arrangements were not done, had also done actions mentioned above. Some replied that drug trough concertation and antibodies were detected before switching. None responded that this was made solely, but always education for personnel and/or patient guiding was done also. For example, in the Statement of The Finnish Society for Rheumatology is recommended to measure drug trough concentration and anti-drug antibodies before switching to a biosimilar. This statement was published in June 2015. Some of the rheumatologists mentioned that infliximab treatment was switched only from chosen patient groups and the criteria were age over 18 years, patients had to be stable with originator infliximab and the switch should have patients' approval. In some cases, treatment of all patients was switched, but in subsequent responses pediatric patients were often told to be excluded. It should be noted, that physicians treating pediatric patients were not included in this survey. It would be interesting to study introduction of biosimilars in pediatric indications. Chief Pharmacists responded that biosimilar infliximab was in one hospital reviewed in the management teams (johtoryhmissä) and in one hospital the pharmaceutical advisory board handling (lääkeneuvottelukuntakäsittely) was made as part of hospital tendering.

The responses of rheumatologists and gastroenterologists were very similar concerning the effects of switches. Most of them experienced, that switching from originator to biosimilar infliximab had not affected the efficacy or safety. Some of them commented that at the moment they could not say if switching had any effect, but there was research on going. One gastroenterology had observed allergic reactions in some patients and two chief pharmacists commented that patients have been switched back to originator infliximab. Switching back has been done, because of side effects and because antibodies were detected. Medical Director and Chief Assessment Physician responded that switching had no effect on the efficacy and safety. One pondered that in some patients, subjective efficacy was worse, and for some of them also antibodies were detected, but unfortunately samples were not taken from all patients prior the switch and conclusions cannot be drawn. It would also be interesting to study, has the educating of patients and personnel affected the success of the switches and from where patients got the biosimilar information. Another interesting topic would be to find out, whether the switching from the original preparation to biosimilars has affected antibody formation.

Maybe a little unexpectedly majority of the respondents answered that there has not been any special follow-up made about switched patients. However, this can be explained by the fact that

the patients in question are already closely monitored. Most often the follow-up was made by determining drug trough concentration and antibodies when seen necessary. Only some replied that drug trough concentration and antibodies were determined in certain intervals. Rheumatologists have followed the reasons for the discontinuation of treatment. One commented that there is intention to prepare a summary of the reasons of interruption. Medical director replied that follow-up is done of the switches by measuring the drug trough concentration and antibodies in certain intervals and by following the causes of the treatment interruptions. One hospital Chief Pharmacist replied that pharmaceutical advisory board had done cost monitoring.

Biosimilar competition is increasing due to fact that, in future, originator biosimilar will have several biosimilar versions in market. Thus, switching between biosimilars (same active substance) might be reality in near future. Majority of gastroenterologists' opinion is that biosimilars with same active substance are interchangeable (switching biosimilar to biosimilar) in hospital care. Chief Pharmacists are on the same line with gastroenterologists and they justified their opinion for example by commenting that in Finland, supervising authority has taken a favorable position about switching. There was some pondering that maybe there should be a similar approach than with infliximab to the matter, and patients should be evaluated, in case there are patients who should not be switched. Rheumatologists, on the other hand, are more cautious in their responses. Almost half of chief rheumatologists were not sure if biosimilars with same active substance are interchangeable. The concerns were for example repeated switches, which would also make treatment follow-up more difficult. Chief assessment physician and medical director did not see problem of switching between biosimilars in hospital care and head of department considered that this should be the responsibility of the pharmaceutical regulatory authorities. Things to consider, when switching from biosimilar to biosimilar, usually were related to antibodies, efficacy and side effects.

When asked which things have slowed down the introduction of biosimilars, most frequently the replies were attitudes and the prejudices or lack of knowledge of physicians, but the attitudes of the patients were also mentioned. It would be interesting to find out what kind of position the patient organizations have taken to the biosimilars, from where these organizations have received their information, and how do they share the it. Some of the responses also highlighted the originator companies' effective marketing organization and that pharmaceutical industry has had strong anti-marketing of biosimilars. As a number of innovative pharmaceutical companies have also begun to develop and market biosimilars, one of the interesting research topics would be to find out how the

biosimilar marketing has changed and how companies that have both originator and biosimilar products (possibly even for the same patient groups), have organized the marketing.

When biosimilar product enters the market, it is expected to reduce prices and thus enable cost savings for hospitals. According to questionnaire, most of the hospitals have attempted to achieved medicinal cost savings by initiating biosimilar infliximab for new patients and by switching patients treated with originator infliximab to biosimilar infliximab. Some replied that, for example, pediatric patients and skeptical patient were not switched. At least in one clinic also pediatricians have initiated infliximab treatments with biosimilar infliximab. No one answered that savings would have been attempted to achieved only by initiating biosimilar infliximab for new patients. Majority of the respondents felt that cost savings were achieved by using biosimilar infliximab. Those who commented that cost savings realized only partly, told that infliximab consumption had increased, some of the patients were using higher and more frequent doses and some patients were switched back to originator infliximab. One chief pharmacist commented that through competitive tendering is achieved as a whole more favorable net price. The new innovations are usually more costly than previous ones and for this reason, usually as a whole, drug costs are not reduced. He / she commented that competition and competitive tendering in itself restrain the growth of medical costs, but do not eliminate it. Gastroenterologists' and rheumatologists' estimates of the cost savings, achieved by using biosimilar infliximab in 2015, ranged from € 40,000 to € 700,000. Some replied that cost saving were not achieved, but this was by the fact that biosimilar infliximab was selected to hospital's pharmaceutical formula first time in 2016. Hospital chief pharmacists' estimates of achieved cost savings varied between 140 000 to 950 000 €. The magnitude of the savings is influenced by the size of the hospital and the amount of infliximab used. When investigated, how the cost savings achieved by using biosimilar infliximab were used, most often the response was, that it was used to hospital medicinal cost management. In chief pharmacists' responses were also emphasized the possibility of commissioning of new medicinal products to the pharmaceutical formulary. In one reply cost savings were used to the operation area and hospital budget generally. One chief pharmacists commented that in the budget, the euros earmarked for medicines cannot be used to recruit staff or vice versa. Based on the answers from chief pharmacists, the share of biosimilar infliximab of the total use of infliximab (calculated on mg) was at highest 71 % and lowest at 4 %. The year, when biosimilar was selected to pharmaceutical formulary, and whether all patients' or only specified patients' treatments were switched, has affected the magnitude of biosimilar share.

Several biological medicinal products are expected to be exposed to biosimilar competition over the next years. In the future in hospitals, majority of the respondents expect biosimilar products to be 20 to 60% cheaper than the originator products. After biosimilars receive marketing authorization, some of the respondents expect originator products to participate price competition and be as affordable as biosimilar products. Only one replied that the originator product price will not decrease. One chief rheumatologists commented, that the originator product strives in price competition to remain on the same level than the biosimilar, but assumes that the biosimilar generally will be a little cheaper than the originator product. One chief pharmacist thinks that the pricing depends on the market situation in the EU and whether the biosimilar will enter Finnish market among the first EU countries or has it already been marketed in other EU countries. He / she stated that often, but not always, the biosimilar offers a cheaper price than the originator product. In the first round of the competition the discounts are often from 10 to 30% and in the longer run sometimes up to 70% can be achieved. Also, another chief pharmacist commented that the effort to direct the use to the dosage forms which have longer patents is very active.

Rheumatologists' and gastroenterologists', as well as medicinal director's estimates of how much biosimilar price competition could cause medicinal cost savings to the hospital over the next five years, varied from 0.1 to 10 million euros. Their estimates were based on current consumptions and price trend. One chief rheumatology commented that a large part of the biological medicines in Rheumatology are already outpatient care products, and not administered or funded by the hospital. He / she thinks that probably in five years more drugs will be administered in subcutaneous in outpatient care (part originator products, part biosimilars) and hospital costs are reducing for this reason also. Hospital chief pharmacists' saving estimates varies between 0,49 – 5 million euros. One of them commented that several monoclonal antibody product patents are going to expire within the next five years and savings depends on how quickly biosimilar products get marketing authorizations after the patents expire. In this hospital, the budget for the next five years is a few hundred million euros. Chief pharmacist commented that in this perspective, the decrease in the net price caused by a single biosimilar is small in percentages, even though millions of euros.

Biosimilar products, which are next expected significantly to affect drug costs in hospitals, are rituximab and trastuzumab. With these biosimilar products hospitals could achieve medicinal costs savings from 0,1 to 2 million euros per year. One Chief Pharmacist comments that price changes are not expected, if authorized biosimilar products will not enter to market.

Spending on pharmaceuticals in hospitals have generally increased and are challenging hospital budgets. In Finland, total hospital medicinal costs in 2015, when calculated in purchase prices, were between 9,5 to 44,2 million euros. All chief pharmacists replied that the cost of medicines has increased the past five years, and the increase varied between 9,6 – 27,7 %. The new expensive medicines are told to be the cause of this. Also, was mentioned, that the use of existing biological medicines has increased. Chief pharmacists replied that hospital medicines costs account for 4,5 to 12,8 % of total hospital expenditure (operating costs excluding investment costs). Estimates made by gastroenterologists and rheumatologists were generally considerably higher than the calculations of chief pharmacists. The external service purchases were not taken into account in calculations and there might be some differences, what external services there are in each hospital. The biological medicinal products accounted up to 42 percent of the hospital's total medicinal expenditure in 2015. One chief pharmacist commented that the costs of other ATC-groups' medicines have increased also and that's why the share of biological medicines has not increased meaningfully. In this hospital, the cost of biological medicines had increased in euros about 2 million in past five years. Chief pharmacists were also asked which were the three most expensive biological medicines at purchase price in 2015 in their hospitals. The most expensive biological medicine was most often rituximab, accounting from 0,8 to 1,4 million euros. Second most expensive biological medicine was usually trastuzumab, accounting from 0,5 to 1,9 million euros and in third place was most often infliximab, accounting from 0,5 to 0,8 million euros. When calculating the cost share of these medicines of the total cost of medicines, rituximab's share varied between 4 – 8 % and trastuzumab's and infliximab's between 4 – 6 %. The cost share of three most expensive biological medicines accounted in the highest 22 percent and in lowest 13 percent of total cost of medicines in hospitals.

Most of the gastroenterologists and rheumatologists are willing to prescribe up-coming biosimilars for patients in outpatient care and they justified it by cost savings, economic reasons and saw it also as possibility to treat more patients with the same amount of money.

9 CONCLUSION

Cost of medicines has increased in the past years and there is pressure, not only in Finland, but globally, to find ways how increase of the medicine costs is managed so that in the future all patients are still able to have the best treatment available with reasonable price.

The results of this study suggest that biosimilars are seen as opportunity to manage the hospitals' cost of medicines. The biosimilars which are expected to influence hospitals' medicinal costs most in next five years are rituximab and trastuzumab. Biosimilar caused price competition is expected to result up to several million savings per hospital in next coming years. In December 2016, Celltrion received initial authorization for its biosimilar rituximab, CT-P10 (reference product MabThera) and it is interesting to see how this will affect product's tender pricing in hospitals. Will the price decrease be as has huge as it was with infliximab and will the competition of pricing start before biosimilar rituximab actually is on the market?

Another question is biosimilar medicines in outpatient care. Amgen received initial authorization for its biosimilar adalimumab, ABP501 (reference product Humira), in January 2017 and it is interesting to see, when this biosimilar will enter Finnish market and how does the company having the originator product react. For example, biosimilar etanercept has not reimbursement in Finland, even if it had marketing authorization in EU already in January 2016. At same time, biosimilar etanercept has taken already big market shares in Norway and Denmark.

In Finland, the New Health Insurance Act involves price regulation concerning biosimilars. In order to increase the use of and price competition between biological medicines and biosimilars, the suggested reimbursable price for the first biosimilar entering the reimbursement system cannot exceed 70 percent of the list price of the original biologic. Also, the list price of the reference medicine will be re-examined, after the biosimilar is launched.

Author's impression is that there still seems to be need for information about biosimilars, especially data about switches is missing. Also, always when new biosimilar enters the market, it should be introduced with proper data about safety, efficacy and similarity to the originator product.

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APPENDICES

PHARMACEUTICAL EXPENDITURES IN FINLAND 2000 – 2015 APPENDIX 1

Year	Total sales on pharmaceuticals, million €	Hospital sales, million €	Share of hospital sales, %
2000	1646	222	13,5
2001	1842	253	13,7
2002	2026	288	14,2
2003	2137	302	14,1
2004	2288	325	14,2
2005	2435	360	14,8
2006	2361	379	16,1
2007	2 500	408	16,3
2008	2 664	438	16,4
2009	2 629	434	16,5
2010	2 619	444	17,0
2011	2 682	479	17,9
2012	2 740	475	17,3
2013	2 824	497	17,6
2014	2 831	514	18,2
2015	2 958	561	19,0

Hospital discounts are not taken into account in calculations. Retail prices (inclusive of tax) were used for calculating sales of medicines in the outpatient selling and wholesale prices were used for sales of medicines sold to hospitals. (Finnish medicines agency Fimea and social insurance institution 2010 – 2016; National agency for medicines and social insurance institution 2008 – 2009; Matveinen et al 2016, liitetaulukko 5a.)

DISTRIBUTION OF MEDICINES SALES APPENDIX 2

		2015					Total sales, 2014	Hospital sales, 2014	2014		
ATC-code	Medicinal agent	Total sales, €	Hospital %	Hospital sales, €	Pharmacy %	Pharmacy sales, €	Change %	Change %	Total sales, €	Hospital %	Hospital sales, €
P	Antiparasitic products, insecticides and repellents	5,2	3,9	0,2	96,1	5,0	- 1,3	- 19,8	5,3	4,8	0,3
V	Various	28,2	90,0	25,4	10,0	2,8	4,0	6,0	27,1	88,3	24,0
D	Dermatologicals	38,6	4,9	1,9	95,1	36,7	1,3	1,3	38,1	4,9	1,9
H	Systemic hormonal preparations	42,2	21,6	9,1	78,4	33,1	2,9	- 2,5	41,0	22,8	9,4
S	Sensory organs	46,6	31,7	14,8	68,3	31,8	9,4	39,3	42,6	24,9	10,6
M	Musculo-skeletal system	97,4	14,4	14,0	85,6	83,4	- 0,9	- 19,4	98,3	17,7	17,4
G	Genito urinary system and sex hormone	111,5	4,7	5 240	95,3	106 239	0,2	0,2	111 267	4,7	5 230
R	Respiratory system	143,6	4,7	6,8	95,3	136,9	- 3,1	8,4	148,2	4,2	6,2
B	Blood and blood forming organs	177,4	37,5	66,5	62,5	110,9	9,4	10,6	162,1	37	60,2
J	Antiinfectives for systemic use	182,1	64,1	116,7	35,9	65 ,4	25,0	29,2	145,8	62,0	90,4
C	Cardiovascular system	202,8	8,5	17,2	91,5	185,6	6,3	0,4	190,8	9,0	17,2
A	Alimentary tract and metabolism	292,1	8,7	25,4	91,3	266,7	5,1	- 0,7	278,1	9	25,6
N	Nervous system	313,0	16,4	51,4	83,6	261,7	- 3,4	- 7,4	324,0	17,1	55,4
L	Antineoplastic and immunomodulating agents	500,2	41,2	206,1	58,8	294,1	8,6	8,0	460,7	41,4	190,7

Distribution of medicines sales between pharmacies and hospitals per the ATC-code in 2015, at wholesale prices (million euros). Hospital and pharmacy sales and change percentages are calculated values. Wholesales of nervous system medicines (ATC-code N) do not include nicotine sales. Hospital discounts are not taken into account in calculations. (Finnish medicines agency Fimea and

social insurance institution 2016, 52-53, 176, 190, 196, 212, 215, 223, 226, 237, 246, 254, 274, 276, 287, 291; Finnish medicines agency Fimea and social insurance institution 2014, 51-52.)

ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS, HOSPITAL SALES APPENDIX 3

ATC-code	Medicinal agent	Total sales, million €	Hospital share of sales, %	Hospital sales, million €
L	Antineoplastic and immunomodulating agents	500,2	41 %	206,1
L01	Antineoplastic agents	192,4	73 %	140,5
L02	Endocrine therapy	35,3	4 %	1,4
L03	Immunostimulants	49,0	12 %	5,9
L04	Immunosuppres-sants	223,4	26 %	58,1

In 2015**,** Hospital sales (at wholesale prices) of antineoplastic and immunomodulating agents, divided to classification level 2. Hospital and pharmacy sales are calculated values. Hospital discounts are not taken into account in calculations. (Finnish medicines agency Fimea and social insurance institution 2016, 237.)

ANTINEOPLASTIC AGENTS, CLASSIFICATION LEVEL 3 APPENDIX 4

ATC-code	Medicinal agent	Total sales, million €	Hospital share of sales, %	Hospital sales, million €
L01	Antineoplastic agents	192,4	73 %	140,5
L01A	Alkylating agents	6,0	68 %	4,1
L01B	Antimetabolites	17,9	71 %	12,7
L01C	Plant alkaloids and other natural products	8,9	85 %	7,5
L01D	Cytotoxic antibiotics and related substances	5,4	100 %	5,4
L01X	Other antineoplastic agents	154,3	71 %	109,5

In 2015, Hospital sales (at wholesale prices) of antineoplastic agents, divided to classification level 3. Hospital and pharmacy sales are calculated values. Hospital discounts are not taken into account in calculations. (Finnish medicines agency Fimea and social insurance institution 2016, 238-239.)

OTHER ANTINEOPLASTIC AGENTS, CLASSIFICATION LEVEL 4 APPENDIX 5

ATC-code	Medicinal agent	Total sales, million €	Hospital share of sales, %	Hospital sales, million €
L01X	Other antineoplastic agents	154,3	71 %	109,5
L01XA	Platinum compounds	0,6	100 %	0,6
L01XC	Monoclonal antibodies	90,0	100 %	90,0
L01XD	Sensitizers used in photodynamic /radiation therapy	0,9	99 %	0,9

In 2015, Hospital sales (at wholesale prices) of other antineoplastic agents, divided to classification level 4. Hospital and pharmacy sales are calculated values. Hospital discounts are not taken into account in calculations. (Finnish medicines agency Fimea and social insurance institution 2016, 239.)

IMMUNOSUPPRESSANTS, CLASSIFICATION LEVEL 4 APPENDIX 6

ATC-code	Medicinal agent	Total sales, million €	Hospital share of sales, %	Hospital sales, million €
L04	Immunosuppressants	223,4	26 %	58,1
L04A	Immunosuppressants	223,4	26 %	58,1
L04AA	Selectice immunosup-pressants	38,4	33 %	12,7
L04B	Tumor necrosis factro al-pha (TNF-a) inhibitors	136,7	29 %	39,6
L04AC	Interleukin inhibitors	13,7	32 %	4,4
L04AD	Calcineurin inhibitors	12,2	5 %	0,6
L04AX	Other immunosuppres-sants	22,4	10 %	2 ,2

In 2015, Hospital sales (at wholesale prices**)** of immunosuppressants, divided to classification level 4. Hospital and pharmacy sales are calculated values. Hospital discounts are not taken into account in calculations. (Finnish medicines agency Fimea and social insurance institution 2016, 237, 244-245.)

MONOCLONAL ANTIBODIES, CLASSIFICATION LEVEL 5 APPENDIX 7

		2015			2014			2013		
ATC-code	Medicinal agent	Total sales, million €	Hospital share of sales, %	Hospital sales, million €	Total sales, million €	Hospital share of sales, %	Hospital sales, million €	Total sales, million €	Hospital share of sales, %	Hospital sales, million €
L01XC	Monoclonal antibodies	90,0	100	90,0	81,4	100	81,4	73,8	99	73,1
L01XC02	Rituximab	31,4	100	31,4	-	-	-	26,9	100	26,9
L01XC03	Trastuzumab	22,5	100	22,5	21,7	100	21,7	20,4	100	20,4
L01XC06	Cetuximab	1,6	100	1,6	1,7	100	1,7	-	-	-
L01XC07	Bevaci-zumab	21,0	100	21,0	18,8	99	18,6	18,3	99	18,2
L04AB	TNF-alpha inhibitors	136,7	29	39,6	127,4	29	36,9	102,1	31	31,7
L04AB01	Etanercept	31,7	0	0	30,1	0	0	28,5	0	0
L04AB02	Infliximab	37,7	100	37,7	35,8	100	35,8	30,2	100	30,2
L04AB04	Adalimumab	46,5	2	0,9	44,8	2	0,9	43,3	3	1,3

In 2015, Hospital sales (at wholesale prices) of monoclonal antibodies, divided to classification level 5. Hospital and pharmacy sales are calculated values. Hospital discounts are not taken into account in calculations. (Finnish medicines agency Fimea and social insurance institution 2016, 239, 244.)

		2015		2014		2013	
ATC-code	Medicinal agent	DDD/ 1000 inh/ day	Hospital share, %	DDD/ 1000 inh/ day	Hospital share, %	DDD/ 1000 inh/ day	Hospital share, %
L04AB01	Etanercept (DDD 7 mg)	0,49	0	0,47	0	0,44	0
L04AB04	Adalimumab (DDD 2,9 mg)	0,68	2	0,65	2	0,63	3
L04AB02	Infliximab (DDD 3,75 mg)	0,89	100	0,77	100	0,71	100

Pharmaceutical consumption in Finland 2013 – 2015 as DDD per 1000 inhabitants per day. Sales to hospitals as a proportion (%) of consumption. (Finnish medicines agency Fimea and social insurance institution 2016, 244; Finnish medicines agency Fimea and social insurance institution 2013, 230.)

PHARMACEUTICAL CONSUMPTION IN NORWAY 2013 – 2015 APPENDIX 9

ATC-code	Medicinal agent	2015, DDD/1000 inh / day	2014, DDD/1000 inh / day	2013, DDD/1000 inh /day
L04A	Immunosuppressants	11,3	10,6	9,8
L04AB	TNF-alpha inhibitors	4,1	3,7	3,3
L04AB01	Etanercept (7mg)	0,8	0,8	0,9
L04AB02	Infliximab (3,75mg)	1,8	1,4	1,2
L04AB04	Adalimumab (2,9mg)	0,7	0,8	0,8

Pharmaceutical consumption in Norway 2013 – 2015 as DDD per 1000 inhabitants per day. The figures are given as the number of DDDs/1000 inhabitants/day, calculated as follows: (DDD/1000 inhabitants/year)/365. (Sakshaug 2016, 9, 66.)

COVER LETTER, CHIEF PHARMACISTS APPENDIX 10 (1/8)

Arvoisa vastaanottaja,

Opiskelen Oulun ammattikorkeakoulussa tekniikan yksikössä teknologialiiketoiminnan tutkinto-ohjelmassa ylempää ammattikorkeakoulututkintoa. Opinnäytetyöni aiheeksi valikoitui biosimilaarit, jotka ovat olleet jo useamman vuoden terveydenhuollon kuuma keskustelun aihe. Opinnäytetyöni ohjaajana toimii tutkintovastaava Hannu Päätalo.

Olen työskennellyt vuodesta 2008 lääkeyrityksessä kolmen eri biosimilaarivalmisteen kanssa (epoetiini alfan, filgrastiimin ja infliximabin) ja työssäni on noussut esiin kysymyksiä mm. siitä, mihin biosimilaareilla säästetyt rahat sairaaloissa käytetään. Opinnäytetyöni tavoitteena on avata **sairaalakäytössä** olevien biosimilaarivalmisteiden, infliximabin ja filgrastiimin, käyttöönottoa, arvioida kustannussäästöjä ja -vaikutuksia, sekä pohtia mihin mahdolliset säästyneet varat on käytetty. Lisäksi tarkoituksena on selvittää, miten lääkevaihdot alkuperäisvalmisteilta biosimilaareille tai biosimilaarin vaihto toiseen biosimilaariin koetaan. Opinnäytetyöni tulee olemaan julkinen ja julkaistaan englanniksi.

Kyselylomakkeen olen lähettänyt yliopisto- ja keskussairaaloiden sairaala-apteekkareille. Vastaukset tulen käsittelemään luottamuksellisesti ja tulokset esitetään yhteenvetona niin, ettei yksittäistä vastaajaa tai sairaalaa voi saada selville.

Kysymyksien laatimiseen olen saanut asiantuntija-apua professori, osastonylilääkäri Tuulikki Sokka-Isleriltä, dosentti, LKT Pekka Kurjelta, sekä sairaala-apteekkarilta.

Toivoisin, että antaisitte kokemuksenne käyttööni täyttämällä tämän kyselylomakkeen ja palauttamalla sen minulle **31.10.** mennessä sähköpostiosoitteeseeni xxx**.** Kyselyn on kahdeksan sivun mittainen.

Tarvittaessa vastaan kysymyksiinne ja annan mielelläni lisätietoja opinnäytetyöstäni xxx tai puh. xxx.

Vastauksistanne kiittäen, Maarit Simi

Arvoisa vastaanottaja,

Opiskelen Oulun ammattikorkeakoulussa tekniikan yksikössä teknologialiiketoiminnan tutkinto-ohjelmassa ylempää ammattikorkeakoulututkintoa. Opinnäytetyöni aiheeksi valikoitui biosimilaarit, jotka ovat olleet jo useamman vuoden terveydenhuollon kuuma keskustelun aihe. Opinnäytetyöni ohjaajana toimii tutkintovastaava Hannu Päätalo.

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Kyselylomakkeen olen lähettänyt yliopisto- ja keskussairaaloiden gastroenterologian, reumatologian, onkologian ja sisätautien ylilääkäreille, tulosalueen johtajille ja sairaanhoitopiirien johtajaylilääkäreille sekä arviointiylilääkäreille. Vastaukset tulen käsittelemään luottamuksellisesti ja tulokset esitetään yhteenvetona niin, ettei yksittäistä vastaajaa tai sairaalaa voi saada selville. Kysymyksien laatimiseen olen saanut asiantuntija-apua professori, osastonylilääkäri Tuulikki Sokka-Isleriltä, dosentti, LKT Pekka Kurjelta, sekä sairaala-apteekkarilta.

Toivoisin, että antaisitte kokemuksenne käyttööni täyttämällä tämän kyselylomakkeen ja palauttamalla sen minulle **31.10.** mennessä sähköpostiosoitteeseeni xxx**.** Kyselyn täyttäminen vie aikaa kohderyhmästä riippuen noin 15 – 30 minuuttia.

Tarvittaessa vastaan kysymyksiinne ja annan mielelläni lisätietoja opinnäytetyöstäni xxx tai puh. xxx.

Vastauksistanne kiittäen, Maarit Simi

Biosimilaarit eli samankaltaiset biologiset lääkkeet ovat alkuperäisten biologisten lääkevalmisteiden kopioita, jotka tulevat markkinoille alkuperäisen biologisen lääkkeen patentti-, dokumentaatio- ja markkinointisuojan umpeuduttua. Biosimilaari sisältää EU:n markkinoilla olevan myyntiluvallisen alkuperäislääkkeen vaikuttavan aineen uuden version ja sen kehittäminen perustuu biosimilaarin ja sen alkuperäisvalmisteen laadun, tehon ja turvallisuuden vertailukelpoisuuden osoittamiseen.

Vuonna 2006 hyväksyttiin EU:n ensimmäinen biosimilaarivalmiste ja 2013 ensimmäinen monoklonaalinen biosimilaarivasta-aine infliksimabi (Ruskoaho 2016, 16). EU:ssa on heinäkuuhun 2016 mennessä arvioitu 32 biosimilaarivalmisteen myyntilupahakemusta, joista 23 johti myyntilupaan (myyntilupa voimassa 21 valmisteella) (taulukko 1). Suomessa kesällä 2016 markkinoilla oli 10 biosimilaarivalmistetta (taulukko 1). Useiden biologisten valmisteiden patentti- ja dokumentaatio suojat ovat umpeutuneet ja useita uusien biosimilaarien myyntilupahakemuksia on arvioitavana (taulukko 1), joten uusia biosimilaareja on tulossa markkinoille lähivuosina (taulukko 2).

2015 Suomen kymmenen myydyimmän lääkevalmisteen joukossa on kahdeksan biologista valmistetta (kuva 1). Kymmenen myydyimmän lääkevalmisteen tukkumyynti 2015 oli noin 276 miljoonaa euroa, josta biologisten osuus oli noin 233 miljoonaa euroa (kuva 1). Lääkkeiden kokonaismyynnistä sairaalalääkkeiden osuus on noin 27 prosenttia (Lääkemarkkinat, viitattu 1.9.2016).

Biologiset lääkkeet ovat pääsääntöisesti huomattavan kalliita ja yksi keskeinen syy korkeille hinnoille on ollut hintakilpailun puuttuminen. Tällä hetkellä biologisten lääkkeiden kustannukset lisääntyvät noin kymmenen prosenttia vuodessa (Kurki & Orvilahti 2016, 41). Biosimilaarien markkinoille tulo on lisännyt kilpailua ja esimerkkinä tästä voisi mainita infliximabimarkkinat, jossa biosimilaarit ovat vallanneet markkinat 90 %:sti (Ruskoaho 2016, 16). Odotusarvona on, että biosimilaarien hinnat ovat alkuperäislääkettä halvemmat ja kilpailu laskee myös alkuperäislääkkeiden hintoja.

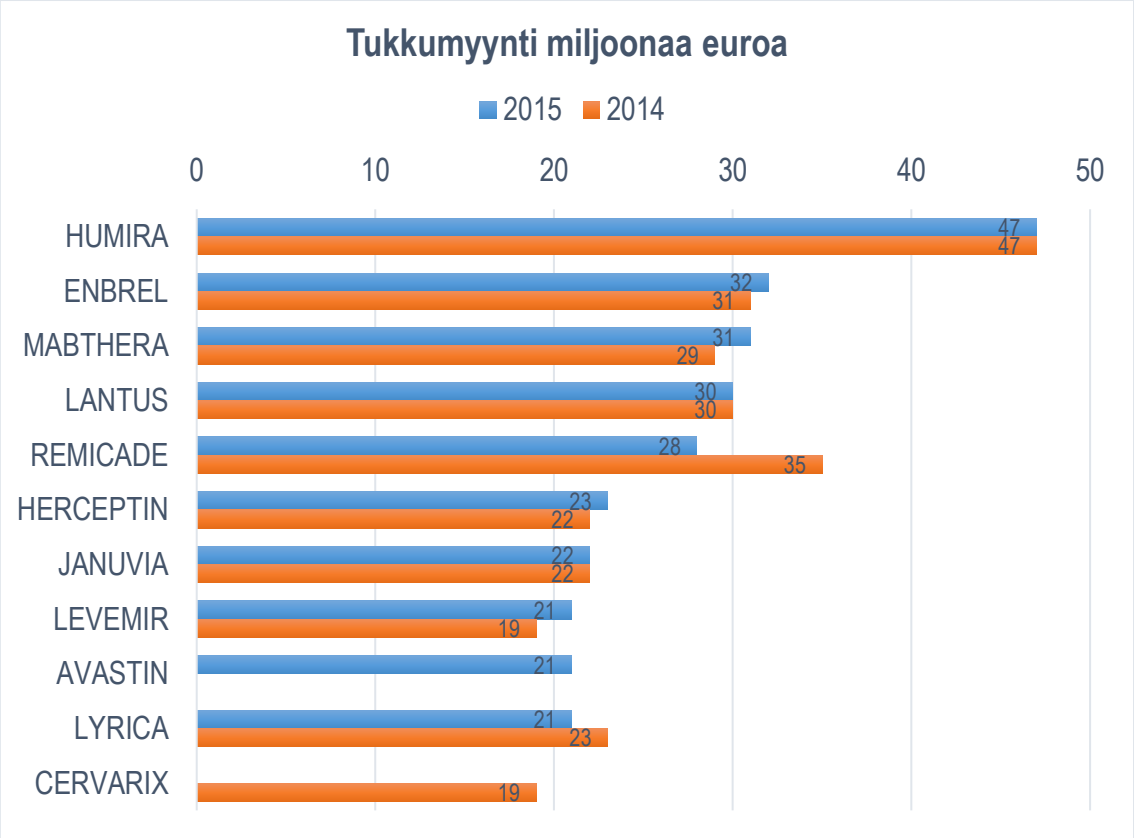
TAULUKKO 1. Biosimilaarit EU:ssa (heinäkuu 2016) (Fimea 2016, viitattu 11.7.2016; European Medicines Agency 2016, viitattu 23.7.2016; European Medicines Agency July 2016, viitattu 23.7.2016; Kurki, Oravilahti & Martikainen 2016, 148)

Käsitellyt myyntilupahakemukset	32	
Myyntilupia myönnetty	23	
Hakija vetänyt pois hakemuksen	7	
Hylätty	2	
Myyntilupa peruutettu yrityksen toimesta	2	
Myyntilupa voimassa	21	5 epoetiinia 1 etanersepti 8 filgrastiimia 2 follitropiinia 1 glargininsuliini 3 infliximabia 1 kasvuhormoni

Käsiteltävänä olevat hakemukset	14	2 adalimumabia 2 enoksapariinia 1 etanersepti 1 glargininsuliini 4 PEG filgrastiimia 2 rituximabia 2 teriparatidea
Suomessa markkinoilla	10	1 kasvuhormoni 3 filgrastiimia 2 epoetiini alfaa 1 follitropiini 2 infliximabia 1 glargininsuliini

TAULUKKO 2. Arvio eräiden biosimilaarien markkinoille tulosta (Ruskoaho 2016, 17; WHO 2015)

Lääkeaine	Vuosi	Farmakoterapeuttinen ryhmä
Enoksapariini	2017	Antitromboottiset lääkeaineet
Pegfilgrastiimi	2017	Immunostimulantit
Aspartinsuliini	2018	Diabeteslääkkeet
Darbepoetiinialfa	2018	Anemialääkkeet
Korifollitropiini alfa	2018	Sukupuolihormonit ja genitaalijärjestelmään vaikuttavat aineet
Pegvisomantti	2018	Aivolisäkkeen ja hypotalamuksen hormonit sekä analogit
Trastutsumabi	2018	Solunsalpaajat
Abatasepti	2018	Immunosuppressantit
Tosilitsumabi	2018	Immunosuppressantit
Omalitsumabi	2018	Obstruktiivisten hengitystiesairauksien lääkkeet
Detemirinsuliini	2019	Diabeteslääkkeet
Adalimumabi	2019	Immunosuppressantit
Romiplostiimi	2020	Hemostaatit
Metoksipolyetyleeniglykoliepoetiini beta	2021	Anemialääkkeet



KUVA 1. Kymmenen myydyintä lääkevalmistetta Suomessa 2014 ja 2015 (tukkumyynti) (Lääketeollisuus ry (a), viitattu 13.7.2016; Lääketeollisuus ry (b), viitattu 13.7.2016)

LÄHTEET:

Applications for new human medicines under evaluation by the Committee for Medicinal Products for Human Use. July 2016. European Medicines Agency. Viitattu 23.7.2016. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/07/WC500209941.pdf.

ATC/DDD Index 2016 2015. WHO Collaborating Centre for Drug Statistics Methodology. Viitattu 13.8.2016. http://www.whocc.no/atc_ddd_index/.

Biosimilaarit Suomessa. Lääkealan kehittämis- ja turvallisuuskeskus Fimea. Viitattu 11.7.2016. http://www.fimea.fi/laaketurvallisuus_ja_tieto/biosimilaarit/biosimilaarit_suomessa.

European public assessment reports. European Medicines Agency. Viitattu 23.7.2016. http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=biosimilar&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars&genericsKeywordSearch=Submit.

Kurki P, Oravilahti T. Biosimilaarit testaavat lääkkeen määrääjien kustannustietoisuuden. SIC! Lääketietoa Fimeasta. 1/2016; 41-44. Viitattu 11.7.2016. https://www.julkari.fi/bitstream/handle/10024/130215/1_16%2041-44%20Biosimilaarit%20testaavat%20laakkeen%20maaraajien%20kustannustietoisuuden.pdf?sequence=1.

Kurki P, Oravilahti T, Martikainen J E. Miksi biosimilaarit kannattaa ottaa käyttöön? Suomen lääkärilehti. 2016 71 (3); 147-151.

Lääkemarkkinat. Lääkemarkkinoiden ydin muodostuu korvattavista lääkkeistä. Lääketeollisuus ry. Viitattu 1.9.2016. http://www.laaketeollisuus.fi/laakkeet/laakemarkkinat.

Ruskoaho, H. 2016 Lääkekorvausjärjestelmän tarkastelua lääkkeiden näkökulmasta vuoden 2017 lääkesäästöihin liittyen. Selvitysmiehen raportti. Sosiaali- ja terveysministeriön raportteja ja muistioita 2016:31. Viitattu 11.7.2016. https://julkaisut.valtioneuvosto.fi/bitstream/handle/10024/74928/RAP2016_31.pdf?sequence=1.

Top 10 tuotteet Suomessa 2015. Lääketeollisuus ry (a). Viitattu 13.7.2016. http://www.laaketeollisuus.fi/sites/default/files/attachments/suomen_myydyimmat_laakevalmisteet_2015.pdf.

10 myydyintä lääkevalmistetta Suomessa 2014. Lääketeollisuus ry (b). Viitattu 13.7.2016. http://www.laaketeollisuus.fi/sites/default/files/attachments/Tilastot/07_top_10_tuotteet_0.pdf.

Valitse alla olevista vaihtoehdoista sopivin/sopivimmat laittamalla rasti ruutuun. Jos et löydä sopivaa vaihtoehtoa, kirjoita kommenttisi vapaan tekstin kenttään. Kaikki biosimilaari- ja alkuperäisvalmisteiden hintavertailut tulee tehdä hankintakilpailutuksessa tarjotuin sairaalan ostohinnoin. Jos et pysty vastaamaan johonkin kysymykseen, jätä kohta täyttämättä. Jos käsittelet vastauksissasi filgrastiimin ja infliximabin biosimilaarivalmisteita, täytä kummastakin oma kysely. Kysely on 8 sivun pituinen.

Kyselylomake tulee tallentaa ennen täyttämisen aloittamista. Palauta tallentamasi liitetiedosto sähköpostiosoitteeseen (xxx) lokakuun loppuun mennessä.

1. **Valitse sairaala, jota edustat**

   ☐ Yliopistollinen sairaala

   ☐ Keskussairaala

   ☐ Muu, mikä? _____

2. **Valitse biosimilaarivalmiste, jota käsittelet vastauksissasi ja identifioi sen asemaa sairaalavalikoimassa tällä hetkellä. Jos haluat käsitellä molempia biosimilaarivalmisteita, täytä kummastakin oma kysely.**

   2.1. Biosimilaarivalmiste, johon otat kantaa

   ☐ Filgrastiimi

   ☐ Infliximabi

   2.2. Voimassaolevan hankintakauden kesto

   Alkoi, vuosi _____, kuukausi _____

   Loppuu, vuosi _____, kuukausi _____

2.3. Valitsemasi biosimilaarivalmisteen asema sairaalan lääkevalikoimassa voimassa olevalla hankintakaudella

☐ Biosimilaarivalmiste on lääkevalikoimassa ensisijainen vaihtoehto

Miksi? _____

☐ Lääkevalikoimassa on myös biosimilaarivalmisteen alkuperäisvalmiste

Miksi? _____

☐ Lääkevalikoimassa ei ole biosimilaarivalmistetta

Miksi? _____

☐ Lääkevalikoimassa on vain biosimilaarivalmiste

Miksi? _____

Muita kommentteja? _____

3. Kysymykset koskien biosimilaarien tehoa, turvallisuutta, vaihtoja ja käyttöönottoa

3.1. Biosimilaarilääkkeen myyntilupaa haettaessa on osoitettava, että mahdolliset erot biosimilaari- ja alkuperäisvalmisteen välillä eivät vaikuta tehoon tai turvallisuuteen. Ovatko biosimilaarivalmisteilta vaadittavat tutkimukset riittävän kattavia tehon ja turvallisuuden osalta ja mistä olet saanut biosimilaarivalmisteista tietoa?

3.1.1. Biosimilaarivalmisteiden tutkimukset ovat

☐ Riittävän kattavia

Miksi? _____

☐ Eivät ole riittävän kattavia

Miksi? _____

Muita kommentteja? _____

3.1.2. Mistä lähteistä olet saanut tietoa biosimilaarivalmisteista?

☐ Lääkeyrityksiltä

☐ Lääkeviranomaisilta

☐ Kollegoilta

☐ Muualta, mistä? _____

3.1.3. Koetko tarvitsevasi lisää tietoa biosimilaareista?

☐ Kyllä

Seuraavista asioista _____

☐ En

3.2. Sairaaloissa on vaihdettu potilaita alkuperäisvalmisteilta biosimilaarivalmisteille. Miten sairaalassa valmistauduttiin vaihtoihin alkuperäisvalmisteelta valitsemallesi biosimilaarivalmisteelle ja vaikuttivatko vaihdot hoidon tehoon ja/tai turvallisuuteen? Onko vaihdoista tehty jälkiseurantaa?

3.2.1. Miten vaihtoihin valmistauduttiin?

☐ Vaihdot eivät aiheuttaneet erillistoimenpiteitä

☐ Määrittämällä vasta-aine- ja lääkeainepitoisuudet ennen vaihtoja

☐ Ohjeistamalla potilas siitä, mikä biosimilaarivalmiste on

☐ Kouluttamalla hoitohenkilökunta siitä, mikä biosimilaarivalmiste on

☐ Määrittelemällä vaihdettavat potilaat

Vaihtokriteerejä olivat: _____

☐ Muuten, miten? _____

3.2.2. Vaikuttivatko vaihdot hoidon tehoon ja/tai turvallisuuteen?

☐ Kyllä

Miten? _____

☐ Ei

☐ En osaa sanoa

Muita kommentteja? _____

3.2.3. Onko vaihdoista tehty jälkiseurantaa?

☐ Ei erityistä seurantaa

☐ Lääkeainepitoisuus- ja vasta-ainemäärityksin

☐ Määritetään tietyin frekvenssein

☐ Määritetään tarvittaessa

☐ Seuraamalla hoidon keskeytymisen syitä

☐ Muuten, miten? _____

Muita kommentteja? _____

3.3. Alkuperäisten biologisten lääkkeiden rinnalle on tulossa yhä enemmän biosimilaarivalmisteita. Ovatko biosimilaarivalmisteet, joilla on sama vaikuttava aine, mielestäsi vaihtokelpoisia keskenään sairaalassa ja mitä asioita vaihdoissa tulisi huomioida?

3.3.1. Ovatko biosimilaarivalmisteet vaihdettavia keskenään?

☐ Kyllä

Miksi? _____

☐ Eivät

Miksi? _____

☐ En osaa sanoa

Miksi? _____

3.3.2. Mitä asioita tulisi huomioida vaihdettaessa biosimilaarivalmisteelta toiseen?

_____

3.4. Mitkä ovat mielestäsi biosimilaarien entistä laajemman käytön tärkeimmät esteet?

_____

4. Kysymykset koskien lääkekustannuksia ja säästöjä

4.1. Kun biosimilaarivalmiste tulee markkinoille, oletetaan sen aiheuttavan hintakilpailua. Kommentoi odotuksiasi valitsemasi biosimilaarivalmisteen hintaerosta alkuperäisvalmisteeseen, sekä sen toteutumista, kun biosimilaari valittiin ensimmäisen kerran sairaalan lääkevalikoimaan. Ensimmäinen biosimilaari filgrastiimi sai myyntilupansa Euroopassa syyskuussa 2008 ja infliximabi syyskuussa 2013.

4.1.1. Ennen biosimilaarivalmisteen markkinoille tuloa, biosimilaarivalmisteen ja sen alkuperäisvalmisteen hintaeroksi arvioit

_____ %

Mihin perustit oletuksesi? _____

4.1.2. Biosimilaari- ja alkuperäisvalmisteen sairaalan ostohintaero verrattuna alkuperäisvalmisteen sairaalan ostohintaan, kun biosimilaarivalmiste valittiin sairaalan lääkevalikoimaan ensimmäisen kerran

_____ %

Vuosi _____

4.1.3. Biosimilaarivalmisteen tullessa hankintakilpailutukseen mukaan ensimmäisen kerran, muuttuiko alkuperäisvalmisteen ostohinta verrattuna edelliseen hankintakilpailutuksessa tarjottuun ostohintaan?

☐ Kyllä

☐ Laski _____ %

☐ Nousi _____ %

☐ Ei

Muita kommentteja? _____

4.2. Biosimilaarivalmisteen käyttöönotto sairaalassa on mahdollistanut lääkekustannussäästöjä. Millä keinoin säästöjä tavoiteltiin ja toteutuivatko säästöt?

4.2.1. Valitsemallasi biosimilaarivalmisteella tavoiteltiin lääkekustannussäästöjä

☐ Aloittamalla uusille potilaille

☐ Vaihtamalla alkuperäisvalmisteelta kaikki potilaat biosimilaarivalmisteelle

☐ Vaihtamalla tietyt potilasryhmät alkuperäisvalmisteelta biosimilaarivalmisteelle

Mitä potilasryhmiä/potilaita ei vaihdettu? _____

Muita kommentteja? _____

4.2.2. Toteutuivatko lääkekustannussäästöt?

☐ Kyllä

Mitkä tekijät edesauttoivat kustannussäästöjen toteutumisessa? _____

☐ Eivät

Miksi eivät? _____

☐ Osin

Mitkä tekijät vaikuttivat siihen, että tavoitteeseen ei päästy? _____

4.2.3. Arviosi valitsemasi biosimilaarivalmisteen avulla saavutetuista kustannussäästöistä lääkeostoissa vuonna 2015

_____ €

☐ Vain biosimilaarivalmiste oli jo edellisellä hankintakaudella sairaalan lääkevalikoimassa, joten lääkekustannussäästöt alkuperäisvalmisteeseen verrattuna eivät olleet enää 2015 ajankohtaisia.

4.2.4. Jos biosimilaarivalmisteella saatiin sairaalalle lääkekustannussäästöjä, mihin vapautuneet varat käytettiin?

☐ Mahdollisti useamman potilaan hoidon kyseisellä valmisteella

☐ Mahdollisti uusien valmisteiden käyttöönoton sairaalavalikoimassa

☐ Lääkekustannusten hallintaan

☐ Henkilökunnan palkkaukseen

☐ Muu, mikä? _____

4.2.5. Valitsemasi bioisimilaarivalmisteen prosenttiosuus lääkeryhmän kokonaislääkemäärästä vuonna 2015. Inflectra mg:sta/filgrastim ruiskumääristä laskettuna. Laskelmassa tulisi olla mukana valmisteet, jotka sisältyvät valitsemasi biosimilaarivalmisteen ATC-koodin alle: L04AB02 infliximabit tai L03AA02 filgrastiimit.

Prosenttiosuus _____ %

4.3. Uusia biosimilaarivalmisteita on tulossa markkinoille lähivuosina. Miten arvioisit niiden vaikuttavan sairaalassa käytettävien alkuperäisvalmisteiden hinnoitteluun ja mitä odotat biosimilaarivalmisteiden hinnoittelulta?

4.3.1. Biosimilaarivalmisteiden hinnoittelulta sairaalahinnoissa tulevaisuudessa odotat

☐ Biosimilaarivalmisteet ovat edullisempia kuin alkuperäisvalmisteet

Arvioimasi hintaero _____ %

☐ Alkuperäisvalmisteet lähtevät hintakilpailuun mukaan biosimilaarivalmisteiden saadessa myyntiluvan ja ovat yhtä edullisia kuin biosimilaarivalmisteet

☐ Alkuperäisvalmisteiden hinta ei laske

☐ Alkuperäisvalmisteet ovat edullisempia kuin biosimilaarivalmisteet

Arvioimasi hintaero _____%

Muita kommentteja? _____

4.3.2. Paljonko seuraavan 5 vuoden aikana arvioit saatavan biosimilaarivalmisteiden aiheuttamien hintakilpailujen avulla sairaalassasi kustannussäästöjä lääkeostoissa?

_____ €/5 vuotta

Perustelut arviollesi _____

4.3.3. Biosimilaarivalmiste, jonka oletat seuraavaksi vaikuttavan sairaalanne lääkekustannuksiin merkittävästi

Valmiste: _____

Arvioitu kustannussäästö lääkeostoissa: _____ €/vuosi

Kustannussäästöarviosi perustuu seuraaviin asioihin: _____

Muita kommentteja? _____

4.4. Lisääntyvät lääkekustannukset ovat haaste sairaaloille. Ovatko lääkekustannukset muuttuneet viimeisen viiden vuoden aikana sairaalassa ja mikä on biologisten lääkkeiden osuus sairaalan kokonaislääkekustannuksista?

4.4.1. Sairaalan kokonaislääkekustannukset ostohinnoin laskettuna 2015?

_____ €

4.4.2. Sairaalan lääkekustannukset ovat viimeisen viiden vuoden aikana?

☐ Kasvaneet _____ %

Miksi? _____

☐ Pienentyneet _____ %

Miksi? _____

☐ Eivät ole muuttuneet

Miksi? _____

4.4.3. Sairaalan lääkekustannusten osuus prosentteina sairaalan kokonaismenoista 2015? Kokonaismenoilla tarkoitetaan toimintakuluja, eli niissä ei ole huomioitu investointimenoja.

Prosenttiosuus _____ %

4.4.4. Biologisten lääkkeiden prosenttiosuus sairaalan lääkkeiden kokonaiskustannuksista vuonna 2015? Laskelmassa tulisi olla mukana valmisteet, jotka sisältyvät seuraavien ATC-koodien alle: A10A (insuliinit), B03XA (anemialääkkeet), H01AC (somatropinit), J06 (immunogobuliinit), L03AA (sytokiinit), L03AB (interferonit), L04AA (immunosupressantit, pois lukien - 06, - 10, - 13, - 27,- 29,- 31,- 32), L04AB (tumoorinekroositekijä alfan estäjät), L04AC (interleukiinin estäjät), L01XC (monoklonaaliset antibodit).

Prosenttiosuus _____ %

4.4.5. Onko edellä mainittujen biologisten lääkkeiden kustannusten osuus kasvanut kokonaislääkekustannuksista viimeisen viiden vuoden aikana?

☐ Kyllä _____ %

Miksi? _____

☐ Ei

Miksi? _____

4.4.6. Sairaalan 3 kustannuksiltaan kalleinta (ostohinnoilla laskettuna) biologista lääkettä vuonna 2015

1. _____, _____ €
2. _____, _____ €
3. _____,_____ €

5. Haluan, että lähetät sähköpostiini linkin, josta pääsen lukemaan opinnäytetyösi

Sähköpostiosoitteeni _____

Valitse alla olevista vaihtoehdoista sopivin/sopivimmat laittamalla rasti ruutuun. Jos et löydä sopivaa vaihtoehtoa, kirjoita kommenttisi vapaan tekstin kenttään. Kaikki biosimilaari- ja alkuperäisvalmisteiden hintavertailut tulee tehdä hankintakilpailutuksessa tarjotuin sairaalan ostohinnoin. Jos et pysty vastaamaan johonkin kysymykseen, jätä kohta täyttämättä. Jos käsittelet vastauksissasi filgrastiimin ja infliximabin biosimilaarivalmisteita, täytä kummastakin oma kysely. Kysely on 8 sivun pituinen.

Kyselylomake tulee tallentaa ennen täyttämisen aloittamista. Palauta tallentamasi liitetiedosto sähköpostiosoitteeseen (xxx) lokakuun loppuun mennessä.

1. **Valitse missä ominaisuudessa vastaat kysymyksiin, sekä sairaala, jota edustat**
   - **1.1. Olet**
     - ☐ Arviointiylilääkäri
     - ☐ Gastroenterologian ylilääkäri
     - ☐ Onkologian ylilääkäri
     - ☐ Reumatologian ylilääkäri
     - ☐ Sairaanhoitopiirin johtajaylilääkäri
     - ☐ Tulos- / palvelualueen johtaja

       Tulos- / palvelusalueeni on _____
     - ☐ Muu, mikä? _____
   - **1.2. Edustamasi sairaala on**
     - ☐ Yliopistollinen sairaala
     - ☐ Keskussairaala
     - ☐ Muu, mikä? _____

2. **Valitse biosimilaarivalmiste, jota käsittelet vastauksissasi ja identifioi sen asemaa sairaalavalikoimassa tällä hetkellä. Jos haluat käsitellä molempia biosimilaarivalmisteita, täytä kummastakin oma kysely.**
   - **2.1. Biosimilaarivalmiste, johon otat kantaa**
     - ☐ Filgrastiimi
     - ☐ Infliximabi

2.2. Voimassa olevan hankintakauden kesto

Alkoi, vuosi _____, kuukausi _____

Loppuu, vuosi _____, kuukausi _____

2.3. Valitsemasi biosimilaarivalmisteen asema sairaalan lääkevalikoimassa voimassa olevalla hankintakaudella

☐ Biosimilaarivalmiste on lääkevalikoimassa ensisijainen vaihtoehto

Miksi? _____

☐ Lääkevalikoimassa on myös biosimilaarivalmisteen alkuperäisvalmiste

Miksi? _____

☐ Lääkevalikoimassa ei ole biosimilaarivalmistetta

Miksi? _____

☐ Lääkevalikoimassa on vain biosimilaarivalmiste

Miksi? _____

☐ En käytä biosimilaarivalmistetta tai sen alkuperäisvalmistetta, koska sairaalassa on siirrytty käyttämään uudempia valmisteita, joilla on sama käyttöaihe/-aiheet kuin biosimilaarivalmisteella

Miksi? _____

Muita kommentteja? _____

3. Kysymykset koskien biosimilaarien tehoa, turvallisuutta, vaihtoja ja käyttöönottoa

3.1. Biosimilaarilääkkeen myyntilupaa haettaessa on osoitettava, että mahdolliset erot biosimilaari- ja alkuperäisvalmisteen välillä eivät vaikuta tehoon tai turvallisuuteen. Ovatko biosimilaarivalmisteilta vaadittavat tutkimukset mielestäsi riittävän kattavia tehon ja turvallisuuden osalta ja mistä olet saanut biosimilaarivalmisteista tietoa?

3.1.1. Biosimilaarivalmisteiden tutkimukset ovat

☐ Riittävän kattavia

Miksi? _____

☐ Eivät ole riittävän kattavia

Miksi? _____

Muita kommentteja? _____

3.1.2. Mistä lähteistä olet saanut tietoa biosimilaarivalmisteista?

☐ Lääkeyrityksiltä

☐ Lääkeviranomaisilta

☐ Kollegoilta

☐ Muualta, mistä? _____

3.1.3. Koetko tarvitsevasi lisää tietoa biosimilaareista?

☐ Kyllä

Seuraavista asioista _____

☐ En

3.2. Sairaaloissa on vaihdettu potilaita alkuperäisvalmisteilta biosimilaarivalmisteille. Miten sairaalassa valmistauduttiin vaihtoihin alkuperäisvalmisteelta valitsemallesi biosimilaarivalmisteelle ja vaikuttivatko vaihdot hoidon tehoon ja/tai turvallisuuteen? Onko vaihdoista tehty jälkiseurantaa?

3.2.1. Miten vaihtoihin valmistauduttiin?

☐ Vaihdot eivät aiheuttaneet erillistoimenpiteitä

☐ Määrittämällä vasta-aine- ja lääkeainepitoisuudet ennen vaihtoja

☐ Ohjeistamalla potilas siitä, mikä biosimilaarivalmiste on

☐ Kouluttamalla hoitohenkilökunta siitä, mikä biosimilaarivalmiste on

☐ Määrittelemällä vaihdettavat potilaat

Vaihtokriteerejä olivat: _____

☐ Muuten, miten? _____

3.2.2. Vaikuttivatko vaihdot hoidon tehoon ja/tai turvallisuuteen?

☐ Kyllä

Miten? _____

☐ Ei

☐ En osaa sanoa

Muita kommentteja? _____

3.2.3. Onko vaihdoista tehty jälkiseurantaa?

☐ Ei erityistä seurantaa

☐ Lääkeainepitoisuus- ja vasta-ainemäärityksin

☐ Määritetään tietyin frekvenssein

☐ Määritetään tarvittaessa

☐Seuraamalla hoidon keskeytymisen syitä

☐Muuten, miten? _____

Muita kommentteja? _____

3.3. Alkuperäisten biologisten lääkkeiden rinnalle on tulossa yhä enemmän biosimilaarivalmisteita. Ovatko biosimilaarivalmisteet, joilla on sama vaikuttava aine, mielestäsi vaihtokelpoisia keskenään sairaalassa ja mitä asioita vaihdoissa tulisi huomioida?

3.3.1. Ovatko biosimilaarivalmisteet vaihdettavia keskenään?

☐ Kyllä

Miksi? _____

☐ Eivät

Miksi? _____

☐ En osaa sanoa

Miksi? _____

3.3.2. Mitä asioita tulisi huomioida vaihdettaessa biosimilaarivalmisteelta toiseen?

_____

3.4. Mitkä ovat mielestäsi biosimilaarien entistä laajemman käytön tärkeimmät esteet?

_____

4. Kysymykset koskien lääkekustannuksia ja säästöjä

4.1. Kun biosimilaarivalmiste tulee markkinoille, oletetaan sen aiheuttavan hintakilpailua. Kommentoi odotuksiasi valitsemasi biosimilaarivalmisteen hintaerosta alkuperäisvalmisteeseen, sekä sen toteutumista, kun biosimilaari valittiin ensimmäisen kerran sairaalan lääkevalikoimaan. Ensimmäinen biosimilaari filgrastiimi sai myyntilupansa Euroopassa syyskuussa 2008 ja infliximabi syyskuussa 2013.

4.1.1. Ennen biosimilaarivalmisteen markkinoille tuloa, biosimilaarivalmisteen ja sen alkuperäisvalmisteen hintaeroksi arvioit

_____ %

Mihin perustit oletuksesi? _____

4.1.2. Biosimilaari- ja alkuperäisvalmisteen sairaalan ostohintaero verrattuna alkuperäisvalmisteen sairaalan ostohintaan, kun biosimilaarivalmiste valittiin sairaalan lääkevalikoimaan ensimmäisen kerran

_____ %

Vuosi _____

4.1.3. Biosimilaarivalmisteen tullessa hankintakilpailutukseen mukaan ensimmäisen kerran, muuttuiko alkuperäisvalmisteen ostohinta verrattuna edelliseen hankintakilpailutuksessa tarjottuun ostohintaan?

☐ Kyllä

☐ Laski _____ %

☐ Nousi _____ %

☐ Ei

Muita kommentteja? _____

4.2. Biosimilaarivalmisteen käyttöönotto sairaalassa on mahdollistanut lääkekustannussäästöjä. Millä keinoin säästöjä tavoiteltiin ja toteutuivatko säästöt?

4.2.1. Valitsemallasi biosimilaarivalmisteella tavoiteltiin lääkekustannussäästöjä

☐ Aloittamalla uusille potilaille

☐ Vaihtamalla alkuperäisvalmisteelta kaikki potilaat biosimilaarivalmisteelle

☐ Vaihtamalla tietyt potilasryhmät alkuperäisvalmisteelta biosimilaarivalmisteelle

Mitä potilasryhmiä/potilaita ei vaihdettu? _____

Muita kommentteja? _____

4.2.2. Toteutuivatko lääkekustannussäästöt?

☐ Kyllä

Mitkä tekijät edesauttoivat kustannussäästöjen toteutumisessa? _____

☐ Eivät

Miksi eivät? _____

☐ Osin

Mitkä tekijät vaikuttivat siihen, että tavoitteeseen ei päästy? _____

4.2.3. Arviosi valitsemasi biosimilaarivalmisteen avulla saavutetuista kustannussäästöistä lääkeostoissa vuonna 2015

_____ €

☐ Vain biosimilaarivalmiste oli jo edellisellä hankintakaudella sairaalan lääkevalikoimassa, joten lääkekustannussäästöt alkuperäisvalmisteeseen verrattuna eivät olleet enää 2015 ajankohtaisia.

4.2.4. Jos biosimilaarivalmisteella saatiin sairaalalle lääkekustannussäästöjä, mihin vapautuneet varat käytettiin?

☐ Mahdollisti useamman potilaan hoidon kyseisellä valmisteella

☐ Mahdollisti uusien valmisteiden käyttöönoton sairaalavalikoimassa

☐ Lääkekustannusten hallintaan

☐ Henkilökunnan palkkaukseen

☐ Muu, mikä? _____

4.2.5. Valitsemasi bioisimilaarivalmisteen prosenttiosuus lääkeryhmän kokonaislääkemäärästä vuonna 2015. Inflectra mg:sta/filgrastim ruiskumääristä laskettuna. Laskelmassa tulisi olla mukana valmisteet, jotka sisältyvät valitsemasi biosimilaarivalmisteen ATC-koodin alle: L04AB02 infliximabit tai L03AA02 filgrastiimit.

Prosenttiosuus _____ %

4.3. Uusia biosimilaarivalmisteita on tulossa markkinoille lähivuosina. Miten arvioisit niiden vaikuttavan sairaalassa käytettävien alkuperäisvalmisteiden hinnoitteluun ja mitä odotat biosimilaarivalmisteiden hinnoittelulta?

4.3.1. Biosimilaarivalmisteiden hinnoittelulta sairaalahinnoissa tulevaisuudessa odotat

☐ Biosimilaarivalmisteet ovat edullisempia kuin alkuperäisvalmisteet

Arvioimasi hintaero _____ %

☐ Alkuperäisvalmisteet lähtevät hintakilpailuun mukaan biosimilaarivalmisteiden saadessa myyntiluvan ja ovat yhtä edullisia kuin biosimilaarivalmisteet

☐ Alkuperäisvalmisteiden hinta ei laske

☐ Alkuperäisvalmisteet ovat edullisempia kuin biosimilaarivalmisteet

Arvioimasi hintaero _____%

Muita kommentteja? _____

4.3.2. Paljonko seuraavan 5 vuoden aikana arvioit saatavan biosimilaarivalmisteiden aiheuttamien hintakilpailujen avulla sairaalassasi kustannussäästöjä lääkeostoissa?

_____ €/5 vuotta

Perustelut arviollesi _____

4.3.3. Biosimilaarivalmiste, jonka oletat seuraavaksi vaikuttavan sairaalanne lääkekustannuksiin merkittävästi

Valmiste: _____

Arvioitu kustannussäästö lääkeostoissa: _____ €/vuosi

Kustannussäästöarviosi perustuu seuraaviin asioihin: _____

Muita kommentteja? _____

4.4. Lisääntyvät lääkekustannukset ovat haaste sairaaloille. Ovatko lääkekustannukset muuttuneet viimeisen viiden vuoden aikana sairaalassa ja millainen osuus lääkekustannukset ovat sairaalan kokonaismenoista?

4.4.1. Sairaalan lääkekustannukset ovat viimeisen viiden vuoden aikana

☐ Kasvaneet _____ %

Miksi? _____

☐ Pienentyneet _____ %

Miksi? _____

☐ Eivät ole muuttuneet

Miksi? _____

4.4.2. Sairaalan lääkekustannusten osuus prosentteina sairaalan kokonaismenoista 2015? Kokonaismenoilla tarkoitetaan toimintakuluja, eli niissä ei ole huomioitu investointimenoja.

Prosenttiosuus _____ %

5. Jos hoidat potilaita avohoidossa, tuletko määräämään uusia myyntiluvallisia biosimilaarivalmisteita avohoidon potilaille?

☐ Kyllä

Miksi? _____

☐ Ei

Miksi? _____

☐ Käytän jo biosimilaarivalmisteita avohoidossa

Mitä valmisteita? _____

Miksi? _____

6. Haluan, että lähetät sähköpostiini linkin, josta pääsen lukemaan opinnäytetyösi

Sähköpostiosoitteeni _____

TERMS USED IN THE FIGURES 15 AND 17 APPENDIX 13

Biosimilar + reference products	
HGH	Genotropin + Humatrope + Omnitrope
EPO (shorter acting)	Epoetin alfa + epoetin zeta
G-CSF (shorter acting)	Filgrastim
Anti-TNF	Infliximab
Biosimilar accessible market products, includes also biosimilar + reference products	
HGH	Norditropin + Saizen + NutropinAq + Zomacton
EPO (shorter acting)	Epoetin beta + epoetin theta
G-CSF (shorter acting)	Lenograstim
Total market products, includes also accessible market products	
HGH	
EPO (longer acting)	Methoxy polyethylene glycol-epoetin beta + darbepoetin alfa
G-CSF (longer acting)	Lipegfilgrastim + pegfilgrastim + molgramostim + sargramostim
Anti-TNF	Etanercept, adalimumab, certolizumab, golimumab

(IMS Health June 2016, 3 - 4, 8 - 16, 24)