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ETHICAL AND REGULATORY ISSUES RELATED TO BIOSIMILAR MEDICINES

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Abstract

Biosimilar medicines are considered by governments as a solution to increase accessibility to very expensive biological medicines. This dissertation attempts to identify the ethical and regulatory issues related to biosimilar medicines through an in-depth literature review.

The first chapter involves literature related to biological medicines and intellectual property regulations in Europe. The second chapter covers the literature on regulation of biosimilar medicines in Europe. In the third chapter, the literature covers an analysis on the expenditure of biologicals and their economic burden, the different models of switching and substitution, their implementation within the public health care system, and the success of biosimilar uptake strategies. Chapter 4 focuses on the literature on the emerging ethical issues.

It is concluded that a 'knowledge gap' of the cell line and the manufacturing process of originator biological medicines hinders other manufacturing companies from producing copies. The extensive intellectual property protection regulations in Europe contribute to the low number of biosimilars authorised in Europe and their delay from reaching the market. The European Medicines Agency (EMA) was at the forefront to set up a regulatory framework for biosimilars, which however are not therapeutically equivalent and therefore not interchangeable. The EMA leaves the decision of interchangeability to Member States. The safety concerns on switching to biosimilars are pronounced. Governments set different policies to improve the uptake including mandatory switching, but there is no coherent policy framework which could lead to inequality whilst the uptake of biosimilars remains low. Globalisation of the pharmaceutical industry led to the need for harmonisation and convergence of regulations which is the 21st century best regulatory practice.

From the ethical perspective, good governance is required to ensure impartiality in decision taking at all levels to improve access to biosimilars and ensure fair competition. Safety is the main ethical issue related to biosimilars, where safe regulation is recommended through physician-led prescribing. Mandatory switching presents

further ethical concerns. A holistic policy framework is required by governments which should be based on the principles of justice, solidarity, precaution and integrity so as to ensure equitable access to medicines on a national, European and global level. Biosimilars may be part of the solution through harmonised regulation and public health care systems that are built on the principle of solidarity.

Keywords: **biosimilar, ethics, accessibility, regulation, solidarity.**

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I am extremely grateful for the help, continuous support and patience of my co-supervisor, Dr Patricia Vella Bonanno, throughout this study. This thesis would not have been possible without her expert advice and detailed feedback on the various aspects related to scientific and regulatory aspects of biosimilars.

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List of Abbreviations

Abbreviation	Full name
ABPI	Association of the British Pharmaceutical Industry
ADA	Anti-Drug Antibody
ADC	Antibody Drug Conjugates
ADR	Adverse Drug Reaction
AIFA	Agenzia Italiana del Farmaco (Italian Medicines Agency)
AS	Ankylosing Spondylitis
ASOs	Antisense oligonucleotides
ATC	Anatomical Therapeutic Chemical
ATMP	Advanced Therapeutic Medicinal Product
BIG	Bioethical Implications of Globalisation
BQ	Biological Qualifier
BsAB	Bispecific Antibodies
BTP	Biotherapeutic product
CD	Crohn's disease
CEO	Corporate European Observatory
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CJEU	Court of Justice of the EU
CKD	Chronic Kidney Disease
CLA	Cell Line Access
CMC	Chemistry, Manufacture and Control
CSF	Colony Stimulating Factor
DanBio	(Danish Registry for Biologic Therapies in Rheumatology

DHSC	Department of Health and Social Care
DNA	Deoxyribonucleic Acid
EAHP	European Association of Hospital Pharmacy
EC	European Commission
ECCO	European Crohn and Colitis Organization
EEA	European Economic Area
EUNETHTA	European Network Health Technology Assessment
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EP	European Parliament
EPAR	European Public Assessment Report
EPO	European Patent Office
ERP	External Reference Pricing
ESMO	European Society for Medical Oncology
EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GaBI	Generics and Biosimilars Initiative
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GDP	Gross Domestic Product
GMP	Good Manufacturing Practice
HCP	Healthcare professional
HTA	Health Technology Assessment

IBD	Inflammatory Bowel Disease
ICESCR	International Covenant on Economic, Social, and Cultural Rights
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (covering Europe, United States of America and Japan)
IFN	Interferon
IGBA	International Generic and Biosimilar Association
IL	Interleukins
IMIDs	immune-mediated inflammatory diseases
INN	International Non-Proprietary Name
IP	Intellectual Property
IQVIA	Intelligence, Q comes from Quintiles or can be interpreted as Quotient and VIA is basically the path of transformation or a helping hand to achieve something formerly Quintiles and IMS Health, Inc.
IRP	Internal Reference Pricing
I.V.	Intravenous
LMWH	Low Molecular Weight Heparin
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
mABs	Monoclonal Antibodies
MAH	Market Authorisation Holder
MCCFF	Malta Community Chest Fund Foundation
MEA	Managed-entry agreement
MRA	Mutual Recognition Agreement
MS	Member State
MSF	Médicins Sans Frontières
NCA	National Competent Authority

NGB	Next generation biotherapeutics
NICE	Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
P & T Committee	Pharmacy & Therapeutic Committee
PAES	Post-authorisation efficacy studies
PASS	Post-authorisation safety studies
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PLANETAS	Program evaLuating the Autoimmune Disease iNvEstigational Drug cT-p13 in AS Patients
PLANETRA	Program evaLuating the Autoimmune Disease iNvEstigational Drug cT-p13 in RA Patients
PRAC	Pharmacovigilance Risk Assessment Committee
PRCA	Pure Red Cell Aplasia
PUMA	Paediatric-use marketing authorisation
R&D	Research and Development
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
RNA	Ribonucleic acid
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SOJA	System of Objectified Judgement Analysis
SPB	Similar Biological Products
SPC	Supplementary Protection Certificate
TFEU	Treaty on Functioning of the European Union

TNF	Tumour Necrosis Factor
TRIPS	Trade Related Aspects of Intellectual Property Rights
UC	Ulcerative Colitis
UDBHR	Universal Declaration on Bioethics and Human Rights
US / USA	United States of America
VPAS	Voluntary Scheme for Branded Medicines Pricing and Access
WHO	World Health Organization
WMA	World Medical Association
WTA	World Trade Organisation Agreement
WTO	World Trade Organisation

Introduction

Overview

The global expenditure on medicines increased from €950 billion in 2012 to €1.1 trillion in 2017, and it is expected that by 2022 biologicals (A glossary of definitions of key terminology used in this dissertation is found in Appendix A) would account for 25% of the pharmaceutical market.[1] Biologicals are used for the treatment of many diseases, including diabetes, chronic kidney disease, cancer and autoimmune conditions, such as multiple sclerosis and rheumatoid arthritis. Unfortunately, biological medicines are very expensive as they require very costly and complex development and manufacturing, making them unaffordable to patients. As for all medicinal products, originator biologicals are covered by intellectual property (IP) protection rights to protect innovation that allows pharmaceutical companies to recoup their investment costs. However, the pharmaceutical industry may take advantage from the monopolistic position in the market and set higher prices.

Once patency protection is lost, it is only possible to produce similar biological medicines through a comparative manufacturing process, known as biosimilars (Refer to Appendix A). As the patency of the first biologicals which were authorised in the 1980's was forecasted to expire, the EU was at the forefront to set a regulatory framework for biosimilars. Globalization has led manufacturing companies to move clinical trials and production of biologicals to Eastern Asian under-developed countries which could be used as a stepping-stone for accessibility of expensive biological medicines to these countries.

The first biosimilar was centrally authorized in Europe in 2006. It was projected that by the year 2020, twenty biologicals would come off-patent in Europe, allowing more biosimilars to reach the market.

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[1] European Commission, *Commission Staff Working Document Impact Assessment Accompanying the document Proposal for a Regulation of the European Parliament and of the Council amending Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products,* (Brussels: 28 May 2018):1-108, 9.

Biosimilars are generally 15-30% cheaper than the originator biologicals, and this could result in significant cost savings, making such medicines more accessible.[2] Biosimilars are not fully therapeutically equivalent to the original biological medicines, however, and as such, they are not interchangeable but recommended that switching from originator biologicals to biosimilars should be physician-led. The European Medicines Agency (EMA) left this decision of interchangeability to the individual Member States (MSs) of the European Union (EU). Through their prescribing and reimbursement policy structures there is no coherent policy framework for biosimilar access across the European MSs. This could result in inequality, which is strongly debatable from an ethical perspective and is the subject of this dissertation. In addition, the different models of interchangeability, which include switching, multiple switching or automatic pharmacy substitution, could have medico-legal and ethical implications. The high expenditure on biological medicines to treat chronic diseases negatively impacts the economy of EU countries, putting pressure on governments to introduce public healthcare system policies that support substitution to biosimilars with the aim of achieving sustainable healthcare. This has led to different implementation policies which could present ethical and medico-legal issues. The World Health Organisation recognised that accessibility of medicines has become a global concern that needs to be addressed.[3]

Thesis question

The current trend in patient access to medicines is to increase the uptake of biosimilar medicines (referred to as biosimilars) in order to improve healthcare sustainability and distributive justice. Switching from originator biological medicines (biologicals) to biosimilars within the current regulatory framework in Europe presents

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[2] Pieter Dylst et al., "Barriers to the uptake of biosimilars and possible solutions: A Belgian case study," *PharmacoEconomic*s 32 (2014): 681-691, 683.

[3] United Nations Educational, Scientific and Cultural Organization (UNESCO), *Universal Declaration of Bioethics and Human Rights*, (France: United Nations Educational, Scientific and Cultural Organization, Division of Ethics of Science and Technology Social and Human Science Sector (UNESCOD): 2006), 6.

ethical dilemmas to healthcare professionals, members of the legal profession and policy makers.

The aim of the dissertation, therefore, is to identify the ethical and regulatory issues related to biosimilars that may lead to the proposal of ethically sound recommendations for the improvement of patient accessibility to biologicals with the aim of improving healthcare sustainability.

Limitations of the study

The EU Directive 2001/83/EC provides a clear definition of biologicals and similar biological products (see Appendix A). Based on these definitions, advanced therapeutic medicinal products (ATMP's) (see Appendix A), vaccines and gene therapy will be excluded from this discussion of biosimilar medicines. This dissertation will only consider a literature review on the regulations of biosimilars in Europe.

In view of the word limit, it will not be possible to present product specific data for biosimilars. Similarly, the individual policies related to biosimilar switching or substitution for each European country and position statements of the various professional associations on switching will not be presented and discussed in this dissertation. In addition, the ethical aspects of patented biologicals in the public healthcare systems are considered beyond the scope of this dissertation.

Methodology

To answer the thesis question, this dissertation will proceed in four steps. First, it will provide a scientific perspective of biologicals and biosimilars. Then, the regulations related to biosimilars for authorisation and prescribing will be discussed. Following this, accessibility and affordability issues of biologicals will be brought to the forelight, which will then lead to an analysis and discussion of the emerging ethical issues identified earlier on. This dissertation will then conclude with a summary of findings and some recommendations.

Chapter 1: Biologicals and biosimilars

This chapter will provide a brief overview on developments in medicine followed by an illustration of the pharmaceutical product life-cycle, from research and development to the post-authorisation stage where, on expiry of the patent, generic medicines and similar biological medicines known as 'biosimilars' reach the market resulting in more competition and lower prices, thereby increasing accessibility. A detailed scientific overview on biological medicines and a definition of 'biosimilars' will be provided followed by an analysis of marketing authorisations in Europe. A critical analysis of the intellectual property rights and other mechanisms will be provided in the final part of this chapter so as to identify any emerging ethical issues.

1.1 Developments in medicine

Up to the early seventies, medicines were mainly derived from chemically-synthesised small molecules for the treatment of conditions such as infections, cardiovascular disorders, respiratory disorders and other common illnesses.[4] The 1970s saw the invention of recombinant Deoxyribonucleic Acid (DNA) technology which led to the development of biological medicines, with the first biological medicines such as insulin and erythropoietin being developed in the 1980s.[5] The more complex biological medicines targeting tumour specific antigens, namely, therapeutic monoclonal antibodies (mABs), were introduced in the 1990s and 2000s and included cytokines, namely interferon (IFN), interleukins (IL), tumour necrosis factor (TNF) and anakinra, as well as fusion proteins.[6] The range of biologicals continued to expand such that it now includes nanobodies, soluble receptors, immune-therapies, synthetic vaccines,

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[4] Christopher J. Leintz and Riddhi Dedhia, "Biosimilars and emerging markets: historical and bioethical considerations," *Journal of Clinical Research and Bioethics* 6, no. 5 (2015): 1-4, 1.

[5] *Ibid*.

[6] Sarantos Kyriakopoulos and Cleo Kontoravdi, "Analysis of the landscape of biologically-derived pharmaceuticals in Europe: Dominant production systems, molecule types on the rise and approval trends," *European Journal of Pharmaceutical Sciences* 48 (2013): 428-441, 433-434.

immunoconjugates, modified proteins (glycosylated and pegylated), etc.[7] New nucleic acid-based products (gene therapies) and engineered cell-based products are the latest biologicals reaching the market.[8]

1.2 Pharmaceutical product life-cycle

Once a new molecule is discovered through basic research, the pharmaceutical product life-cycle kicks off where the manufacturing company performs research and development (R&D).[9]

1.2.1 Research and development (R&D)

The first step involves pre-clinical studies on animals to evaluate the safety, toxicity, pharmacokinetic and pharmacodynamic properties of the molecule. For biotechnology-derived pharmaceuticals, manufacturing companies must also meet International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines (covering Europe, United States of America and Japan) on the preclinical safety evaluation of such molecules in view of safety concerns that may arise from impurities or contaminants.[10] If found to be satisfactory, the molecule undergoes four phases of clinical studies in humans for quality, safety and efficacy as illustrated in Figure 1.

Phase I clinical trials evaluate the medicine's safety and identify the initial safety and tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) and drug activity in a small group of 20-100 healthy volunteers. Once this is completed satisfactorily, research enters into Phase II where further clinical studies are performed on a larger group of

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7 Eva Rahman Kabir et al., "The Breakthrough of Biosimilars: A Twist in the Narrative of Biological Therapy," *Biomolecules 9* No. 410 (2019):1-34, https://doi:10.3390/biom9090410.

8 Gary Walsh, "Biopharmaceutical benchmarks 2018," *Nature Biotechnology* 36, no. 12 (2018): 1136-1145, 1136.

9 Hye-Na Kang & Ivana Knezevic, "Regulatory evaluation of biosimilars throughout their product life-cycle," *Bulletin of the World Health Organization 96* (28 February 2018): 281-285, accessed on May 11, 2020, https://dx.doi.org/10.2471/BLT.17.206284.

10 European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), *ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals - Step 5*, EMA/CHMP/ICH/731268/1998, (European Medicines Agency, June 2011).

100-300 participants affected by the disease to evaluate the therapeutic efficacy and determine the dose, potential endpoints and therapeutic regimen. The product then enters into Phase III where the medicine is assessed on a larger group of 300-3000 participants affected by the disease to confirm the preliminary evidence from Phase II studies.

Figure 1. Medicines development process

On average, only one to two of every 10,000 molecules will successfully pass all the required stages of development and reach the market.[11] Clinical trials are regulated at the European level by the European Medicines Agency (EMA), which is responsible for the authorisation and monitoring of medicines in Europe, through the Good Clinical Practice (GCP) Directive 2005/28/EC and the Clinical Trials Directive 2001/20/EC which has now been replaced by the Clinical Trials Regulation (EC) 536/2014, even though it is not yet in force. High production and research costs have forced pharmaceutical companies to operate their manufacturing, development and clinical trials on a global

[11] European Federation of Pharmaceutical Industries and Associations (EFPIA), *The Pharmaceutical Industry in Figures - Key Data 2018*, (Brussels: EFPIA, 2018), 6.

level, whilst seeking marketing authorisation in Europe. This necessitates more cooperation between the EMA and other regulatory authorities in other countries outside the EU, which could benefit from regulatory harmonisation and convergence.[12]

1.2.2 Authorisation and post-authorisation stage

All results of clinical studies are presented to the regulatory authority for assessment as part of the Marketing Authorisation Application (MAA) submission and, if the medicine is found to be of positive therapeutic effect in relation to the risks, the medicine is granted Marketing Authorisation (MA) granted. Subsequently, the pharmaceutical company, referred to as the Market Authorisation Holder (MAH), will produce the medicine on a large scale and prepare for the product launch on the market. Post-authorisation monitoring for adverse effects and benefit-to-risk is continued on an ongoing basis, referred to as Phase IV, which is also known as pharmacovigilance.

Once an MA is granted, the medicinal product is launched on the market and follows the cycle through market growth, maturity and decline. Following loss of patency and market exclusivity protection, competitive manufacturing companies may produce copies of the medicine, referred to as generic medicines, and place them on the market. The introduction of generics on the market would drive competition, putting prices down, thus making the medicine more accessible to patients.[13] The originator product life-cycle is illustrated in Figure 2. The 1984 US Food and Drug Administration (FDA) Hatch-Waxman Act allowed generic companies to prove the interchangeability of small molecules through an abbreviated pathway.[14] The 2000 ruling of the World Trade

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[12] European Commission, "Legal framework governing medicinal products for human use in the EU," accessed January, 13, 2020, accessed on May 11, 2020, https://ec.europa.eu/health/human-use/legal-framework_en.

[13] European Commission, *Report from the Commission to the Council and the European Parliament - Competition enforcement in the pharmaceutical sector (2009-2017)*, (Brussels: COM 17, 28 January, 2019) 1-45, 22.

[14] Jeremy A. Green, "Commentary – The disappointment of the biosimilar," *Journal of Law, Medicine and Ethics* Fall (2018): 791-793, 792.

Organisation Bolar case law[15] on intellectual property rights removed the barrier to competition.[16]

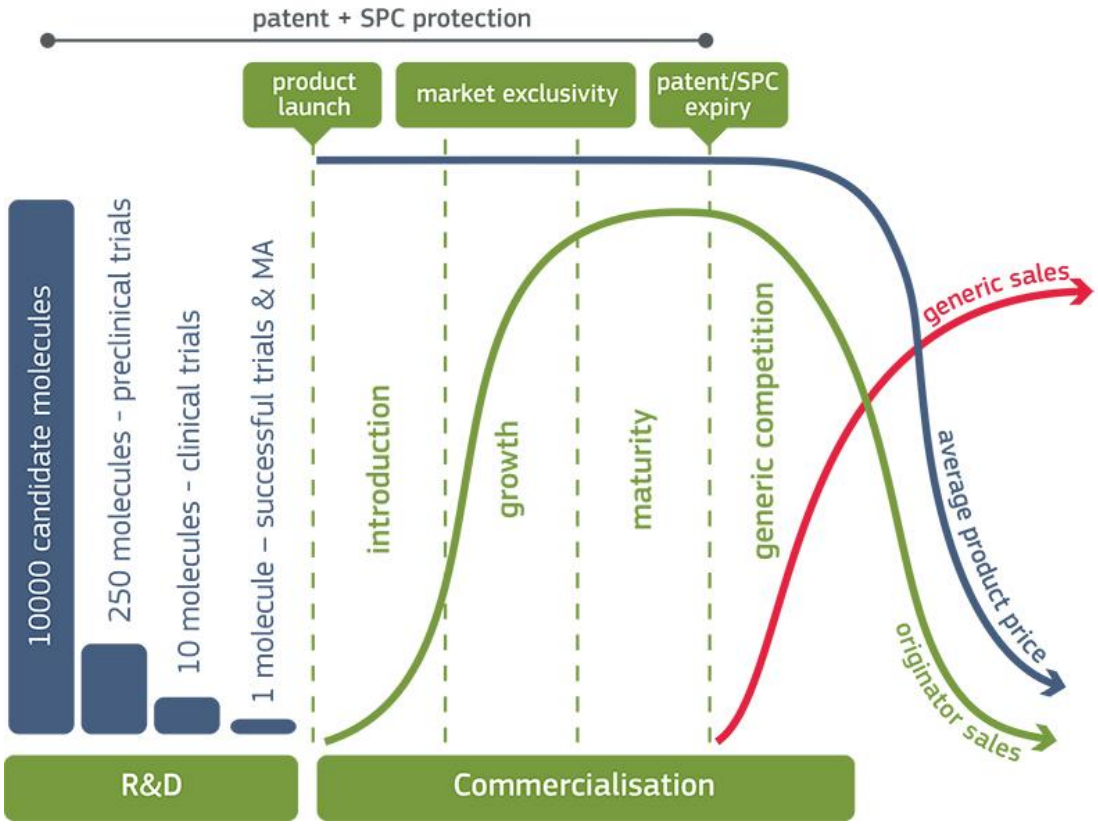

Figure 2: Pharmaceutical product life-cycle[17]

In Europe, companies may seek authorisation for generic products through the abridged regulatory procedure through the national and mutual recognition authorisation systems.[18] This will be explained in more detail in Section 2.1. On average, the price of an innovator medicine drops by 40% on entry of a generic medicine to the market, whilst the price of generics is on average 50% lower than the original price of

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15 The Bolar exemption to patent rights allowed generic companies to complete the tests necessary to register a generic product prior to patent expiration of the originator medicine such that they can market the generic product immediately on expiry of the patent.

16 Green, "Commentary – The disappointment of the biosimilar," 792.

17 European Commission, *Report from the Commission to the Council and the European Parliament - Competition enforcement in the pharmaceutical sector (2009-2017),* 19.

18 Irish MEP Avril Doyle. Cited in Arthur Rogers, "European Parliament approves pharma law overhaul," *The Lancet* 360 November 2 (2002): 1397-1398.

the originator.[19] Biological medicines undergo a similar life-cycle to chemically-synthesised molecules, but in view of the complexity of the molecule and manufacturing process, an identical biological product with the same composition cannot be produced.[20] Instead, manufacturers perform reverse engineering to set up a new cell line and their own manufacturing process in order to produce a similar biological product, termed as 'biosimilar', which undergoes Phase III clinical trials in order to provide assurance regarding product similarity to the originator.[21] In view of the high development and production costs, however, the price reductions of up to 66% achieved with generics cannot be achieved with biosimilars.[22] Prices of biosimilars are estimated to be 15% to 30% of the originator product.[23] The complexity of biosimilar development presents delays for them to reach the market, such that originator biological products do not face the 'patent cliff' as for chemically-synthesised products.[24]

1.3 Biological medicines

Biological medicines, also known as 'biopharmaceuticals' or 'biologicals,' are "medicines whose active substance is made by a living organism (most commonly produced by *Escherichia coli,* yeast or mammalian cells, most commonly Chinese hamster ovary (CHO) cells)."[25] Gary Walsh , professor of industrial biotechnology at the University of Limerick, defines biopharmaceuticals as "recombinant proteins, including

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19 European Commission, *Report from the Commission to the Council and the European Parliament - Competition enforcement in the pharmaceutical sector (2009-2017),* 24.

20 Leintz & Dedhia, "Biosimilars and emerging markets: historical and bioethical considerations," 1.

21 George Dranitsaris et al., "Biosimilars of Biological Drug Therapies Regulatory, Clinical and Commercial Considerations," *Drugs* 71, no. 12 (August 2011): 1527-36, 29.

22 Alessandra Ferrario et al., "Strategy procurement and international collaboration to improve access to medicines," *Bulletin World Health Organization* 95 (2017):720-722, 720-721.

23 Pieter Dylst et al., "Barriers to the uptake of biosimilars and possible solutions: A Belgian case study," *PharmacoEconomics* 32 (2014): 681-691, 683.

24 Richard G. Frank, "Friction in the path to use of biosimilar drugs," *New England Journal of Medicine* 378, no. 9 (2018): 791-793792.

25 European Medicines Agency, "Biological medicine," accessed September 21, 2019, https://www.ema.europa.eu/en/glossary/biological-medicine.

recombinant antibody-based products, and nucleic acid–based and genetically engineered cell-based products."[26]

Biological medicines are complex proteins that vary in size from 5,800 Daltons (for insulin), 10,000 Daltons (for filgrastim), 22,000 Daltons (for growth hormone) to 150,000 Daltons (for rituximab and infliximab) as illustrated in Figure 3 below, in contrast to chemically-synthesised molecules which are structurally simple chemical compounds with small molecular weight (less than 1000 Daltons) that are produced through a step-by-step chemical purification process.[27]

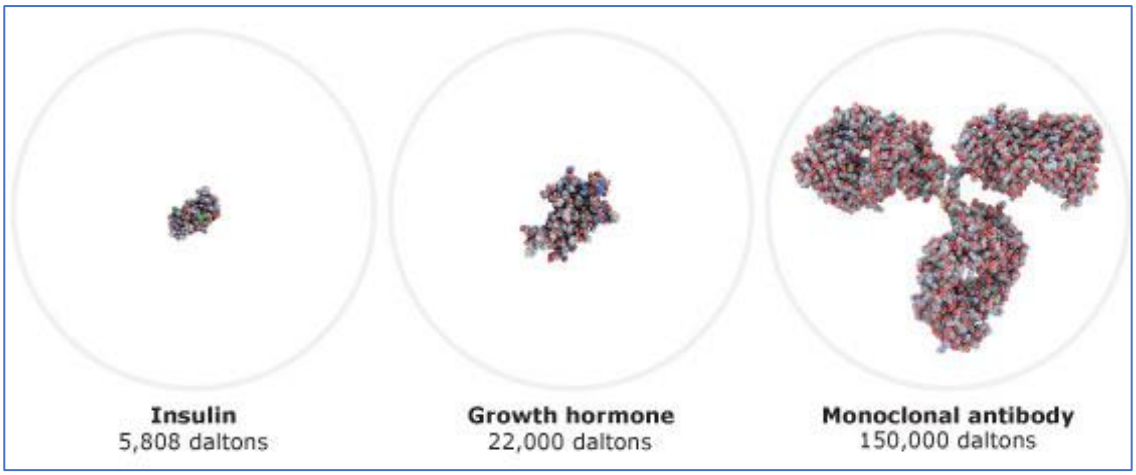

Figure 3: Examples of types of proteins in biological medicines approved in the EU[28]

1.3.1 Main categories of biological medicines

Biological medicines are categorised according to generation as detailed below.

1.3.1.1 First-generation biologicals

These refer to the relatively simple molecules as per Table 1 below.

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[26] Walsh, "Biopharmaceutical benchmarks 2018," Table 1.

[27] Gustavo Grampp et al., "Policy considerations for originator and similar biotherapeutic products," Pharmaceuticals Policy and Law 18 (2016): 121-139, 122.

[28] European Medicines Agency, "Biosimilar medicines: Overview," accessed on October 10, 2019, https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview.

Table 1: First generation biologicals by type and clinical indication[29]

Type	Name of biological medicine	Clinical indication
Growth factors	Erythropoietin	Anaemia especially related to chronic kidney disease (CKD)
Colony Stimulating Factors (CSFs)	Filgrastim	Neutropenia resulting from cancer treatment
Hormones	Insulin and insulin analogues	Diabetes
	Growth hormone (Somatropin)	Growth deficiency
	Follicle stimulating hormone (FSH) Chorionic gonadotropin	Infertility

1.3.1.2 Second-generation biologicals

Due to their more complex structures, these are termed as 'complex' products, referring to mAbs and fusion proteins.[30] The first therapeutic mAb was rituximab for the treatment of B-non-Hodgkin's lymphoma.[31] Therapeutic mAbs developed further to the present antibody-based therapeutic mAbs for the treatment of cancer, diabetes, stroke, heart attacks and autoimmune conditions, such as multiple sclerosis and rheumatoid arthritis.[32] Table 2 below provides a list of second generation biologicals and their clinical indications.

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[29] Kyriakopoulos and Kontoravdi, "Analysis of the landscape of biologically-derived pharmaceuticals in Europe: Dominant production systems, molecule types on the rise and approval trends,"434.

[30] L. Pasina et al., "Biological agents and biosimilars: essential information for the internist," European Journal of Internal Medicine 33 (2016): 28-35. Cited in Vito Annese et al., "Biosimilars in Italy: a gastroenterologist's view," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 5, no. 3 (2016): 131-3, 2.

[31] Josée Golay and Martino Introna, "Mechanism of action of therapeutic monoclonal antibodies: Promises and pitfalls of in vitro and in vivo assays," *Archives of Biochemistry and Biophysics* 526 (2012): 146-153, 146.

[32] *Ibid*.

Table 2: Second generation biologicals and their clinical indications[33]

Name of biological	Clinical indications
Adalimumab (Humira®)	Ankylosing Spondylitis, Rheumatoid Arthritis, Uveitis, Ulcerative Colitis, Psoriatic Arthritis, Psoriasis, and Crohn Disease.
Infliximab (Remicade®)	Ankylosing Spondylitis, Rheumatoid Arthritis, Psoriasis, Crohn Disease, Psoriatic Arthritis and Ulcerative Colitis.
Etanercept (Enbrel®)	Ankylosing Spondylitis, Juvenile Rheumatoid Arthritis, Psoriatic Arthritis, Psoriasis and Rheumatoid Arthritis.
Certolizumab	Rheumatoid Arthritis
Golimumab	Psoriatic, Arthritis, Ankylosing, Spondylitis, Ulcerative Colitis, and Rheumatoid Arthritis
Trastuzumab (Herceptin®)	Breast cancer
Interferon beta-1a (Avonex® and Rebif®)	Multiple sclerosis
Interferon beta-1b (Rebif®)	Multiple sclerosis
Secukinumab (Cosentyx®)	Psoriatic Arthritis, Psoriasis and Ankylosing Spondylitis
Ixekizumab (Taltz®)	Psoriasis
Brodalumab (Kyntheum®)	Psoriasis

With genetic engineering it is possible to modify the antibodies and antibody fragments, thus producing different antibody-based compounds with one or more functional activities depending on the desired use of the final product.[34] Nevertheless, despite the success achieved with therapeutic mAbs, the mechanism of action in vivo does not reflect the results of pre-clinical studies.[35] mAbs were followed by better versions or formulations, for example rituximab and trastuzumab for sub-cutaneous use and pegylated interferon for the treatment of multiple sclerosis.[36]

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33 Data by author using data from: "Medicines - Download Medicine data," accessed January, 25, 2020, https://www.ema.europa.eu/en/medicines/download-medicine-data.

34 Golay and Introna, "Mechanism of action of therapeutic monoclonal antibodies: Promises and pitfalls of in vitro and in vivo assays," 146

35 *Ibid*., 152.

36 Henry Grabowsky et al., "Biosimilar competition: lessons from Europe," *Nature Reviews* 15 (2014): 99-100, Box S1, 4.

1.3.1.3 Next generation biotherapeutics (NGBs)

These include the more recent nanobodies, recombinant enzymes and nucleic acid-based products [gene therapies, DNA & ribonucleic acid (RNA) vaccines and antisense oligonucleotides (ASOs)] and cell-based products that obtained regulatory approval.[37] Caplacizumab is the first nanobody approved by EMA in August 2018 for the treatment of acquired thrombocytopenic purpura (a rare, life-threatening, autoimmune blood clotting disorder).[38] Glybera® is the first gene therapy approved for adults suffering from familial lipoprotein lipase deficiency whose European marketing authorisation, however, was not renewed due to a lack of demand as a result of the exorbitant price.[39] Nine cell-based therapies, gene therapies and regenerative medicines are now available on the global market.[40]

1.3.2 Development of biologicals

Recombinant DNA technology involves several complex processes, namely, the isolation of a targeted gene sequence, its cloning, and the use of a DNA vector to transfer the targeted DNA into a gene expression system (gene encoded by DNA designed to produce protein). This is then inserted into a bacterial cell resulting in a cell line which undergoes further fermentation and purification.[41] Each biological medicine has a specific sequence of amino acids thus providing a unique pharmacological action.[42] Figure 4 shows a simplified diagram of recombinant DNA technology of a biological medicine, namely, human growth hormone. The cell line is "a well-established, living system of cultured (grown in a laboratory) cells that will continue to grow and produce new cells indefinitely, so long as the cells receive nourishment and have space to

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37 Walsh, "Biopharmaceutical benchmarks 2018," 1142.

38 *Ibid*.

39 *Ibid*.

40 IQVIA Institute for Human Data Science, *The Global Use of Medicine in 2019 and Outlook to 2023*, (New Jersey: IQVIA Institute for Human Data Science, January 2019), 25.

41 Steven D. Lucio et al., "Biosimilars: Implications for health-system pharmacists," *American Journal of Health System Pharmacy* 70 (15 Nov. 2013): 2004-2017, 2006.

42 *Ibid.*

develop." Each manufacturing company has its own unique cell line and develops a proprietary manufacturing process.

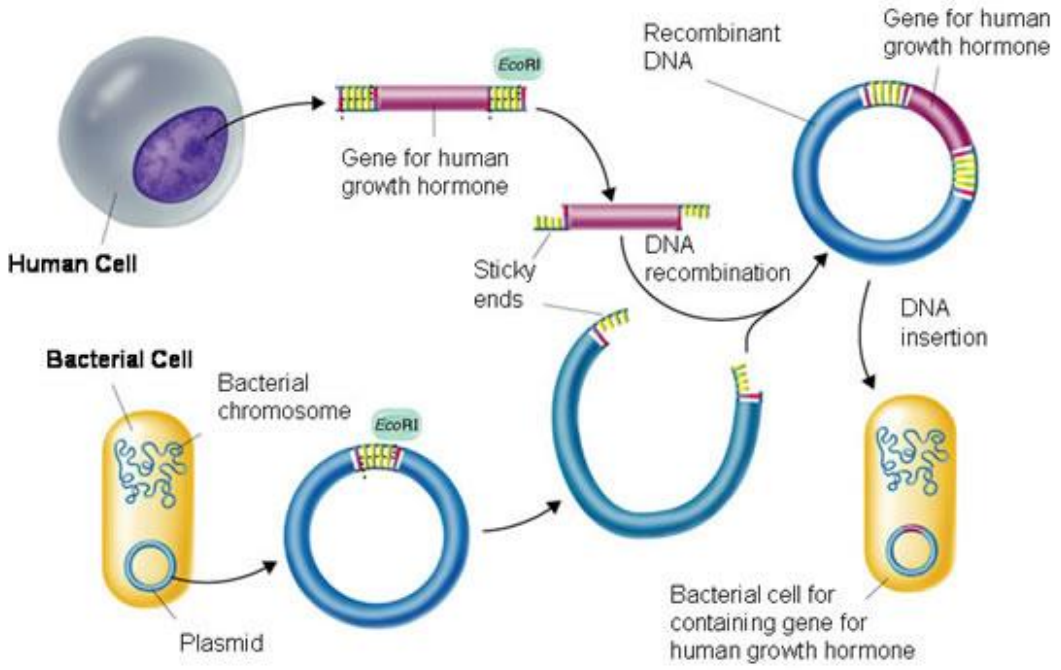

Figure 4: Process of Recombinant DNA Technology (Genetic Engineering)[43]

The manufacturing process involves multiple complex processes which include cell expansion, filtration, centrifugation, purification, product characterisation and determination of product stability of the purified bulk product as illustrated in Figure 5.

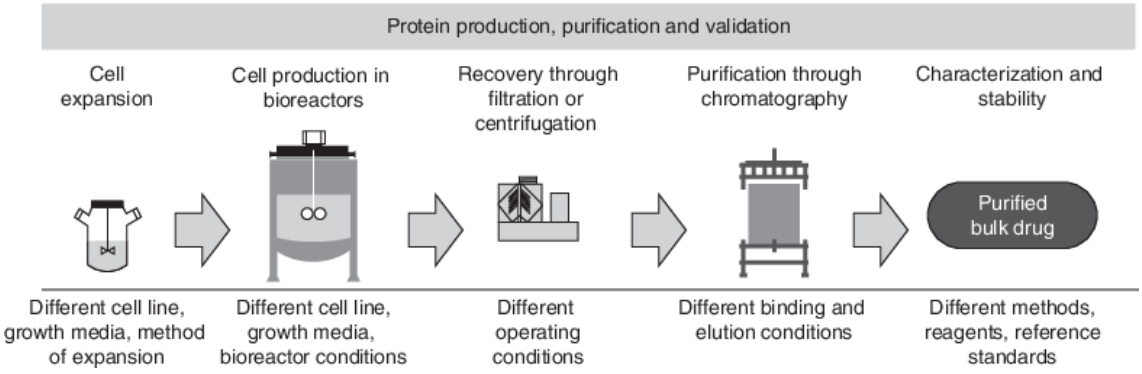

Figure 5: The manufacturing process for biological medicines[44]

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[43] Muhammad Tayyab, "Process of Recombinant DNA Technology (Genetic Engineering)," Simple Biology Blog, accessed on September 29, 2019, https://simplebiologyy.blogspot.com/2016/02/process-of-recombinant-dna-technology-genetic-engineering.html.

[44] Hakan Mellstedt et al., "The challenge of biosimilars," *Annals of Oncology* 19 (2008): 411-419, 412.

Being manufactured by living organisms, a minor degree of inherent variability, termed 'microheterogeneity', is expected, for example, in glycosylation (sugar molecules attached to the protein), but without affecting the amino acids. This is expected to occur between different batches of the same biological medicine. The degree of variability, however, must be within acceptable limits so as to retain the same level of efficacy and safety.[45] The quality of each batch of biological medicine undergoes rigorous testing of the product's specific physicochemical properties, biological activity, purity, sterility and stability.[46] Small changes in the manufacturing process may impact the quality, safety, efficacy, and/or interchangeability of biologicals,[47] as a result of "excursions in product attributes, defined as product drift," and if out of the established range, would lead to product evolution,[48] and ultimately could lead to product divergences.[49] In view of the high complexity of the process, over 250 in-process tests are performed so as to ascertain that the product meets the set specifications so as to maintain safety and efficacy of the product over time.[50] During the lifetime of a product, variations in the manufacturing process are made for various reasons, for example: to increase the efficiency of the manufacturing process, or the purity of the final product, or change the excipients, raw materials or packaging materials, or to comply with new regulations, etc.[51] For each change, a comparability exercise is required to demonstrate that the new version has a similar profile in terms of quality, safety and efficacy. The analysis performed is dependent on the type of change made to the process, which

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45 European Commission and European Medicines Agency, *Biosimilars in the EU - Information guide to healthcare professionals,* Last update October 02, 2019), https://www.ema.europa.eu /en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf. 1-36, 6.

46 *Ibid*., 7.

47 Sundar Ramanan and Gustavo Grampp, "Drift, Evolution, and Divergence in Biologics and Biosimilars Manufacturing," *BioDrugs* 28 (2014): 363–372, http://doi.org/10.1007/s40259-014-0088-z.

48 Product evolution is defined as "quality attributes which could shift outside of established acceptable ranges as the result of a known manufacturing change." Ramanan and Grampp, "Drift, Evolution, and Divergence in Biologics and Biosimilars Manufacturing."366.

49 Product divergences are defined as "clinically meaningful differences among biologics, including among originator products across regions and among originator products and biosimilar products." Ramanan and Grampp, "Drift, Evolution, and Divergence in Biologics and Biosimilars Manufacturing,"363.

50 Grampp et al., "Policy considerations for originator and similar biotherapeutic products," 123.

51 *Ibid*.

could involve analytical and process-related comparisons. If these are found to be insufficient, however, preclinical and/or clinical assessment may be necessary.[52]

1.3.3 Immunogenicity

Immunogenicity is defined as "the ability of a substance to provoke an immune response or the degree to which it provokes a response."[53] In view of their large molecular size and complexity, biological medicines have the potential to induce unwanted immune reactions which could be life-threatening, referred to as anti-drug antibody (ADAs) responses.[54] Various factors may contribute to the type of immune response, such as the patient's clinical condition, product-related factors (e.g. aggregations and host-cell proteins), patient factors (age, sex and genetic background), and treatment factors (concomitant drugs, route of administration, etc).[55] Minor changes in the manufacturing process could result in changes to the molecular properties of the final product that may lead to increased immunogenicity or change in the product function.[56] Skin reactions are a frequent side-effect, but these however are mild and are mainly related to the formulation and rarely to the pharmacological or immunological effect.[57] Transient and low concentration of binding antibodies could result in either a mild or no clinical effect, whilst persistent and high concentrations of antibodies could result in loss of efficacy, generally seen with mAbs, though infusion reactions are also reported to be strongly linked to immunogenicity.[58] Rare cases of pure red cell aplasia (PRCA), a serious life-threatening reaction, were reported with erythropoietin alfa as a result of antibodies being generated against erythropoietin,

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52 Grampp et al., "Policy considerations for originator and similar biotherapeutic products," 124.

53 Medical Dictionary online accessed on March 30, 2020, https://medical-dictionary.thefreedictionary.com/immunogenicity.

54 Lucio et al., "Biosimilars: Implications for health-system pharmacists," 2006.

55 European Commission, *What you need to know about biosimilar medicinal products - A consensus information document*, 9.

56 Corrado Blandizzi et al, "Transitioning from first- to second-generation biosimilars: An appraisal of regulatory and post-marketing challenges," *Pharmaceutical Research* 128 (2018): 306-314, 309.

57 Huub Schellekens et al., "Safety and efficacy of biosimilars in oncology," *The Lancet Oncology* 17, no. 11 (2016): e502-e509, e504.

58 *Ibid*., e504.

neutralizing the medicine's effect, which was attributed to a change in the manufacturing process.[59] Similar reports were made with erythropoietin beta and darbopoetin alfa.[60] In view of the high risk of immunogenicity, more rigorous post-marketing surveillance is required for biologicals.

1.3.4 Biosimilars

Biosimilars are often wrongly referred to as copies of biological medicines or generic biological medicines (also referred to as 'non-innovator' or 'copy-version products'), which are licensed as generic products. Hence, they are also referred to as 'biogenerics'.[61] This term is incorrect as it is not possible to produce an exact copy of a biological and they do not meet the conditions that qualify them as generics.[62] The EU was at the forefront to set a regulatory pathway for similar biological products, referred to as the 'biosimilar pathway.'[63] There is no scientific definition of a 'biosimilar,' but it is a regulatory designation by EMA and is defined as

> a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product) in the European Economic Area (EEA). Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safe and efficacy based on a comprehensive comparability exercise needs to be established.[64]

Other regulatory authorities, such as the FDA in the US, Canada, and Japan have adopted the same definition as EMA with some changes.[65] The WHO defines a biosimilar as "a biotherapeutic product (BTP) similar in terms of quality, safety and efficacy to an already licensed reference product."[66] In the light of globalisation of pharmaceutical

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59 David Goldsmith et al., "Epoetin biosimilars in the treatment of renal Anemia: What have we learned from a decade of European experience?" *Clinical Drug Investigation* 38 (2018): 481–490, 484.

60 Blandizzi et al., "Transitioning from first- to second-generation biosimilars: An appraisal of regulatory and post-marketing challenges," 308.

61 Kang & Knezevic, "Regulatory evaluation of biosimilars throughout their product life-cycle."

62 Grampp et al., "Policy considerations for originator and similar biotherapeutic products," 123.

63 European Medicines Agency (EMA), *Guideline on similar biological medicinal product* (Committee for Medicinal Products for Human Use (CHMP), October 2014, 437/04 Rev 1, 1-7, 1.

64 "Biosimilar medicines: Overview."

65 Schellekens et al., "Safety and efficacy of biosimilars in oncology," e504.

66 Kang & Knezevic. "Regulatory evaluation of biosimilars throughout their product life-cycle."

industry, a common definition for 'biosimilars' is essential which would also require harmonisation of regulations.

1.4 Authorisations of biologicals and biosimilars in Europe

Since 1995, biotechnology-derived medicines must be assessed centrally by EMA, and if found to be satisfactory, a single marketing authorization is issued by the European Commission.

1.4.1 Biological authorisations in Europe

An analysis of medicines authorised by EMA until the end of December 2019 showed that the total number of medicines authorised was 1124, 43% of which were biological products as shown in Figure 6 below.

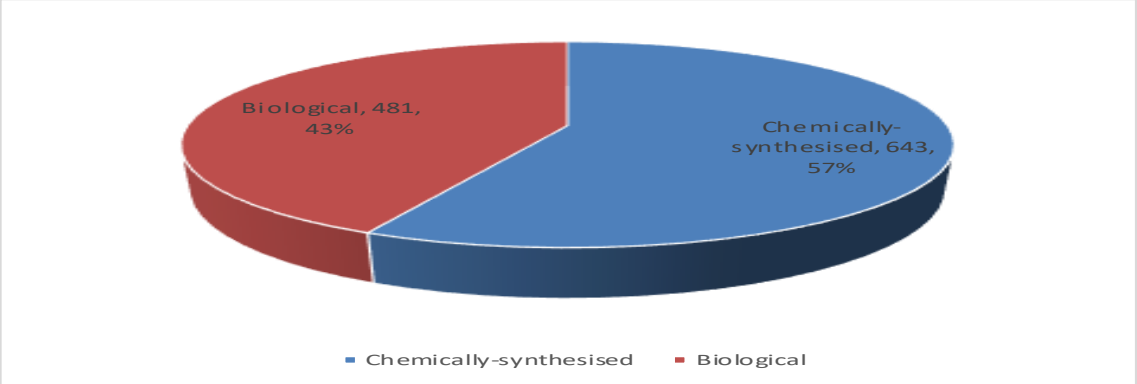

Figure 6: Centrally authorised medicines by EMA by category.[67]

Figure 7 shows an increase in biologicals (comprising also of biosimilars) in comparison to chemically synthesized medicines including generics. Walsh confirmed that in the period January 2014 to July 2018, mAbs dominated the biopharmaceutical approvals.[68]

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[67] Chart produced by author from data downloaded from "Medicines - Download medicine data," accessed January, 25, 2020, https://www.ema.europa.eu/en/medicines/download-medicine-data.

[68] Walsh, "Biopharmaceutical benchmarks 2018," 1137.

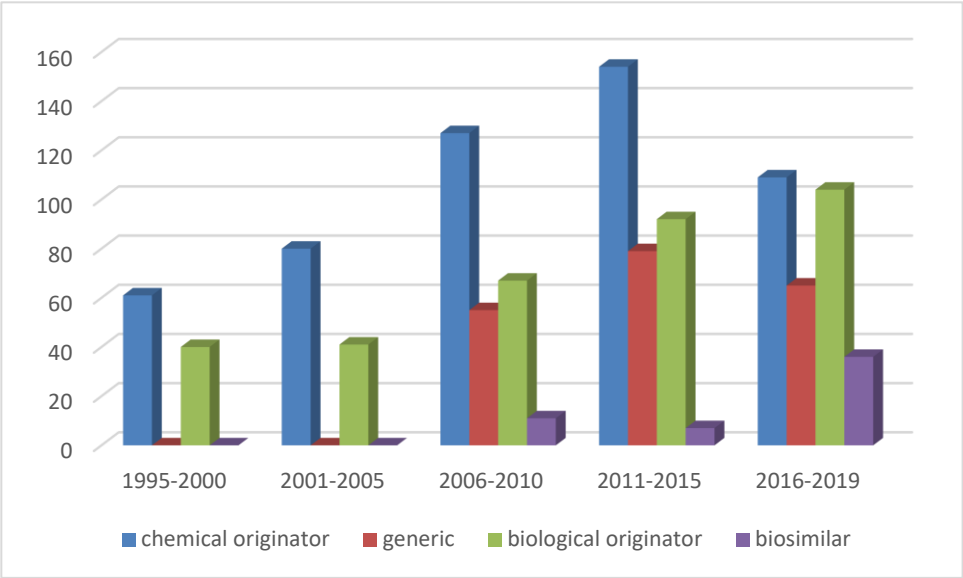

Figure 7: EMA Authorisations by medicine type (1995-2019).[69]

1.4.2 Biosimilars authorised in Europe

As the first biological medicinal products produced by DNA recombinant techniques were approved in the 1980s, in 2003 it was already envisaged that the patents of many biological medicines were to expire within the subsequent decade.[70] The first biosimilar which was approved in Europe in 2006 was Omnitrope® (containing somatropin).[71] Erythropoietin biosimilar was first approved in August/December 2007 and filgrastim biosimilars between September 2008 and June 2009.[72] Blandizzi and colleagues refer to these as the first-generation biosimilars. Infliximab was the first biosimilar mAb to be authorised by EMA under the brands Inflectra® and Remsima® in October 2013. However, they could only be marketed following patent expiry of Remicade® in February 2015.[73]

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69 Chart produced by author from data downloaded from "Medicines - Download medicine data," accessed January, 25, 2020, https://www.ema.europa.eu/en/medicines/download-medicine-data.

70 European Commission, *What you need to know about biosimilar medicinal products - A consensus information document*, 7.

71 Joan O'Callaghan et al., "Assessing awareness and attitudes of healthcare professionals on the use of biosimilar medicines: A survey of physicians and pharmacists in Ireland," *Regulatory Toxicology and Pharmacology* 88 (2017): 252-261, 252.

72 Grabowsky et al., "Biosimilar competition: lessons from Europe," Supplement Box S1, 1.

73 *Ibid*.

Figure 8 below shows the number of biosimilar authorisations in Europe by year showing an acceleration in recent years.

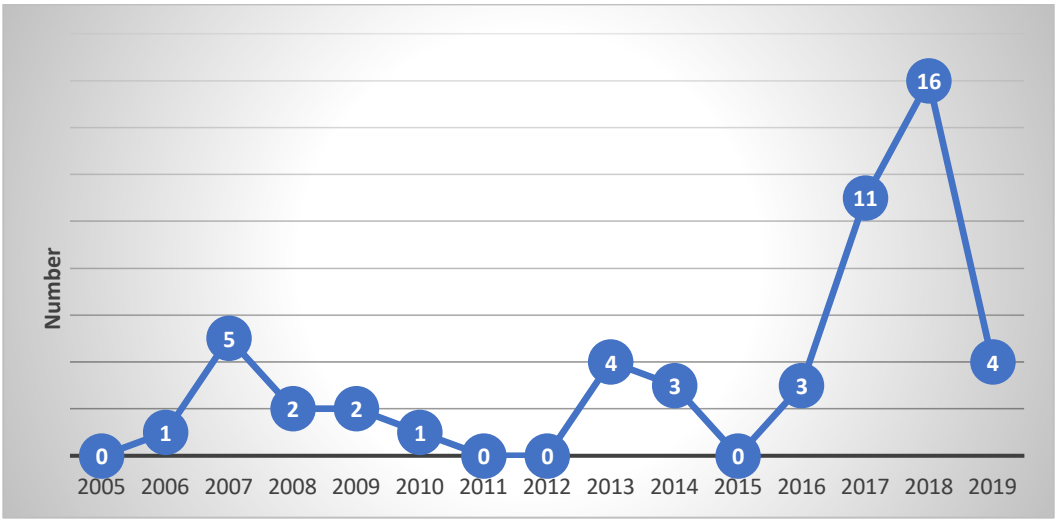

Figure 8: Number of EMA Biosimilar authorisations by year[74]

The number of biosimilar MAAs received by EMA is shown in Figure 9 below, where out of 91 applications submitted till July 2019, 80 were reviewed and 54 hold a valid marketing authorisation, 24 were withdrawn, whereas two received a negative opinion by the Committee for Medicinal Products for Human Use (CHMP), meaning that they were rejected, whilst 11 are still under review.

[74] Figure by author using data from: "Medicines - Download medicine data" European Medicines Agency, accessed January 25, 2020, https://www.ema.europa.eu/en/medicines/download-medicine-data.

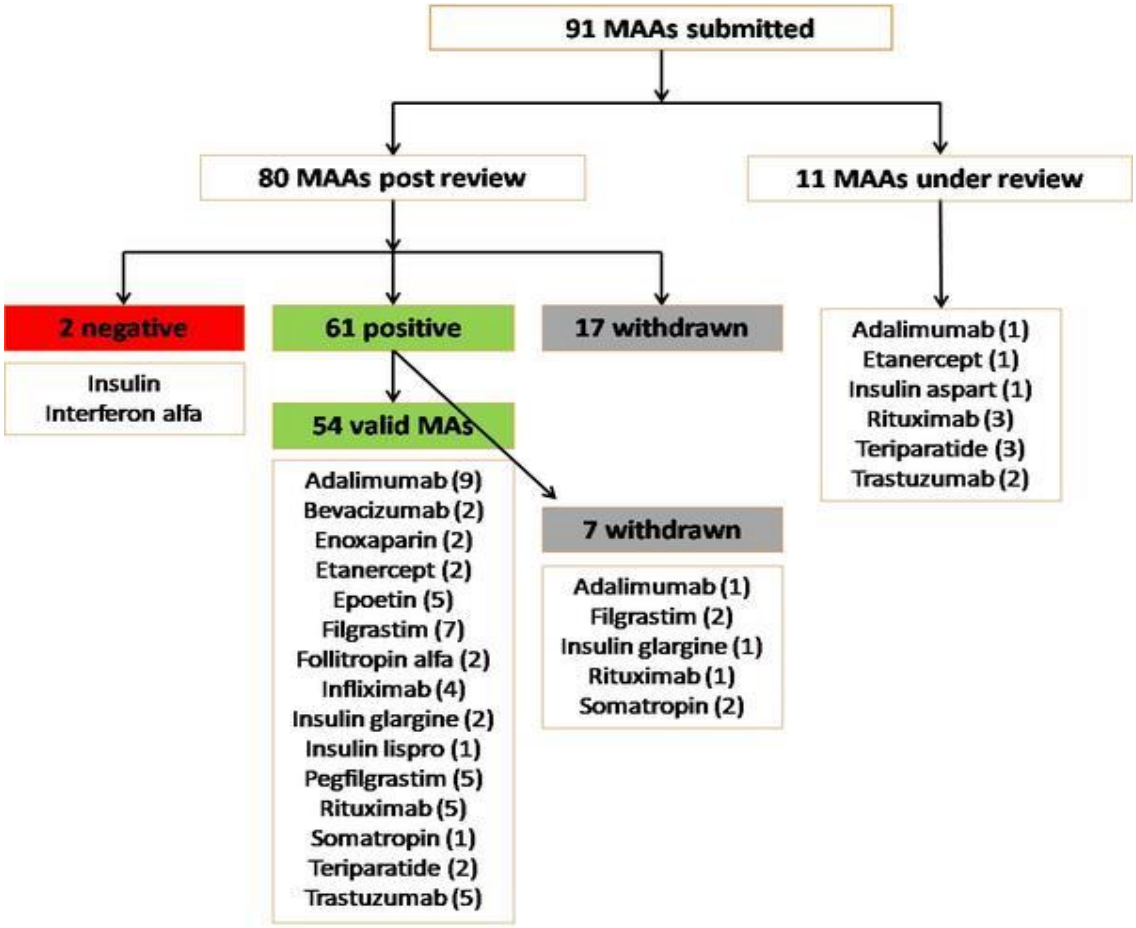

Figure 9: Marketing Authorisation Applications (MAAs) for biosimilars received by EMA till July 2019.[75]

In 2011 it was projected that by the year 2020, twenty biologicals were to come off-patent in Europe.[76] Biosimilars of mAbs and fusion proteins, referred to as second-generation biosimilars, were to have a significant impact on a large number of patients suffering from auto-immune disorders and cancer.[77] It is estimated that until July 2018, 260 biosimilars were approved globally, but only 52 were approved in Europe whilst a further 188 biosimilars were in development globally, 50 of which were in development

[75] "Biosimilars applications reviewed in the EU," GaBi (Generics and Biosimilars Initiative) online, posted October 04, 2019, accessed December 11,2019, http://gabionline.net/Biosimilars/Research/Biosimilars-applications-reviewed-in-the-EU.

[76] Paul Cornes, "The economic pressures for biosimilar drug use in cancer medicine," *Oncologie* 13 (2011): 222-233, 229.

[77] Blandizzi et al., "Transitioning from first- to second-generation biosimilars: An appraisal of regulatory and post-marketing challenges," 308.

in the US and Europe, while 61 of them were in Phase III trials.[78] In 2018 it was estimated that over 700 biosimilar products were in the pre-clinical or clinical phase.[79]

The above shows that for the same biological entity, one or more biosimilars were available on the market at the end of 2019 with 54 authorised biosimilars for only 16 unique biological molecules. The low number of biosimilars and their delay in reaching the market could be attributed to the intellectual property (IP) protection enjoyed by originator companies.

1.5 Intellectual property (IP) rights

The pharmaceutical industry invests huge sums of money in R&D with a high risk of failure of a medicine ever reaching the market. The expenditure on R&D in Europe in 2017 was of €35.2 billion which nearly doubled since the year 2000.[80] Manufacturers aim to recoup this cost of investment through various methods, including trade secrets, patent applications made very early during R&D and market exclusivity for a number of years. IP protection for biologicals contributes to the high cost of US$100-200 million in bringing a biosimilar to the market when compared to that of US$ 1-5 million for a generic medicine.[81]

1.5.1 Trade secrets

In the EU, trade secrets (referring to undisclosed know-how and business information) are protected at both European and national levels. At the EU level, Regulation 2309/93 provides protection against commercialisation of trade secrets contained in applications for medicinal products.[82] Furthermore, the European

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78 Walsh, "Biopharmaceutical benchmarks 2018," 1144.

79 Blandizzi et al., "Transitioning from first- to second-generation biosimilars: An appraisal of regulatory and post-marketing challenges," 308.

80 European Commission, *Report from the Commission to the Council and the European Parliament - Competition enforcement in the pharmaceutical sector (2009-2017),* 3.

81 Dzintars Gotham, "Cell line access to revolutionise the biosimilars market," *F1000 Research 7:537,* last updated 12 July 2018 (2018): 1-7, 2, https://doi.org/10.12688/F1000RESEARCH.14808.1

82 "Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a

Community is subject to the World Trade Organisation Agreement (WTA) on Trade-related aspects of IP rights (TRIPS).

A new directive, (EU) 2016/943 on trade secrets in Europe came into force in June 2016 aimed at achieving harmonisation for protecting and defending trade secrets across the EU.[83] Companies resort to trade secrets over and above patents so as to protect certain IP rights perpetually.[84] Data resulting from research, clinical trial data and manufacturing processes of biologicals and proprietary biological databases and cell-lines are examples of data considered to be trade secrets.[85] Such information is essential for the identity, purity and potency of the biological medicine.[86] In order to create a copy of the original biological, the originator cell line would be necessary for the "follow-on" applicants.[87] This creates a 'knowledge gap' between the originator company and the biosimilar company.[88]

This gap could be closed or eliminated through disclosure of manufacturing information. Dzintars Gotham, a physician affiliated with Imperial College, London, and who is known for his research in global health, has therefore proposed cell line access (CLA).[89] A similar proposal had been made by Knowledge Ecology International[90] and

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European Agency for the Evaluation of Medicinal Products," *Official Journal of the European Communities.* L214, Article 12.4 (24.8.93): 6.

83 "Directive (EU) 2016/943 of the European Parliament and of the Council of 8 June 2016 on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure," *Official Journal of the European Union*, L157 (15.6.2016).

84 Dechert LLP, "Trade secrets in the life sciences sector," posted April 25, 2018 (Lexology) 1-2, 1, accessed May 11, 2020, https://www.lexology.com/library/detail.aspx?g=09ecc65e-8daf-43d2-b131-48db583fb57d.

85 *Ibid.,* 2.

86 United States Committee on the Judiciary, *The law of Biological medicine: Hearing before the Committee on the Judiciary, United States; One-hundred and eight Congress Second Session, June 23, 2004,* (Washington: U.S. Government Printing Office, 2004), 10.

87 Yaniv Heled, "The case for disclosure of biologics manufacturing information," *Journal of Law, Medicine and Ethics* 4784 (2019): 54-78, 68.

88 Lisa Diependaele et al., "Why biosimilars are not the solution," *Journal of Law, Medicine and Ethics* Fall (2018): 776-790, 777.

89 Gotham, "Cell line access to revolutionise the biosimilars market," 2.

90 D Singhroy, "Policies about access to knowledge, data and materials to make it easier to make biosimilar drugs", May 2, 2017. Presented at the WHO Consultation on Biosimilar Drugs. Cited in *Ibid.*

Price & Rai who had proposed incentives to encourage disclosure of company secrets.[91] Gotham proposed that a living vial of the cell line is deposited to the regulatory authority on regulatory approval.[92] Diependaele and colleagues recommended some form of compensation to originator companies granting CLA in terms of a contractual agreement with the generic competitor.[93] Heled, however, claimed that developers could have access to whatever knowledge and material of the originator which was needed to create a copy at the expiration of the data exclusivity period.[94] This law professor argued that sample depositing and sharing requirements have already been incorporated in US patent as well as food and drug law, and therefore advised in favour of providing access to information of original biologicals.[95] EU law also already allows for sample depositing of cell lines, for example, for advanced therapeutic medicinal products and also for patenting. This would result in lower prices, increased competition and faster entry to the market as a result of lower manufacturing costs since reverse-engineering and comparability clinical studies will not be required.[96] Sharing of information will make the quality, efficacy and safety profile of "follow-on" biologicals very close to that of the originator, thus minimising the risk of harm whilst avoiding the ethical quagmire related to comparability studies.[97] Clinical benefits would also be achieved as the "follow-on" product will be interchangeable similar to batch-to-batch variations.[98] This proposal, however, requires further analysis from the legal and regulatory perspectives. The ethical aspect of trade secrets of living cell lines and data on manufacturing processes will be discussed in more detail in Chapter 4.

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91 W. Nicholson Price and A. K. Rai, "Drug Development. Are trade secrets delaying biosimilars?" *Science* 348, no. 6231 (2015): 188–189. Cited in *Ibid*.

92 *Ibid*.

93 Diependaele et al., "Why biosimilars are not the solution," 785.

94 Heled, "The case for disclosure of biologics manufacturing information," 58.

95 *Ibid*., 68.

96 Gotham, "Cell line access to revolutionise the biosimilars market," 2.

97 Heled, "The case for disclosure of biologics manufacturing information," 62.

98 *Ibid*.

1.5.2 Patent system

Patent law dates back to the Age of Enlightenment and is aimed at rewarding the inventor for disclosing one's invention to make it freely available for the benefit of society.[99] Patents were originally introduced in biotechnology by farmers over a hundred years ago.[100] These may cover "the active ingredient, formulations, methods of medical treatment, method of manufacturing and chemical intermediaries."[101] Originally, physicians and pharmacists were opposed to patenting of clinical and pharmaceutical inventions based on the 'moral economy' concept on the grounds of physicians' and pharmacists' virtue, protection of public health and preparation of remedies not on the Pharmacopoeia.[102] Finland granted the first patent of a living organism in 1843, whereas in 1873 the US Patent Office granted a patent to Louis Pasteur for a yeast free from organic germs of disease.[103] In the decade following World War II, the big capitalistic corporations of pharmaceuticals and the setting up of research facilities led to the need of patents in European countries.[104] Patents for genetic engineering were granted in the early 1960's. In 1992, the Group of Advisors to the European Commission on Ethics of Biotechnology in its considerations of ethical issues related to "the legitimacy of patenting living matter, the need to protect human dignity, the production of transgenic animals and the preservation of biodiversity" stated that

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99 European Union, "Opinion on ethical questions arising from the Commission proposal for a Council Directive on legal protection for biotechnological inventions," Opinion of the Group of Advisors on the Ethical Implications of Biotechnology to the European Commission, (September 30, 1993), 1, accessed May 11, 2020, https://op.europa.eu/en/publication-detail/-/publication/a01f0708-252b-11e9-8d04-01aa75ed71a1/language-en/format-PDF/source-120515586.

100 "Biotechnology patents at the EPO," European Patent Office, accessed December 12, 2019, https://www.epo.org/news-issues/issues/biotechnology-patents.html.

101 Nicoleta Tuominen, "Patenting strategies of the EU pharmaceutical industry - Crossroad between patent law and competition policy," European Legal Studies - Research Papers in Law 1 (2011): 1-29, 13.

102 Jean-Paul Gaudillière, "How pharmaceuticals became patentable: the production and appropriation of drugs in the twentieth century," *History and Technology* 24, no. 2 (2008): 99-106, 101, https://doi.org/10.1080/07341510701810906.

103 "Opinion on ethical questions arising from the Commission proposal for a Council Directive on legal protection for biotechnological inventions," 5.

104 Gaudillière, "How pharmaceuticals became patentable: the production and appropriation of drugs in the twentieth century," 101.

there are no ethical grounds against patenting inventions relating to living matter, though it recognised some reservation for biological inventions. It concluded that there are no ethical objections on patenting of biotechnological inventions, though genes and partial gene sequences whose functions are unknown are non-patentable.[105] The group agreed to patenting of inventions related to living matter wherever ethically possible.[106]

Intellectual property rights were regulated by the World Trade Organisation (WTO) on a global level for WTO member countries through the setting up of TRIPS which, since 1994 mandates that medicinal products be covered "by patent protection for a minimum of twenty years from the filing date of a patent application for any pharmaceutical product or process that fulfils the criteria of novelty, inventiveness, and usefulness."[107] Since the year 2000, in the EU an inventor may choose to apply for a national patent or with the European Patent Office (EPO), in which case the inventor should indicate the Contracting State this would apply to within the EU.[108]

1.5.3 Regulatory incentives

Originator companies aim to retain monopoly status by setting high barriers to entry to competitors in order to recoup investment costs, the R&D costs and the high risk of failure.[109] From a patent period of 20 years, generally, 12-13 years are required for a new active substance to finally reach the market, which means that only eight years of patent protection remain, which is not considered sufficient by originator companies to obtain a return on investment.[110] The European Commission (EC) legislator argued that "without effective means of enforcing intellectual property rights, innovation and

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105 "Opinion on ethical questions arising from the Commission proposal for a Council Directive on legal protection for biotechnological inventions," no. 1.

106 *Ibid*., no. 2.

107 Sisule Musungu, "Intellectual property and access to medicines," in *Management Sciences for Health*, ed. Marian Ryan (Virginia: Management Sciences for Health, Inc 2012), 3.6, https://www.msh.org/sites/default/files/mds3-jan2014.pdf.

108 Tuominen, "Patenting strategies of the EU pharmaceutical industry - Crossroad between patent law and competition policy," 9.

109 Tuominen, "Patenting strategies of the EU pharmaceutical industry - Crossroad between patent law and competition policy," 8.

110 EFPIA, *The Pharmaceutical Industry in Figures - Key Data 2018*, 6.

creativity are discouraged and investment diminished."[111] The EC therefore has provided a number of incentives to the pharmaceutical industry through different regulations with the aim of protecting innovation and accessibility to newer therapies, whilst keeping a balance to provide accessibility through more affordable generic or biosimilar medicines.[112] Various regulatory mechanisms were introduced in Europe which include the Supplementary Protection Certificate (SPC), data exclusivity through the "8+2+1" regime, Paediatric use marketing authorisation (PUMA) and marketing exclusivity for orphan drugs.

1.5.3.1 Supplementary Protection Certificate (SPC)

As per Regulation (EC) 469/2009,[113] at the end of the patent life, a maximum five-year extension may be granted to a patent right. The Supplementary Protection Certificate (SPC) may be extended by a further six months if studies are performed in the case of paediatric indications, so as to ensure that children also benefit from innovative therapy, referred to as the Paediatric Investigation Plan (PIP) (Refer to Figure 10.) Multiple SPCs exist for the same product across Europe as an SPC is granted by the national patent office. Different interpretations of the regulation by national patent offices and courts resulted in inconsistencies across Member States (MSs) which led to a ruling by the European Court of Justice (CJEU) that concluded that there was the risk that the SPC mechanism was being abused.[114] An SPC manufacturing waiver was approved by the European Parliament and Council[115] in April 2019 allowing EU-based generic and biosimilar companies to produce SPC-protected medicines only for export to non-EU countries where protection of the SPC expired or is non-existent or for

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[111] Tuominen, "Patenting strategies of the EU pharmaceutical industry - Crossroad between patent law and competition policy," 7.

[112] European Commission, *Report from the Commission to the Council and the European Parliament - Competition enforcement in the pharmaceutical sector (2009-2017)*, 21.

[113] "Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products," *Official Journal of the European Union*, L152 (16.6.2009).

[114] "European SPC waivers come closer to becoming a reality," GaBi online (Generics and Biosimilars Initiative), posted February 01, 2019, http://gabionline.net/Guidelines/European-SPC-waivers-come-closer-to-becoming-a-reality.

[115] amended by Regulation (EU) 2019/933 of the European Parliament and of the Council

stockpiling during the final 6 months of an SPC before entry into the EU market.[116] However, Médecins Sans Frontières (MSF) argued that the changes made to the SPC manufacturing waiver do not address the issue of affordability and accessibility of medicines in Europe.[117] The Corporate European Observatory (CEO) criticized the pharmaceutical industry's strong representation on the Commission's advisory groups, which could have influenced EU decisions related to the SPC manufacturing waiver.[118]

1.5.3.2 Data exclusivity through the "8+2+1" regime

The 8+2+1 regime harmonises the EU period of protection of data for innovative products, which starts at the point of global marketing authorisation. It provides eight years of data protection, (during which the data of the reference product, which is considered as trade secrets, cannot be used by other manufacturing companies to obtain marketing approval for the generic product), plus two years market exclusivity (during which regulatory authorities cannot grant a marketing authorisation to the generic product), plus one year for new therapeutic indications, such that an originator product may benefit from a maximum of 11 years data exclusivity (Refer to Figure 10).[119] An investigation that was commissioned by the government of the Netherlands to evaluate the cumulative costs of the supplementary protections to the Dutch healthcare system for three drugs did not confirm whether innovation was improved with the 8+2+1 regimen, thus calling for further investigation.[120]

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116 "European SPC waivers come closer to becoming a reality."

117 Rachel Tansey, *High prices, poor access: What is Big Pharma fighting for in Brussels?* ed. Katharine Ainger, (Brussels: Corporate Europe Observatory, May 2019), Chapter 4, https://corporateeurope.org/en/2019/05/high-prices-poor-access-eu-medicines-market-and-big-pharma.

118 *Ibid*., 1.

119 Carolyn Hathaway et al., "Exclusivity strategies in the United States and European Union," *Food and Drug Law Institute* no. 3 (May/June 2009): 34-39, 37.

120 European Parliament, *Options for improving access to medicines – European Parliament Resolution of 2 March 2017 on EU options for improving access to medicines*, (2016/2057(INI) No. P8_TA (2017)0061. (Brussels: European Parliament, 2017,) Recommendation No. 27. https://www.europarl.europa.eu/doceo/document/TA-8-2017-0061_EN.html.

1.5.3.3 Paediatric-use marketing authorisation regulation (PUMA)

An additional data exclusivity of 8 years and market exclusivity of 10 years from the date of marketing authorisation may be granted for those medicinal products authorised exclusively for children, and which are not protected by an SPC or SPC qualifying patent. Its aim is to drive innovation in medicines for children, especially in oncology and neonatology, which is still lacking behind.

1.5.3.4 Marketing exclusivity for orphan drugs

An orphan medicine is a "medicine for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10,000 people in the EU or where the medicine is unlikely to generate sufficient profit to justify research and development costs." [121] Supplementary marketing exclusivity for orphan medicines is granted at the point of marketing authorisation for each specific indication (refer to Figure 10) and is aimed to protect innovation of medicines intended for rare diseases or where the medicine is unlikely to generate sufficient profit due to very high R&D costs. It is known, unfortunately, that research tends to be focused on the development of 'blockbuster' drugs which render a high return on investment, resulting in the disproportionate allocation of resources, at the expense of leaving other diseases untreated, which is a violation of the principle of justice.[122] The EP recommended reviewing the prioritization system of unmet medical needs and the definition of orphan drug designation by revising the rare disease register, whilst calling on the Commission to revise the requirements of public funded research in this regard.[123] The patency and regulatory mechanisms are very complex and the relationship between the various mechanisms are illustrated in Figure 10 below.

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[121] Definition of orphan medicine, accessed October 05, 2019, https://www.ema.europa.eu/en/glossary/orphan-medicine.

[122] Michael Payette and Jane M. Grant-Kels, "Brand name versus generic drugs: The ethical quandary in caring for our sophisticated patients while trying to reduce health-care costs: Facts and controversies," *Clinics in Dermatology* 31 (2013): 772-776, 775.

[123] European Parliament, *Options for improving access to medicines – European Parliament Resolution of 2 March 2017 on EU options for improving access to medicines*, Recommendation No. 76.

From the above analysis, it appears that the various IP protection incentives could be the result of the strong influential of pharmaceutical industry's representation on the European Commission's advisory boards. This raises ethical questions vis-a-vis conflicting interests, which will be discussed in Section 4.1.

1.5.4 Manufacturers' strategies to extend patent protection

The pharmaceutical industry employs various strategies termed as '*evergreening'* to further extend patent protection with the aim to retain monopoly.[124] These strategies include:

Patent "thickets" or "clusters": The originator pharmaceutical company files in numerous patents for the same molecule, which may vary from a broad patent to more specific patents. A classic example is Humira (adalimumab), to treat inflammatory disease, which is known to have a "patent thicket" in Europe of 76 patent applications.[125] Generic companies are deterred from applying for a marketing authorisation, or otherwise risk litigation, which in itself would take years to resolve, such that the originator company would still have gained more time in patent protection.

Secondary patents or follow-on patents: Innovator companies file for applications for improvements to the medicine just before expiry of the patent so as to extend the product's life cycle, presenting delays in competition. For example, a new variation, such as a different formulation or different salt.

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[124] Tuominen, "Patenting strategies of the EU pharmaceutical industry - Crossroad between patent law and competition policy," 13.

[125] W. Nicholson Price II and Arti K. Rai, "How logically impossible patents block biosimilars," *Nature Biotechnology* 37 (2019): 862-863, 862, https://doi.org/10.1038/s41587-019-0196-x.

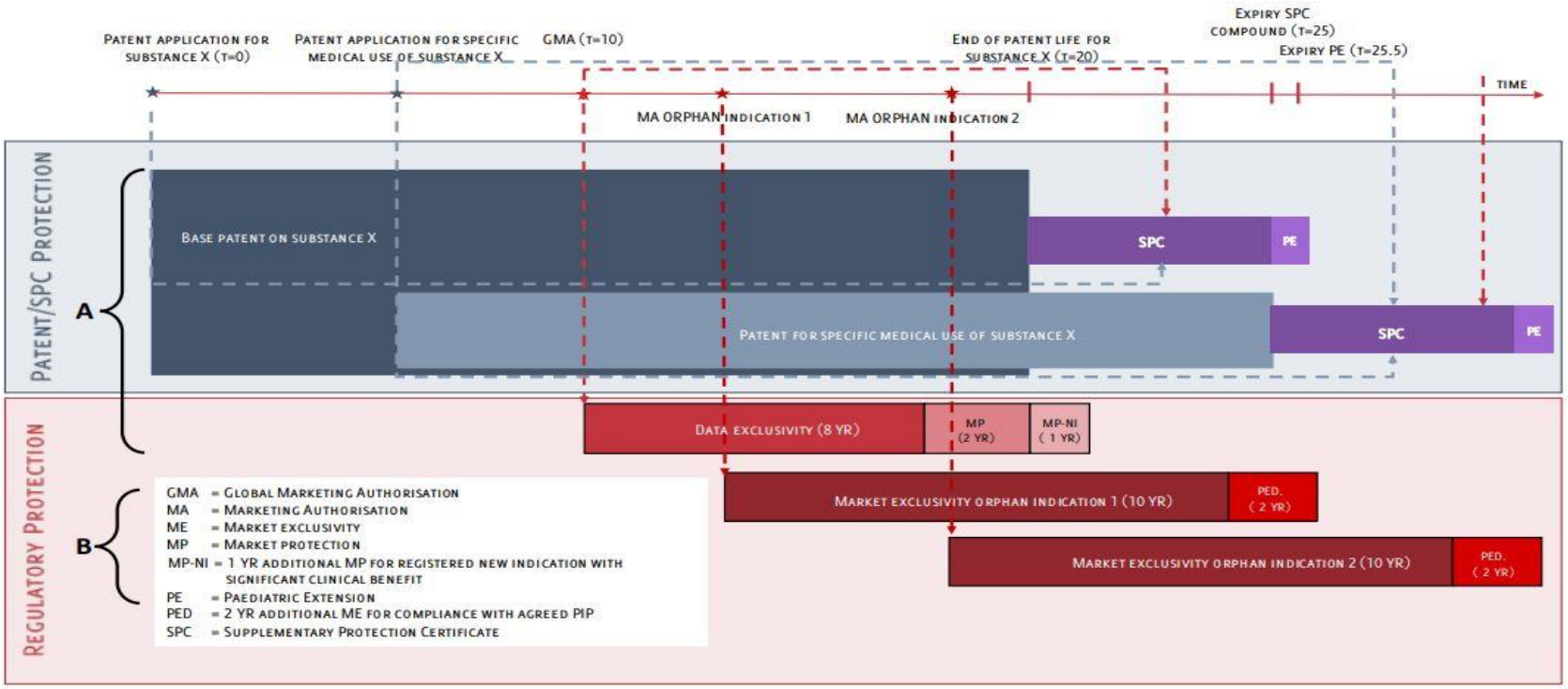

Figure 10: Relations between the various Intellectual Property mechanisms in Europe[126]

Blue part - patency period and its extension through the SPC; for a basic patent of Substance X, it is extended to 25 years; extended by 6 months for paediatric indications; for a specific medical use of Substance X, patency and SPC period commence at the date of patent application for that medical use.

Red part - data exclusivity ("8+2+1" regime); for orphan medicines, market exclusivity rights of maximum of 10 years, extended by two years for paediatrics; for a new indication of the orphan medicine, the market exclusivity right commences at the time of market authorisation for the new indication.]

[126] Thyra de Jongh et al., *Effects of supplementary protection mechanisms for pharmaceutical products*, (The Netherlands: Technopolis Group Final Report, May 2018), 155.

Patent settlements or Pay-for-delay: "A variety of diverse agreements between patent owners and alleged infringers that involve a transfer of consideration from the patent owner to the alleged infringer" lead to disruption to free competition.[127] The validity of such agreements would need to be considered under cartel law or the scope of a property right.[128]

Withdrawing Marketing Authorisation:[129] The originator product will no longer be available on the market and is replaced by a new formulation such that generic companies cannot apply for an abridged Marketing Authorisation whilst the originator product will be available only in the new formulation at a higher price.

Downgrading the generic name:[130] Bad naming of generic brands by originator companies such that healthcare professionals are reluctant to use the generic product and the originator product remains the preferred choice.

Mergers between originator and biosimilar companies:[131] Acquisitions or mergers between originator and biosimilar companies are made so as to achieve control over which product to place on the market preventing biosimilars from entering the market.

Offer bonuses and other incentives to healthcare professionals:[132] Originator companies woo healthcare professionals to favour their products making it difficult to shift to generic products.

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127 Christopher M Holman, "Do reverse payment settlements violate the antitrust laws?" *Santa Clara Computer & High Tech Law Journal* 23 (2007): 489. Cited in Tuominen, "Patenting strategies of the EU pharmaceutical industry - Crossroad between patent law and competition policy," 16.

128 Tuominen, "Patenting strategies of the EU pharmaceutical industry - Crossroad between patent law and competition policy," 15.

129 European Commission, *Report from the Commission to the Council and the European Parliament - Competition enforcement in the pharmaceutical sector (2009-2017),* 27.

130 *Ibid*., 28.

131 *Ibid.,* 37.

132 Tansey "High prices, poor access: What is Big Pharma fighting for in Brussels?" Box 1.

Collusion between competitors for price fixing:[133] Hidden agreements between competitors for products within the same therapeutic class could result in fixing an agreed price such that the price of medicines remains high.

The 'evergreening' strategies employed by pharmaceutical industry are indicative of a lack of transparency and conflicting interests between the different stakeholders. This raises ethical concerns which will be discussed in Section 4.1.

1.5.5 Impact of intellectual property rights

Biological medicines are considered to be prohibitively expensive with prices ranging in the thousands of Euro, making them unaffordable to patients and governments.[134] The European Federation of Pharmaceutical Industries and Associations (EFPIA), which represents the European pharmaceutical industry, defends the high prices attributing them to the high research and development costs, estimated in 2016 at €1,926 million (US$2,558 million dollars).[135] Tuominen, however, observed that originator companies invest heavily in marketing and retain huge profits.[136] For example, the price for Humira (the originator for Adalimumab) in the US increased by 18% annually from 2012 to 2016 and also in later years as a result of monopoly.[137]

As per estimates by Gotham, the costs of manufacturing for the active ingredient of blockbuster drugs are "0.001-6% of the current lowest prices in the US and 0.004-14% of prices in the UK."[138] In addition, manufacturing companies invest only 15% of the profits in R&D whilst one third to two thirds of R&D costs are covered through public

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133 European Commission, *Report from the Commission to the Council and the European Parliament - Competition enforcement in the pharmaceutical sector (2009-2017)*, 33.

134 Tansey, "High prices, poor access: What is Big Pharma fighting for in Brussels?" 1.

135 Joseph A. DiMasi et al., "Innovation in the pharmaceutical industry: New estimates of R&D costs," *Journal of Health Economics* 47 (2016): 20-33. Cited in EFPIA, *The Pharmaceutical Industry in Figures - Key Data 2018*, 6.

136 Tuominen, "Patenting strategies of the EU pharmaceutical industry - Crossroad between patent law and competition policy," 5.

137 Price II and Rai, "How logically impossible patents block biosimilars," 862.

138 Gotham, "Cell line access to revolutionise the biosimilars market," 1.

funding, for example through Horizon 2020 and Innovative Medicines Initiative (IMI).[139] The European Commission confirmed that part of research is public funded or funded through research facilities (universities and specialized laboratories of research).[140] The CEO reported that monopolies are resulting in excessive prices of innovative biologicals which are disproportionate to the research and development costs, resulting in accessibility problems.[141]

High prices may result from agreements or cartels between associations which are prohibited by the Treaty on Functioning of the European Union (TFEU) as they may disrupt free competition within the internal market (Article 101), and may lead to abuses related to the dominant position on the market (Article 102).[142] Regulation (EC) No 1/2003 empowers the EU Commission and National Competent Authorities (NCAs) to investigate any arrangements that do not observe the TFEU.[143] Due to different interpretations, the EP called on the Court of Justice of the EU (CJEU) "to clarify, in accordance with Article 102 TFEU, what constitutes an abuse of a dominant position by charging high prices."[144] The EC also called for more transparency in costs of R&D including those obtained from public funding and costs for marketing;[145] monitoring and investigating patent settlements (pay-for-delay);[146] and enforcement of EU competition legislation.[147]

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139 Tansey, "High prices, poor access: What is Big Pharma fighting for in Brussels?" Chapter 1.

140 European Commission, *Report from the Commission to the Council and the European Parliament - Competition enforcement in the pharmaceutical sector (2009-2017)*, 19.

141 Tansey, "High prices, poor access: What is Big Pharma fighting for in Brussels?" Chapter 1.

142 *Ibid*.

143 European Commission, *Pharmaceuticals: EU refines intellectual property rules*, (European Commission, 17/04/2019), 7, https://ec.europa.eu/growth/content/pharmaceuticals-eu-refines-intellectual-property-rules_en.

144 European Parliament, *Options for improving access to medicines – European Parliament resolution of 2 March 2017 on EU options for improving access to medicines*, Recommendation No. 97.

145 *Ibid*., Pharmaceutical Market Point No.9.

146 European Parliament, *Options for improving access to medicines – European Parliament resolution of 2 March 2017 on EU options for improving access to medicines*, Recommendation No.81.

147 *Ibid*., Recommendation No. 83.

The exorbitant prices of the blockbusters, especially mAbs, are presenting accessibility problems also in developed countries, such that European Governments are considering using the Doha Declaration through the use of the compulsory licencing for biologicals.[148] In the 2001 Doha Declaration, WTO members declared that TRIPS "should be implemented in a manner supportive of WTO members' right to protect public health and, in particular to promote access to medicines for all," with the aim of protecting health of populations in developing countries.[149] A compulsory licence "allows a patent to be used without the consent of the patent holder for a reasonable royalty payment."[150] Governments may use compulsory license allowing production or importation or procurement of generic or biosimilar medicines where the price of the originator medicine is considered to be unaffordable.[151] However, it may not be possible to obtain compulsory licence for medicinal products which are authorised through the centralised procedure due to the EU data exclusivity directive (known as the '8+2+1' regime), which applies even when a patent expired or a compulsory licence was issued.[152] The EP called on the Commission and MSs to make use of flexibilities under the WTO TRIPS agreement and to coordinate and clarify their use where necessary.[153] The trade agreements could raise ethical issues with regards to equitable access, which will be discussed in Section 4.3.3.

1.6 Conclusion

The product life cycle for biologicals is unique as originators do not face the 'patent cliff' as a result of the complex manufacturing process of a biosimilar, which involves the

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148 Pascal Boulet et al., "European Union Review of Pharmaceutical Incentives: Suggestions for Change," in *Medicines Law and Policy*, ed. Jacquelyn Veraldi and Kaitlin Mara, (Medicines Law and Policy: June 2019), www.medicineslawandpolicy.org, 28.

149 Musungu, "Intellectual property and access to medicines," 3.5

150 "Improving access to medicines: the Doha Declaration on the TRIPS Agreement," GaBi online (Generics and Biosimilars Initiative), posted September, 06, 2019, accessed December 11, 2019, http://www.gabionline.net/Generics/Research/Improving-access-to-medicines-the-Doha-Declaration-on-the-TRIPS-Agreement.

151 "Improving access to medicines: the Doha Declaration on the TRIPS Agreement,"

152 Boulet et al., "European Union Review of Pharmaceutical Incentives: Suggestions for Change," 28.

153 European Parliament, *Options for improving access to medicines – European Parliament resolution of 2 March 2017 on EU options for improving access to medicines*, Recommendation No. 98.

development of a new cell line through reverse engineering. By December 2019 there were only 54 authorised biosimilars in Europe for 16 unique biological molecules compared to 481 authorised biologicals. The various regulatory mechanisms to protect the innovation, including trade secrets of cell lines and EU regulatory incentives, resulted in high prices of originator biologicals. These are disproportionate to investment costs on R&D, resulting in delays in biosimilars reaching the market, and contribute to the problem of accessibility. The pharmaceutical industry also implements 'evergreening' strategies, which involve hidden agreements between pharmaceutical companies and other stakeholders, that raise ethical questions vis-à-vis conflicting interests. Various strategies were implemented by the European Commission and governments with the aim to address the abuse related to IP protection, with limited success. As discussed in this chapter, this was possibly due to the existing conflicting interests with the pharmaceutical industry, and will be discussed in detail in Section 4.1. In the next chapter, a deeper understanding of the biosimilar regulation in Europe will be provided.

Chapter 2: Regulation of biosimilars in Europe

As seen in the previous chapter, following completion of R&D, a marketing authorisation application is submitted to the regulatory authority so as to seek authorisation to place the medicine on the market. This chapter will now provide an overview of the European regulatory medicines system covering the authorisation and post-authorisation of medicinal products in Europe, with an emphasis on biologicals. A detailed illustration of the Biosimilar Regulatory Pathway, and other regulations for extension of authorisation to other clinical indications (known as extrapolation) and post-market surveillance will be presented with the aim of identifying ethical issues. Finally, since globalisation of the pharmaceutical industry raises the need for harmonization of medicines regulations, these will be explored further.

2.1 Medicines regulation in Europe

The primary objective of medicines regulation is to ensure a high level of public health protection through set standards built on three criteria, namely, quality, safety and efficacy of medicines.[1] As already illustrated in Section 1.2.2, the EU legal framework ensures that for new medicines, Marketing Authorisation applicants (MAA) are required to provide documentation that shows that the medicinal product is of suitable quality and that it provides a positive benefit-to-risk balance on the basis of results of clinical trials, which must follow EU legislation.

A medicinal product may be authorised either through a centralised procedure or by national competent authorities through a mutual recognition, decentralised (Refer to Appendix A) or national procedure following assessment of the marketing authorisation application by the relevant regulatory authority.[2] In Europe, the requirements and procedures for marketing authorisation of medicinal products were laid down in

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1 "Legal framework governing medicinal products for human use in the EU," European Commission accessed January 13, 2020, https://ec.europa.eu/health/human-use/legal-framework_en.

2 *Ibid.*

Directive 2001/83/EC[3] for national procedures, and Regulation (EC) No 726/2004 for centralised procedures.

The centralised procedure applies only for innovative medicines which must be assessed centrally and if found to have a positive benefit-to-risk, a single marketing authorisation is issued by the European Commission (EC).[4] This 'mandatory scope' is set through the Annex of Regulation (EC) 726/2004, where innovative medicines include biotechnologically derived medicinal products and those designated as orphan medicinal products among others.[5]

Pharmaceutical companies are required to submit a full product dossier for the medicinal product for active substances (see definition in Appendix A) in line with Directive 2001/83/EC Annex I which was amended by Directive 2003/63,[6] the requirements of which are set out in Table 3 below.

Table 3: Annex I Part I Standardised Marketing Authorisation dossier requirements

Module 1	Administrative information
Module 2	Summaries and overviews of quality, non-clinical and clinical data
Module 3	Chemical, pharmaceutical and biological information
Module 4	Reports of non-clinical studies including Pharmacokinetic (PK), Pharmacodynamic (PD) and Toxicology studies
Module 5	Human clinical study reports including bioavailability and bioequivalence, PK, PD and efficacy & safety studies

[3] "Directive 2001/83/EC of the European parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use" *Official Journal of the European Union*, L311 (28.11.2001).

[4] European Commission, *What you need to know about biosimilar medicinal products - A consensus information document*, (Brussels: European Commission, 2013): 1-41, 9.

[5] "Regulation (EC) No 726/2004 of the European Parliament and of The Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency," *Official Journal of the European Union*, (Amended 05.06.2013), 1-70, 33.

[6] "Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use," *Official Journal of the European Union*, L159/46, 49 (27.6.2003).

As per Directive 2001/83, Article 8 (3), a full product dossier is required for biological medicines to support the marketing authorisation application. [7] The requirements are set out in Annex I Part III (1) of Directive 2003/63/EC.[8]

Orphan medicines are indicated for rare diseases and the requirements for authorisation are detailed in Directive 2001/83/EC Part III (5),[9] and in Regulation (EC) No 141/2000. They may be either of a chemical structure or biological medicines, in which case the regulatory requirements for these product types will also apply.

Generic companies can utilise an abridged authorisation procedure by referring to data of Phase I, II and III clinical trials from already authorised medicines. They are only required to demonstrate that the generic product is "bioequivalent", that is, "if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailability after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same." [10] The PK properties must be similar to the originator as demonstrated through bioavailability and bioequivalence studies required through Directive 2001/83/EC Module I, 2 & 3 of Part I of Annex I.[11] The abridged authorisation procedure permits companies to seek authorisation for generic medicines within two to five years from date of application of MA, at less expensive production costs. The provisions laid in Directive 2001/83 Article 10(1)(a) (iii) for essentially similar medicinal products (also referred to as generics)[12] are

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7 "Directive 2001/83/EC of the European parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use," 74.

8 "Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use," 51.

9 *Directive 2001/83/EC of the European parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human* Use, Consolidated document, (16.11.2012), 1-176, 163, accessed June 20, 2020, https://ec.europa.eu/health/sites/health/files/file/eudrale/vol1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf.

10 European Medicines Agency - *Committee for Proprietary Medicinal Products (CPMP), Note for Guidance on the Investigation of Bioavailability and Bioequivalence*, Committee for Proprietary Medicinal Products (CPMP), London, 26 July 2001) 1-18, 4.

11 *Directive 2001/83/EC of the European parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human* Use, Consolidated document, (16.11.2012), 152, Annex I, Part II.

12 *Ibid*., 144.

not considered to be sufficient for similar biological medicines. Specific requirements were set out in Part II (4) for similar biological medicinal products (commonly known as biosimilars).[13]

Regulation (EC) 726/2004 (Article 9) defines the time frames for the Committee for Medicinal Products for Human Use (CHMP) within the European Medicines Agency (EMA) to complete the assessment of the product dossier submitted by the MAH. Based on the CHMP's recommendation, the EC then issues a legally binding decision to authorise the product in Europe.[14]

The regulatory process of biosimilars will be explained in more detail in Section 2.2.

2.2 Regulation of biosimilars in Europe

The EMA set the requirements for an abridged authorisation procedure for similar biological medicines, referred to as biosimilars, in Directive 2001/83/EC amended in 2003 by Directive 2003/63/EC.[15] Additional data must be provided by the applicant of the MA, as set out in Module 4 and Module 5 of Table 3, as for the reference biological medicinal product but with some differences as per guideline for the comparability of biosimilars to the reference medicinal products which was adopted by EMA's Committee for Medicinal Products for Human Use (CHMP) in 2004, (last updated in 2014).[16] It ensures a transparent regulatory stepwise approach,[17] which covers:

(i) Pharmaceutical quality analysis;

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13 *Directive 2001/83/EC of the European parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human* Use, Consolidated document, 153.

14 "Regulation (EC) No 726/2004 of the European Parliament and of The Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency," 14.

15 "Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use*," Official Journal of the European Union*, L159/49 (27.6.2003).

16 European Medicines Agency (EMA), *Guideline on similar biological medicinal product (Committee for Medicinal Products for Human Use* (CHMP), October 2014), 437/04 Rev 1, 1-7, 4.

17 *Ibid.*, 6.

(ii) Comparative quality studies with the reference medicinal product authorised in the European Economic Area (EEA) instead of the non-clinical studies needed for reference product;

(iii) Comparative studies to demonstrate safety and efficacy, PK/PD and immunogenicity;

(iv) An RMP during post-licensing phase (which will be discussed in more detail in Section 2.5.)

Figure 11 shows the data comparison requirements for approval between biosimilar and reference products.[18]

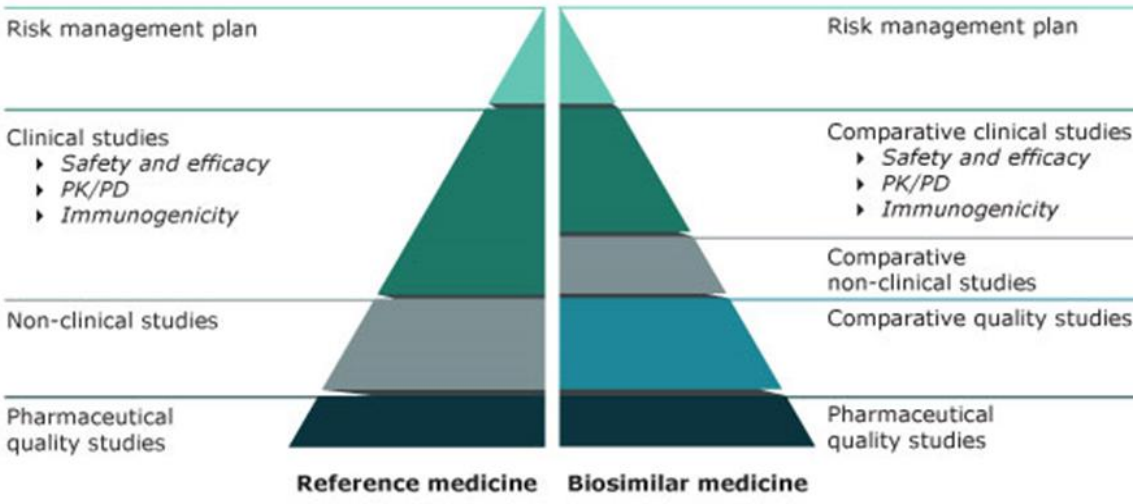

Figure 11: Comparison of data requirements for approval of a biosimilar versus the reference medicine[19]

The comprehensive comparability studies with the reference biological medicine must demonstrate that:

> the biological medicine is highly similar to the reference product not withstanding variability inherent to all biological medicines and that there are no clinically meaningful differences between the biosimilar and the reference medicine in terms of quality, safety and efficacy.[20]

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18 *Directive 2001/83/EC of the European parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use*, Consolidated document, 153.

19 European Medicines Agency, *Guideline on similar biological medicinal product*, 6.

20 European Medicines Agency, "Biosimilar medicines: Overview," accessed October 10, 2019, https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview.

The studies that are required depend on the complexity of the biological molecule, the clinical indications and the degree of immunogenicity, and additional clinical in vivo studies would be required if there are significant physicochemical and biological characterisation differences.[21] Over the years, EMA set up product specific scientific guidelines for different classes of molecules, such as medicinal products containing recombinant erythropoietin, insulin and insulin analogues, Granulocyte colony-stimulating factor (G-CSF), low molecular weight heparin (LMWH), beta-interferon, recombinant follicle stimulating hormone (FSH), somatropin, monoclonal antibodies (mAbs) and biologically-derived proteins as active substance.[22] The reference biological product to be used as comparator should be authorised in the EEA but for certain in vivo clinical studies and non-clinical studies a comparator product authorised in other countries outside EEA but with similar scientific and regulatory standards may be considered.[23]

Biosimilar companies face various challenges in performing comparability studies, namely, the difficulty to obtain stock of the batch of the originator product, changes to the dosage strength or formulation of the originator product, and the continuous changes (improvement in the manufacturing process) of the innovator that could result in changes to the protein structure.[24] In fact, 35 changes were reported to Remicade®, 20 for Enbrel® and 15 for Humira®.[25] The 'residual uncertainties' surrounding biosimilars require that comparability studies be undertaken for each route of administration, for example, the sub-cutaneous (S.C.) and intravenous (I.V.) route.[26]

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21 European Medicines Agency, *Guideline on similar biological medicinal products*, 6.

22 European Medicines Agency, "Multidisciplinary: biosimilar - Overarching biosimilar guidelines," accessed September 23, 2019, https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar#Product-specific biosimilar guidelines.

23 "Multidisciplinary: biosimilar - Overarching biosimilar guidelines."

24 Francois-Xavier Frapaise, "The End of Phase 3 Clinical Trials in Biosimilars Development?" *BioDrugs* 32 (2018): 319–324, 320, https://doi.org/10.1007/s40259-018-0287-0.

25 *Ibid.,* 320.

26 Hakan Mellstedt et al., "The challenge of biosimilars," *Annals of Oncology* 19 (2008): 411-419, 415.

The Biosimilar Regulatory Pathway should aim to avoid unnecessary clinical trials provided that healthcare professionals have access to reliable information on biosimilars.[27] Advances in technology may bring about changes in biosimilar approval requirements by regulatory agencies. For smaller molecules there is no need of animal studies but PK and PD Phase I clinical studies on healthy volunteers should suffice.[28] For anti-cancer biosimilars, the comparability data on safety and efficacy is very limited resulting in greater reliance on post-marketing pharmacovigilance safety data.[29] This is endorsed by the European CanCer Organisation (ECCO), which accepts in vitro testing rather than clinical studies for biosimilar Infliximab, but requires long-term safety monitoring.[30]

In 2017, the US FDA and the EMA considered statistical approaches (namely, state-of-the-art orthogonal methods) to evaluate analytical similarity, which should be sufficient to compare the structural and biological activity between reference biologicals and candidate biosimilars.[31] Chemistry, Manufacture and Controls (CMC)/PK data and well-designed post-marketing studies should replace the very expensive Phase III clinical studies which are presenting a barrier for companies to develop biosimilars.[32] Based on ethical principles, EMA considered reducing the clinical studies so as to avoid duplication of expensive clinical trials.[33] In fact, a specific comparative efficacy study is no longer required for insulin, LMWH, and (peg)filgrastim, and instead physicochemical, functional, comparative PK and PD studies are sufficient, but not for the more complex biologicals with multiple indications where comparative efficacy and safety trials are

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27 Sean Milmo, "A question of quality," *Pharmaceutical Technology Europe* July (2017): 11-12, 11.

28 Frapaise, "The End of Phase 3 Clinical Trials in Biosimilars Development?" 321.

29 Mellstedt et al., "The challenge of biosimilars," 411.

30 Frapaise, "The End of Phase 3 Clinical Trials in Biosimilars Development?" 322.

31 *Ibid.,* 321.

32 *Ibid*., 324.

33 Anurag S. Rathore et al., "Challenges with successful commercialization of biosimilars," *BioPharm International* May (2019): 22-31, 24.

required.[34] The following PD endpoints for the various biosimilars were identified by molecule size: (1) for small less-complex proteins e.g. G-CSF, the absolute neutrophil count; (2) for insulin, the blood glucose concentration in specific studies; (3) for interferon-β, magnetic resonance imaging-related endpoints, and for teriparatide, serum calcium levels; and (4) for LMWHs, anti-Factor X and anti-Factor II activity.[35]

It may be concluded that although the EMA rigorous regulatory pathway aims to demonstrate similarity between the biosimilar and the innovator, a degree of uncertainty will remain at the point of authorisation which may only be resolved through post-authorisation surveillance for efficacy and safety (as per authorised RMP) throughout the product life-cycle. The 'residual uncertainties' related to biosimilars raise ethical issues with regard to the safety of biosimilars, which will be discussed in Section 4.2.

The need for additional comparability studies raises ethical questions especially since biosimilars do not provide any clinical advantage over reference biological medicines. One would also question why clinical studies are needed for a new clinical indication or for a new formulation at extra expense and delays in authorisation. The above ethical questions will be discussed in more detail in Section 4.2.1.

2.3 Interchangeability of biosimilars

The clinical comparability studies required by the regulators discussed in Section 2.2 above are aimed at determining the therapeutic equivalence of the biosimilar with the reference biological product. Whether this is sufficient to make biosimilars interchangeable will be discussed next.

The EMA states that

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[34] "Clinical data requirements for biosimilars in the EU," GaBi online (Generics and Biosimilars Initiative), posted October 11, 2019, accessed December 11, 2019, http://gabionline.net/Biosimilars/Research/Clinical-data-requirements-for-biosimilars-in-the-EU.

[35] *Ibid*.

> A medicinal product is therapeutically equivalent with another product if it contains the same active substance or therapeutic moiety and, clinically shows the same efficacy and safety as that product whose efficacy and safety has been established.[36]

Where generic and reference medicinal products are shown to be identical in chemical composition and bioequivalent, they are considered to be therapeutically equivalent.[37]

The EMA and the European Commission define 'interchangeability' as "the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. For biologicals, this could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another."[38] It advises that replacement can either refer to switching, which involves the prescriber or automatic substitution by the pharmacist.

As illustrated in Section 1.3.4, although the clinical indication of the biological reference product is known, the clinical properties of the protein and the manufacturing process remain under company secrecy resulting in differences between the reference product and biosimilar medicine, making it difficult to ascertain the same efficacy.[39] The comparative safety and efficacy studies of biosimilars cannot make biosimilars therapeutically equivalent to the originator and therefore interchangeable.[40] Kurki and colleagues, however, claimed that the comparable efficacy and safety data on a population level should not trigger or enhance immunogenicity on an individual level, such that biosimilars are interchangeable, provided that the patient is monitored closely and receives information and training on the administration of the biosimilar if required.[41] In fact, the regulatory framework imposes on the biosimilar marketing

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[36] European Medicines Agency Committee for Proprietary Medicinal Products (CPMP), *Note for Guidance on the Investigation of Bioavailability and Bioequivalence,* https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf.

[37] Mellstedt et al., "The challenge of biosimilars," 415.

[38] European Commission and European Medicines Agency, *Biosimilars in the EU - Information guide to healthcare professionals*, 29.

[39] Mellstedt et al., "The challenge of biosimilars," 412.

[40] *Ibid*., 415.

[41] Pieter Dylst et al., "Barriers to the uptake of biosimilars and possible solutions: A Belgian case study," *PharmacoEconomics* 32 (2014): 681-691, 688.

authorisation applicant the obligation to perform additional clinical studies and post-marketing surveillance in order to address any residual uncertainties related to biosimilar therapeutic equivalence.[42]

The EMA, however, specifically states that switching to biosimilars is not within its remit as it would not have evaluated whether the biosimilar is interchangeable with the reference medicine, claiming that the "decision is a prescribing decision taking into account any policies that the country might have regarding the prescribing and use of biological medicines."[43] The EMA, therefore, leaves the decision on interchangeability and therefore switching or substitution to Member States (MSs). It states that it has no mandate on reimbursement issues and such decisions should be taken by "a qualified healthcare professional."[44] The European Commission specifically states that switching to biosimilars requires the involvement of the prescriber not via pharmacy substitution.[45] Different authors argued as to whether the decision to switch should have been left to MSs. Ebbers and colleagues argued that EMA's remit as set by European regulation is only to evaluate the product dossier of the biosimilar product in accordance with the legal basis and if the benefit-to-risk profile of the biosimilar is found to be satisfactory, to issue a positive opinion and marketing authorisation for the biosimilar product.[46] Moorkens and colleagues, however, argued that the recommendations for interchangeability and substitution should be taken by EMA, which holds detailed scientific data and expertise.[47] De Mora and colleagues also

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42 Rathore et al., "Challenges with successful commercialization of biosimilars," 28.

43 European Commission and European Medicines Agency, *Biosimilars in the EU - Information Guide to Healthcare Professionals*, 29.

44 Ebbers et al., "The safety of switching between therapeutic proteins," 1474.

45 Grampp et al., "Policy considerations for originator and similar biotherapeutic products," 130.

46 Hans C. Ebbers et al., "The safety of switching between therapeutic proteins," *Expert Opinion on Biological Therapy* 12, no. 11 (2012): 1473-1485, 1474.

47 Evelien Moorkens et al., "Policies for biosimilar uptake in Europe: An overview," *Public Library of Science (PLoS ONE)* 12 (2017): 1-17, 11.

suggested that since EMA has the expertise on biosimilars, it should provide a list of products that may be substituted.[48]

While the practical implementation of interchangeability by MSs will be discussed in more detail in Section 3.3, the question of whether the position of the European Commission to leave the decision on 'interchangeability' to MSs is ethically justified will be discussed in Section 4.2.2.

2.4 Extrapolation of clinical indications of biosimilars

Extrapolation is "the extension of the efficacy and safety data from a therapeutic indication for which the biosimilar has been clinically tested to another therapeutic indication approved for the reference medicine."[49]

From the economic perspective, extrapolation would reduce the cost of development, wasteful resources and unnecessary repeated studies, which is accepted provided that competent authorities provide the necessary guarantees to patients and healthcare professionals regarding the safety and efficacy of biosimilars.[50] Extrapolation is generally accepted for generic medicines which are therapeutically equivalent based on bioavailability studies without the need of additional clinical studies. For biosimilars, however, there is no absolute therapeutic equivalence, leading to uncertainty in relation to extrapolation of the clinical indication. Directive 2001/83/EC specifically states that for biosimilars, if the originator has more than one indication, the efficacy and safety of the biosimilar should be justified or, if necessary, demonstrated separately for each clinical indication.[51] EMA guidelines permit extrapolation of comparability data to other clinical indications provided that the mechanism of action is the same.[52] For second

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48 Fernando de Mora et al., "Biosimilar and interchangeable: Inseparable scientific concepts?" *British Journal of Clinical Pharmacology* 85 (2019): 2460-2463, 2461.

49 European Medicines Agency and European Commission, *Biosimilars in the EU - Information guide to healthcare professionals*, 34.

50 Silvio Danese et al., "ECCO Position statement on the use of biosimilars for inflammatory bowel disease - an update," *Journal of Crohn's and Colitis* 11 no.1 (2017): 26-34, 26, https://doi.org/10.1093/ecco-jcc/jjw198.

51 *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use*, Consolidated document, 145.

52 Mellstedt et al., "The challenge of biosimilars," 415.

generation biologicals, however, including biosimilar mAbs, the mechanism of action may be complex and not fully known, in which case extrapolation will probably remain on a case by case basis, based on the totality of evidence provided.[53] Extrapolation of a clinical indication was first applied to LMWH where the indication was extended from venous embolism to arterial embolism.[54] Schneider argued that for reference biologicals, extrapolation was already being applied, as the safety and efficacy data was not required for each clinical indication in case of batch variations, and therefore questioned its requirement for biosimilars.

Following extensive debates, CT-P13 was the first biosimilar mAb of infliximab originator, Remicade®, to obtain approval on the basis of extrapolation in 2013 from rheumatoid arthritis (RA) to inflammatory bowel disease (IBD) based on totality of evidence, through physicochemical analysis, in vitro and in vivo PK/PD, potency tests and biological analysis for the two recommended doses.[55]

In cancer treatment, where a biosimilar may be indicated for different types of cancer, the biosimilar would have different end-points for the different cancers, for example, the end-point in one cancer with poor prognosis would be totally different from that in another cancer which is curable.[56] This makes the choice of the end point for each therapeutic indication in cancer studies crucial.[57] In the light of the above, the European Society of Medical Oncology (ESMO) endorsed extrapolation for anti-cancer biosimilars, provided there is solid scientific information and a clear justification.[58]

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53 Christian K. Schneider et al., "Setting the stage for biosimilar monoclonal antibodies," *Nature Biotechnology* 30, no. 12 (2012): 1179-1185, 1182.

54 *Ibid*., 1181.

55 Schneider et al., "Setting the stage for biosimilar monoclonal antibodies," 1181.

56 Emilio Bria and Pierfranco Conte, "Biosimilars as a strategy to improve sustainability," *European Society for Medical Oncology* 2, issue 2 (2017): 1-2, 1, https://doi.org/10.1136/esmoopen-2017-000192.

57 *Ibid*., 2.

58 Josep Tabernero et al., "Biosimilars: a position paper of the European Society of Medical Oncology, with particular reference to oncology prescribers," *European Society for Medical Oncology* 1, issue 6 (2016): 1-5, 2, https://doi.org/10.1136/esmoopen-2016-000142.

This is compounded further if the therapeutic indication is still under patent protection for the reference product, such that extrapolation for that clinical indication is prohibited.[59] The need to request clinical comparability studies for extrapolation to other clinical indications is therefore strongly debatable from the ethical perspective and will be discussed in Section 4.2.1.

2.5 Safety of biosimilars

As for all medicinal products, as illustrated in Section 1.2.2, monitoring of safety is continued during the post-authorisation stage for biosimilars, which involves reporting of suspected adverse drug reactions (ADRs) to the regulatory authority, referred to as passive reporting system, or the pharmacovigilance reporting system. Regulation (EC) No 726/2004 laid down Community procedures for the authorisation, supervision and pharmacovigilance of medicinal products for human and veterinary use, and to establish a European Medicines Agency. Article 23 of Regulation (EC) 726/2004 requires that "the package leaflet of medicinal products shall include a statement 'This medicinal product is subject to additional monitoring'. That statement shall be preceded by a black symbol …and shall be followed by an appropriate standardised explanatory sentence." applicable to both originator biologicals and biosimilars which should be identified by brand name at the time of prescription and also for pharmacovigilance monitoring. Regulation EC No. 1235/2010[60] and Directive 2010/84/EU[61] oblige MAHs to perform post-authorisation safety and efficacy studies (PASS and PAES).

The 'Pharmacovigilance Regulation,' Regulation (EC) 520/2012 requires Market Authorisation Holders (MAHs) to perform pharmacovigilance activities and reviews of

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59 George Dranitsaris et al., "Biosimilars of Biological Drug Therapies Regulatory, Clinical and Commercial Considerations," *Drugs* 71, no.12 (August 2011): 1527-36, 33.

60 "Regulation 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards Pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products" Official Journal of the European Union, L348/74 (31.12.2010).

61 "Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use," *Official Journal of the European Union,* L348/1 (31.12.2010).

the benefit-to-risk balance throughout the product life-cycle.[62] This allows ADRs to be evaluated centrally both by the MAH and independently by EMA. As from September 2015, MAHs are required to submit a Risk Management Plan (RMP)[63] which obliges the MAH to actively perform risk minimisation measures i.e. how the risks will be prevented or minimised in patients (referred to as risk minimisation measures), and how the MAH plans to measure these risks and study the safety and efficacy of the product at post-marketing stage. Another type of reporting system is active surveillance which involves examining databases or patient registries.[64] Patient registries are aimed to collect uniform observational data on a specific disease population, which may be useful in benefit-to-risk assessment.[65]

The concern about the safety of switching to biosimilars justifies the need for a robust post-marketing pharmacovigilance system that clearly identifies the biological or biosimilar so as to capture any ADRs on switching. The EU pharmacovigilance system requires that ADRs are reported by active substance (also referred to as the International Non-proprietary Name (INN)) and the World Health Organisation Anatomical Therapeutic Chemical (WHO ATC) Code,[66] and for biologicals (including biosimilars), also by brand name and batch number so as to achieve full traceability. Though no safety signals have emerged from switching to and from biologicals including

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62 "Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council," *Official Journal of the European Union,* L159 (20.6.2012).

63 European Medicines Agency, "Risk Management Plan," accessed November 22, 2019, https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management/risk-management-plans.

64 Rathore et al., "Challenges with successful commercialization of biosimilars," 29.

65 European Medicines Agency, "Patient registries," accessed January 22, 2020, https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries.

66 The list of active substances is maintained by the World Health Organisation through the Anatomical Therapeutic Chemical (ATC) Classification, which is an internationally accepted classification system for medicines. The WHO assigns ATC codes to all active substances contained in medicines based on the therapeutic indication for the medicine (https://www.whocc.no/atc/application_for_atc_codes/)

biosimilars, robust methods of reporting are needed to guarantee the safety of biologicals.[67]

An INN Greek letter suffix was initially used by WHO, for example erythropoietin zeta, which was used on a voluntary basis by regulatory authorities.[68] In 2015, the WHO introduced the Biological Qualifier (BQ) coding system (which consists of four random consonants and an optional 2-digit checksum) on a voluntary basis for naming biologicals including biosimilars with the aim to harmonize the pharmacovigilance reporting system across national regulatory authorities, which is separate from the INN.[69] This was stopped in October 2017, as no consensus was reached as to whether to proceed with its implementation.[70]

Inconsistencies were reported between countries on the naming of medicines when reporting ADRs, suggesting the need of a global INN naming system for biologicals and biosimilars.[71] The EU naming system is endorsed by various associations, including the European Association of Hospital Pharmacists (EAHP), DanBio (Danish Registry for Biologic Therapies in Rheumatology) and International Generic and Biosimilar Association (IGBA). Other regulatory authorities, such as the US FDA, recommend the addition of a four-letter suffix to the INN for each biological product to distinguish between different biosimilars and its respective reference product, for example "filgrastim-sndz" and "infliximab-dyyb." In Japan, the same INN as for the biological product is used followed by the word 'biosimilar' and a number relating to the order of

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67 Hans C. Ebbers et al., "The safety of switching between therapeutic proteins," *Expert Opinion on Biological Therapy* 12, no. 11 (31 July 2012): 1473-1485, 1481, https://doi.org/10.1517/14712598.2012.711308.

68 Grampp et al., "Policy considerations for originator and similar biotherapeutic products," 128.

69 Peter J. Pitts, and Michael S. Reilly. "Medicines regulation in the MENA region and the importance of the World Health Organization's INN proposal of Biological Qualifier." *Generics and Biosimilars Initiative Journal (GaBi Journal)* 7, no. 3 (2018): 97-100.

70 Jack Syrop, "WHO Will Not Proceed With Biological Qualifiers for Biosimilars," accessed May 03, 2020, https://www.centerforbiosimilars.com/news/who-will-not-proceed-with-biological-qualifiers-for-biosimilars.

71 Michael Sarshad et al., "The need for distinct nomenclature for originator and biosimilar products," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 7, no. 4 (2018): 192-197, 192.

approval of the biosimilar.[72] The US Federal Trade Commission argued that different INN naming could result in a lack of prescribers' confidence in using biosimilars thus presenting a barrier to the uptake of biosimilars, though this was not supported by US market data on Zarxio (a biosimilar G-CSF).[73] The EAHP also argued against other naming systems, such as the US FDA system of randomly assigning suffixes, which could lead to confusion to prescribers and other healthcare professionals.[74] However, 25% of ADRs reported in the EU between March 2017 and February 2018 for infliximab were ambiguous.[75] The biosimilar must be distinguished from the reference product for better tracking of adverse events that are specific to the biosimilar.[76] A distinguishable naming system for biologicals and biosimilars is necessary such that ADR reporting is accurate and specific to the biological or biosimilar product providing fast traceability to the manufacturer, thereby improving patient safety and ensuring accessibility of high quality medicines.[77] It is imperative that both passive and active pharmacovigilance reporting systems are such as to clearly differentiate between biosimilars.[78] The WHO Biological Qualifier program may provide a universal solution.[79] Dr Sabine Straus, Chair of the EU Pharmacovigilance Risk Assessment Committee (PRAC), reported that following a study carried out in 2018 on biologicals and biosimilars, products were clearly identified but not to batch level.[80] "Well-designed, post-approval, long-term, follow-up studies (pharmacovigilance studies, real world evidence data and registries)"

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72 Andras Sule et al., "Biosimilar medicines," *European Journal of Hospital Pharmacy* 26 (2019): 117-118, 117.

73 Sarshad et al., "The need for distinct nomenclature for originator and biosimilar products," 192.

74 Sule et al., "Biosimilar medicines," 117.

75 *Ibid*.

76 Sarshad et al., "The need for distinct nomenclature for originator and biosimilar products," 192.

77 Pitts and Reilly, "Medicines regulation in the MENA region and the importance of the World Health Organization's INN proposal of Biological Qualifier," 1.

78 Rathore et al., "Challenges with successful commercialization of biosimilars," 29.

79 Grampp et al., ""Policy considerations for originator and similar biotherapeutic products," 129.

80 "Challenges for European pharmacovigilance," GaBi online (Generics and Biosimilars Initiative), posted September 06, 2019, accessed December 11, 2019, http://www.gabionline.net/Reports/Challenges-for-European-pharmacovigilance.

are needed so as to reduce uncertainties.[81] In view of the above, pharmaceutical companies and the clinical field should safeguard patients' safety by investing in robust pharmacovigilance systems that obtain real-world data through, for example, bar-code scanning and electronic patient records.[82]

2.6 Regulation in a globalised pharmaceutical industry

The globalisation of the pharmaceutical industry led to the setting up of sites in emerging markets (mainly Asia) where manufacturing and production costs are low and clinical trial participants may be provided with attractive incentives.[83] Within the global scenario, a medicine may be manufactured in various countries and incorporated in a finished product in another country before being exported for sale in another country.[84] Since 1998, Good Clinical Practice (GCP) guidelines must meet International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (covering Europe, United States of America and Japan) (ICH) guidelines, with the aim to avoid duplication of clinical trials, provided that the standards set by ICH are met.[85] The EMA, however, warned that clinical trials conducted outside the EU/EEA which are GCP-non-compliant would not be accepted.[86]

As discussed in Section 1.3.4, in the absence of a regulatory framework for similar biological medicines prior to 2003, national regulatory authorities set their own regulatory framework for similar biological medicines, some claimed that they are "biogenerics," while others required the similar biological medicine to be authorised as

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81 Frapaise, "The End of Phase 3 Clinical Trials in Biosimilars Development?" 324.

82 Barbara Claus, "Is pharmacovigilance of biologicals cost-effective?" *International Journal of Clinical Pharmacy* 40 (2018): 787-789, 789.

83 Christopher J. Leintz and Riddhi Dedhia "Biosimilars and emerging markets: historical and bioethical considerations," *Journal of Clinical Research and Bioethics* 6, no. 5 (2015): 1-4, 1.

84 Lawrence O. Gostin et al. "Regulating medicines in a globalized world with increased recognition and reliance among regulators," *Journal of the American Medical Association* March 5 (2020): E1-E2, E1, https://doi.org/10.1001/jama.2019.21793.

85 European Medicines Agency - Committee for Human Medicinal Products, *ICH E6 (R2) Good clinical practice*, EMA/CHMP/ICH/135/1995, (European Medicines Agency, 1 December 2016).

86 European Medicines Agency, *Position paper on the non-acceptability of replacement of pivotal clinical trials in cases of GCP non-compliance in the context of marketing authorisation applications,* (European Medicines Agency 26 November 2015 EMA/448853/2015).

a ‘stand-alone’ medicine. The US FDA set its own abbreviated pathway for approval of biosimilars through the Price Competition and Innovation Act of 2009, which came into effect in March 2010 as part of the Affordable Care Act.[87] The US FDA guidelines are similar to those of the EMA, though differences exist in the definition of interchangeability and naming and pharmacovigilance systems.[88] Countries like Australia and Japan adopted the EMA guidelines for biosimilars in 2009, followed by Canada in 2010.[89] There is no recognition of quality, safety and efficacy of medicines between EMA, FDA, Japan and Canada such that medicines are regulated independently which means duplication of review.[90] Mutual Recognition Agreements (MRAs) between the EMA and third countries (namely, US FDA, Japan, Canada, Australia, Israel, New Zealand and Switzerland) are in place only for Good Manufacturing Practice (GMP) inspections and batch certification that is required as part of the assessment process for the authorisation of medicines by the regulatory authority.[91] However, as Gostin points out, “no regulator, even if highly resourced, has the capacity to fully protect the public’s health.” [92] In this light, MRA’s would avoid duplication of inspections and maximise resources to increase inspection coverage, especially of large production sites like China and India.[93]

The regulatory requirements in other countries like China and India, however, are not as comprehensive as those of EMA such that their products cannot be considered

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87 Henry G. Grabowski et al., “Regulatory and cost barriers are likely to limit biosimilar development and expected savings in the near future,” *Health Affairs* 33 no. 6 (June 2014): 1048-1057, 1057.

88 Eva Rahman Kabir et al., “The Breakthrough of Biosimilars: A Twist in the Narrative of Biological Therapy,” *Biomolecules* 9 no. 410 (2019):1-34 doi:10.3390/biom9090410, 7.

89 Islah Ahmed et al., “Biosimilars: Impact of Biologic Product Life Cycle and European Experience on the Regulatory Trajectory in the United States," *Clinical Therapeutics* 34 No. 2 (2012): 400-419, 407.

90 Gostin et al., “Regulating medicines in a globalized world with increased recognition and reliance among regulators,” E1.

91 European Medicines Agency, “Mutual recognition agreements,” accessed May 06, 2020 https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra.

92 Gostin et al., “Regulating medicines in a globalized world with increased recognition and reliance among regulators,” E2.

93 *Ibid*.

to be 'biosimilar'.[94] These are also referred to as 'biomimics', since they are of questionable safety and efficacy.[95] These copies of biological products do not undergo the same rigorous testing in humans as that for originator biological and biosimilars, compromising the product's quality or patient's safety, presenting high risk to patients.[96] This raises concern that medicines authorised in India and China are substandard. The WHO refers to 'substandard' pharmaceuticals as those resulting from poor manufacturing processes, inadequate quality control processes, incorrect storage or inappropriate packaging, which do not meet the quality standards and specifications of national regulatory authorities.[97] Inadequate regulatory enforcements by regulatory authorities contribute to substandard pharmaceuticals of both branded and generic products on the market.[98] In 2008, contaminated heparin was discovered originating from China, which was then withdrawn from the global market.[99] Non-innovator biologicals have been manufactured in India since 2007, that is, prior to the adoption of the Indian regulatory guidelines published in 2012, which allows these products to be classified as biosimilars.[100] Soni reported several deficiencies in the manufacturing processes as a result of lack of expertise in the development of biosimilars and at regulatory level, which raise questions on the quality, safety and efficacy of the biosimilars authorised by the Indian regulatory authority.[101]

In 2009, WHO set to establish the regulatory framework of biosimilars for all national regulatory authorities. Inconsistencies still exist, however, between regulatory

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94 Dranitsaris et al., "Biosimilars of Biological Drug Therapies Regulatory, Clinical and Commercial Considerations," 33.

95 Kabir et al., "The Breakthrough of Biosimilars: A Twist in the Narrative of Biological Therapy," 3.

96 Leintz and Riddhi Dedhia "Biosimilars and emerging markets: historical and bioethical considerations," 3.

97 Y Tony Yang et al., "Generic oncology drugs: are they all safe?", *The Lancet Oncology* 17 no. 11 (2016): e493-e501, e499, e494.

98 *Ibid.,* e495.

99 Gostin et al. "Regulating medicines in a globalized world with increased recognition and reliance among regulators," E1.

100 GR Soni, "Overview of non-innovator biological products in India," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 9, no. 1 (2020): 1-10, http://gabi-journal.net/overview-of-non-innovator-biological-products-in-india.html.

101 *Ibid.*

authorities on the reference product, comparability studies and extrapolation which could create uncertainty.[102] A global regulatory framework would ensure that the biosimilars produced are of high quality, safe and effective whilst ensuring traceability, pharmacovigilance and data collection.[103] It will be challenging to harmonise the standards across all regulatory authorities considering the high standards set by EMA through its rigorous regulatory pathway. The WHO also identified the need of regulatory authorities to have sufficient expertise and resources to be able to properly evaluate applications for biosimilars with the aim to increase efficiency in the regulatory process and improve access to biosimilars whilst increasing clinicians' and patients' confidence on the quality, safety and efficacy of biosimilars.[104]

In order to address global public health priorities, in 2017 the WHO piloted a prequalification system for biosimilars where, if quality, safety and efficacy is found to be comparable to the reference biological product, the biosimilar medicine may be listed by the WHO as eligible for procurement, thus increasing accessibility to biological medicines, especially in low-income countries.[105] In December 2019, a trastuzumab biosimilar for the treatment of breast cancer by Samsung Bioepis NL B.V. (Netherlands) was listed by WHO, thus making this life saving medicine accessible to many women globally.[106] In May 2020, rituximab biosimilar, for the treatment of non-Hodgkin's lymphoma and leukaemia, by Celltrion (CT-P10) was granted WHO prequalification status.[107] A prequalification programme for biosimilar insulin kicked off in November

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[102] Kabir et al., "The Breakthrough of Biosimilars: A Twist in the Narrative of Biological Therapy," 4.

[103] Leyre Zuniga and Begona Calvo, "Regulatory aspects of biosimilars in Europe," *Trends in Biotechnology* 27 no.7 (2009): 385-387, 387.

[104] Zuniga and Begona Calvo, "Regulatory aspects of biosimilars in Europe," 387.

[105] World Health Organisation, "WHO to begin pilot prequalification of biosimilars for cancer treatment," World Health Organisation, Geneva, May 4, 2017, https://www.who.int/news-room/detail/04-05-2017-who-to-begin-pilot-prequalification-of-biosimilars-for-cancer-treatment.

[106] World Health Organisation, "WHO prequalifies first biosimilar medicine to increase worldwide access to life-saving breast cancer treatment," World Health Organisation, Geneva, December 18, 2019, https://www.who.int/news-room/detail/18-12-2019-who-prequalifies-first-biosimilar-medicine-to-increase-worldwide-access-to-life-saving-breast-cancer-treatment.

[107] "WHO prequalifies first rituximab biosimilar," GaBi online (Generics and Biosimilars Initiative), posted June 05, 2020, accessed June 20, 2020, http://www.gabionline.net/Biosimilars/General/WHO-prequalifies-first-rituximab-biosimilar.

2019.[108] Other biosimilars will surely be listed by WHO in the future, thus resulting in better access of life-saving medicines.

Considering the high costs involved in manufacturing and bringing the product to the market, Dr Gillian Woolett, healthcare consultant for Avalare Health, in her presentation at the 17th Biosimilar Medicines Conference in The Netherlands in March 2019, recommended harmonization and regulatory convergence with the aim of avoiding repetitive unnecessary clinical studies, thus reducing the price of the biological resulting in better patients' accessibility to biologicals.[109] Gostin and colleagues recommended MRA's between regulatory authorities as the 21st century best regulatory practice in the globalised world.[110]

2.7 Conclusion

Public health is protected through regulation of medicines, which should meet suitable quality standards and achieve a positive benefit-to-risk balance prior to being granted a marketing authorisation. The EMA was at the forefront in setting a Biosimilar Regulatory Pathway through a step-wise approach aimed at demonstrating that there is no clinically meaningful difference between the biosimilar and the originator through clinical comparator studies, which are also required for other clinical indications with a different mechanism of action and different formulations. At the same time, new advances in analytical testing may eliminate the need of repetitive or unnecessary studies. The need to conduct clinical comparability studies for biosimilars, and also for extrapolation to other clinical indications and formulations raises ethical questions which will be discussed in Section 4.2.1. Nevertheless, it is still debatable whether biosimilars are fully therapeutically equivalent to their reference biological product, and the issue of interchangeability of biosimilars remains debatable, which the EMA left to the different MSs to decide. This could raise ethical questions but before being able to

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[108] "WHO prequalifies first rituximab biosimilar."

[109] "Achieving consistent regulation for biosimilars," GaBi online (Generics and Biosimilars Initiative), posted July 26, 2019, accessed December 11, 2019, http://gabionline.net/Reports/Achieving-consistent-regulation-for-biosimilars.

[110] Gostin et al., "Regulating medicines in a globalized world with increased recognition and reliance among regulators," E1.

analyse these, it is first necessary to look at the national policies, which will therefore be discussed in the next chapter.

The uncertainties may only be minimised through pharmacovigilance and risk minimisation measures throughout the product life-cycle, necessitating robust post-marketing surveillance (both passive and active systems), supported by an appropriate universal naming system that is capable of capturing any ADRs on switching to biosimilars, through real-world data. The lack of a universal naming system could hinder safety issues from being captured when switching to biosimilars.

The globalisation of the pharmaceutical industry and the inconsistencies across different regulatory authorities have led to the need of regulatory harmonization and convergence for biosimilars, which could provide advantages as repetitive clinical studies will be minimised, thus increasing patients' accessibility to biologicals. It also raises questions, however, related to the level of standards set by different regulatory authorities, which present challenges to the harmonisation of the regulatory framework. As discussed in this chapter, no regulatory authority has the sufficient resources to protect public health on its own, such that the use of MRA's between regulatory authorities was identified as a 21st century best regulatory practice in the globalised world. The WHO is already working on the harmonisation of regulatory standards for biologicals and biosimilars. In 2017, a prequalification system for biosimilars was piloted by the WHO and the first trastuzumab biosimilar was listed in December 2019, followed by rituximab in May 2020, which could lead to better access to life-saving medicines globally.

As discussed in this chapter the regulation of biosimilars made it possible for European governments to bring essential biological medicines to the market at more affordable prices. However, their accessibility is reliant on other factors such as prescribing policies and national price-setting strategies by national governments. These will be explored in the next Chapter.

Chapter 3: Accessibility and affordability of biologicals

As discussed in Chapter 1 the high development costs of biologicals lead to high prices impacting the pharmaceutical expenditure. An overview of the expenditure of biologicals, which are funded through national healthcare systems and the burden of disease on the economy will thus be provided in this chapter. The high cost of biologicals presents problems of accessibility and strategies implemented by policymakers will also be identified. As discussed in Chapter 2, interchangeability is left up to the individual Member States (MSs) and therefore the various models of switching and substitution and the positions of the MSs in this regard will be analysed with the aim to identify ethical issues. The impact of the national healthcare system and reimbursement policies on prescribing of biologicals will be evaluated and any emerging ethical issues will be presented. The success rate in terms of biosimilar market penetration and cost savings will be presented so as to identify the extent of the problem of accessibility.

3.1 Pharmaceutical expenditure

The global pharmaceutical market is estimated to reach over €1000 billion annually and is the fastest growing market in emerging economies. Globally, 80% of medicines are generics or biosimilars, with the EU representing 14% of the global market with 4000 manufacturing companies.[1] IQVIA, (formerly Quintiles and IMS Health, Inc.),[2] projected that the global pharmaceutical market will exceed US$ 1.5 trillion by 2023, based on an estimated annual compounding growth of 3- 6 % over 5 years.[3] Europe accounts for

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1 European Commission, *Supplementary protection certificate for medicinal products: Frequently Asked Questions (FAQs),* (European Commission, 28 May 2018), https://ec.europa.eu/commission/presscorner/detail/en/MEMO_18_3908.

2 IQVIA (Intelligence-Quintiles-VIA I is taken from IMS Health or can be interpreted as Intelligence, Q comes from Quintiles or can be interpreted as Quotient and VIA is basically the path of transformation or a helping hand to achieve something) is an American multinational company serving the combined industries of health information technology and clinical research.

3 IQVIA Institute for Human Data Science, *The global use of medicine in 2019 and outlook to 2023* (New Jersey: IQVIA Institute for Human Data Science, January 2019), 2.

23.2% of the world pharmaceutical market, compared to 48.9% for North America.[4] Generic substitution resulted in US$ 1.2 trillion savings to the healthcare system in the USA between 2003-2012 (and contributed to the well-being of many people). The US Healthcare system saved US$ 1.67 trillion over the past decades as a result of low-cost generics.[5] For biosimilars, the potential cost savings are projected to be US$ 54 billion over 10 years.[6]

As shown in Table 4, the total market value of pharmaceuticals in the EU increased from €89.5 billion in 2000 to €220 billion in 2018, 60% of which are for ambulatory care.[7]

Table 4: Key Data from European Federation of Pharmaceutical Industries and Associations (EFPIA) Report January 2019[8]

	2000 (in millions)	**2010** (in millions)	**2017** (in millions)	**2018** (in millions)
Total Pharmaceutical Market Value (ex-factory prices)	€89,449	€153,685	€208,949	€228,000
Payment for Pharmaceuticals by statutory health insurance system (Ambulatory system)	€76,909	€129,464	€133,775	€137,000

The official annual growth rate of the pharmaceutical market for the EU-5 countries was forecasted to be 2.9% as per official price or 1.5% net estimate price for the period 2017 – 2021.[9] In 2019, IQVIA reported that this annual growth rate was expected to slow from 3.8% for the period 2013-2018 to 1 - 4% by 2023, as a result of measures taken due to the economic crisis.[10] It is estimated that 25% of all new medicines developed are

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4 IQVIA Institute for Human Data Science (MIDAS) May 2019 cited in EFPIA, *The Pharmaceutical Industry in Figures - Key Data* 2019, 14.

5 Raluca Gavrila et al., "Biostatic, legislative and ethical problems of comparative clinical studies. I. Generic and biosimilar drugs case," *Farmacia* 66, no. 6 (2018): 930-937, 935.

6 *Ibid*.

7 EFPIA, *The Pharmaceutical Industry in Figures - Key Data 2019*, (Brussels: EFPIA 2019), 3.

8 *Ibid*.

9 OECD/European Union, *Pharmaceutical Expenditure Health at a Glance: Europe 2018: State of Health in the EU Cycle* (Brussels: OECD Publishing, Paris/European Union, 2018), 140.

10 IQVIA Institute for Human Data Science, *The global use of medicine in 2019 and outlook to 2023*, 2.

biologicals, accounting for 25% of global sales.[11] In 2018, the global biological market was worth approximately US$276 billion with 10 blockbuster drugs being biologicals, which increased from 3 such drugs in 2003.[12] In September 2019, monoclonal antibodies (mAbs) featured in the top 10-selling blockbuster prescription medicines globally by revenue, with adalimumab (Humira®) being the number one with US$19.9 billion sales and accounting for 7% of all global sales on the market despite the launch of biosimilars.[13] Table 5 below shows the net sales of the top selling biologicals in relation to patent expiry.

Table 5: Top-selling biologicals by net sales, patent expiry and biosimilar availability

Position	Brand name	INN	Net Sales (US$ Billions)[14]	Patent expiry[15]	Biosimilar in Europe (Y/N)[16]
1	Humira	Adalimumab	19.9	October 2018	Yes
2	Eliquis	Apixaban	9.8	May 2026	No
3	Revlimid	Lenalidomide	9.7	July 2022	No
4	Keytruda	Pembrolizumab	7.1	June 2028	No
5	Enbrel	Etanercept	7.1	August 2015	Yes
6	Herceptin	Trastuzumab	7.0	July 2014	Yes
7	Avastin	Bevacizumab	6.9	January 2022	No
8	Eylea	Aflibercept	6.7	May 2020	No
9	Opdivo	Nivolumab	US$6.7	May 2026	No

[11] Michael S Reilly and Philip J Schneider, "Policy recommendations for a sustainable biosimilars market: lessons from Europe," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 9, no. 2 (2020), http://gabi-journal.net/the-evolution-of-the-european-biosimilars-market.html.

[12] Derbyshire, Michelle and Sophie Shina, "Patent expiry dates for biologicals: 2018 update," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 8, no. 1 (2019): 24-31, http://gabi-journal.net/patent-expiry-dates-for-biologicals-2018-update.html.

[13] Pharmaceutical Technology, "The top-selling prescription drugs by revenue: Ranking the top ten," accessed 18th September 2019, https://www.pharmaceutical-technology.com/features/top-selling-prescription-drugs/.

[14] *Ibid.*

[15] Data by author using data from: "SPC Snapshot," Intellectual Property Office, Ireland, Accessed November 2019; https://www.ipoi.gov.ie/en/ip-search-tools/patents-search/spc-database-snapshot/.

[16] Data by author using data from: "Medicines - Download medicine data," European Medicines Agency, accessed January 25, 2020, https://www.ema.europa.eu/en/medicines/download-medicine-data.

3.2 Economic burden of disease

Chronic diseases present a burden on the economy both via direct (i.e. the cost of medicines) and indirect costs (i.e. cost as a consequence of the disease, for example, unemployment), referred to by the WHO as the economic burden of disease or the 'cost-of-illness.'[17] In 2017, healthcare spending in Europe was estimated at approximately 8.6% of the Gross Domestic Product (GDP) though this varies significantly across countries.[18]

Cancer is considered as one of the greatest global health challenges with a burden of 18.1 million new cases and 9.6 million deaths in 2018, with significant differences in survival rates between high income and low-income countries.[19] In 2008, it was estimated that in Europe there were approximately 3 million sufferers of RA resulting in an annual economic burden of €45 billion.[20] In Europe, medicines for RA and cancer account for 10% of the total disease cost.[21] Other diseases that present a significant economic burden include psoriasis, inflammatory bowel disease (IBD) and Crohn's disease (CD). The annual cost for psoriasis per patient per year in 2014 was reported to be €11,928 in Sweden, €6707 in Germany and €8372 in Italy.[22] The total direct costs of IBD were estimated to be €5.6 billion/year. The economic burden of ulcerative colitis (UC) was estimated to be €12.5 - €29.1 billion/year, whereas that for CD was estimated to be €2.1 - €16.7 billion/year.[23]

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17 World Health Organization, "Economic Burden of Disease," *Health Economics*, accessed March 29, 2020, https://www.who.int/choice/economicburden/en/.

18 EFPIA, *The Pharmaceutical Industry in Figures - Key Data 2019*, 22.

19 "WHO considers cost of cancer drugs and how to increase access," GaBi online (Generics and Biosimilars Initiative), posted January 11, 2019, accessed December 11, 2019, http://www.gabionline.net/Reports/WHO-considers-cost-of-cancer-drugs-and-how-to-increase-access.

20 Daniel C. Baumgart et al., "Biologic therapies in immune-mediated inflammatory diseases: Can biosimilars reduce access inequities?" *Frontiers in Pharmacology* 10, no. 279 (March 2019): 1-13, 7.

21 EFPIA, *The Pharmaceutical Industry in Figures - Key Data 2019*, 25.

22 Baumgart et al., "Biologic therapies in immune-mediated inflammatory diseases: Can biosimilars reduce access inequities?" 7.

23 *Ibid*.

The pharmaceutical industry plays a critical role in the global economy to produce innovative medicines through R&D whilst making a profit.[24] Innovation is considered to be the major driver of healthcare costs.[25] The key drivers for the increase in pharmaceutical expenditure are medicines for cancers, autoimmune disorders and diabetes.[26] This is challenging to all governments as the high expenditure of biologicals significantly impacts healthcare systems.

As per Article 168 (7) of the Treaty on the Functioning of the European Union (TFEU),[27] MSs are free to set prices and policies for reimbursement of prescription medicines according to their economy through government, social funds or private payers.[28] Pricing and reimbursement systems are very complex and national authorities may decide which treatments may be reimbursed under their social security system according to political and other priorities. These policies directly impact on the national prescribing regulations concerning biosimilars.[29]

3.3 Regulations for prescribing of biosimilars

In most European countries international non-proprietary name (INN) prescribing of medicinal products is well-established for non-biologicals but biologicals and biosimilars

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[24] Matthew Lee and Julian Kohler, "Benchmarking and Transparency: Incentives for the Pharmaceutical Industry's Corporate Social Responsibility," *Journal of Business Ethics* 95, no. 4 (September 2010): 641-658, 641.

[25] Jamie Espin et al., "Projecting Pharmaceutical Expenditure in EU5 to 2021: Adjusting for the Impact of Discounts and Rebates," *Applied Health Economics and Health Policy* 16, no. 6 (2018): 803–817, 804.

[26] Sabine Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* (World Health Organisation Regional Office for Europe, 2018): 8, https://www.euro.who.int/en/about-us/partners/observatory/publications/policy-briefs-and-summaries/ensuring-access-to-medicines-how-to-redesign-pricing,-reimbursement-and-procurement.

[27] "Consolidated version of the Treaty on the functioning of the European Union," *Official Journal of the European Union*, C326 (26.10.2012): 123.

[28] Alexander Roediger et al., "What pricing and reimbursement policies to use for off-patent biologicals? - Results from the EBE 2014 biological medicines policy survey," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 4, no. 1 (2015): 17-24, 17.

[29] "Transparency Directive," European Commission, accessed February 29, 2020, https://ec.europa.eu/growth/sectors/healthcare/competitiveness/products-pricing-reimbursement_en.

are exempt from INN prescribing and are prescribed by brand name.[30] Implementing Directive 2012/52/EC, which emanates from the Cross Border Directive 2011/24/EU, is aimed at ensuring recognition of prescriptions in cross-border care. [31] Directive 2012/52/EC specifies that prescriptions for biological products should be written by brand name.[32]

As per European Commission (EC), interchangeability refers to physician-led switching and is defined as "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."[33] As discussed in Section 2.3, EMA leaves the decision on replacement to biosimilars in the remit of national MSs, through their national regulations and guidelines with regards to reimbursement and prescribing.[34] This is referred to as a 'soft law.'[35] The EMA and the European Commission provide clear definitions of switching and substitution. 'Switching' refers to "when the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent,"[36] whereas 'substitution' refers to "the practice of dispensing one medicine instead of another equivalent and interchangeable

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30 Roediger et al., "What pricing and reimbursement policies to use for off-patent biologicals? - Results from the EBE 2014 biological medicines policy survey," 20.

31 "Commission implementing Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare," *Official Journal of the European Union, 2011*, L88 (4.4.2011): Article 11, 60.

32 "Commission implementing Directive 2012/52/EU of 20 December 2012 laying down measures to facilitate the recognition of medical prescriptions issued in another Member State," *Official Journal of the European Union,* L356 (22.12.2012): Annex, 70.

33 European Commission, *What you need to know about biosimilar medicinal products - A consensus information document*, (Brussels: European Commission, 2013), 1-41, 40.

34 Enrico Adriano Raffaelli and Fausto Massimino, "Biosimilars' between competition and patient protection: considerations in light of the EU and Italian legal framework," *Generics and Biosimilars Initiative Journal (GaBI Journal)* 8 no. 1 (2019): 5-23.

35 *Ibid.*

36 European Medicines Agency and European Commission, *Biosimilars in the EU: Information guide to healthcare professionals*, posted October 02, 2019, accessed on December 30, 2019, https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf, 1-36, 29.

medicine at pharmacy level without consulting the prescriber."[37] A better understanding on switching and substitution is first required, which will be further evaluated below.

3.3.1 Substitution or switching?

The concept of substitution was first introduced with generic medicines where the patient is prescribed a medicine for the first time from a list of products including brand name and several generics containing the same active substance, in which case the patient is termed as 'naïve.'[38] If the patient is already under treatment with a medicine and the physician wants to change it with a bioequivalent one, this is then termed as switchability or interchangeability.[39]

The different models for replacement will be presented in the sub-sections below.

3.3.1.1 Prescribing biosimilars to naïve patients

The EMA and EC Information guide on biosimilars to healthcare professionals consider that naïve patients i.e. those who were not taking the biological medicine, may be safely prescribed biosimilars.[40] Following 10 years of experience, erythropoietin biosimilars are considered to be a safe and effective option for the treatment of renal anaemia.[41] The Italian Medicines Agency (AIFA) distinguishes between 'primary naïve' patients (those who were never exposed to biologicals) and 'secondary naïve' patients (those with a previous exposure to the originator but with an adequately long wash-out period based on the judgement of the clinician).[42] A detailed definition of 'secondary

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37 European Medicines Agency and European Commission, *Biosimilars in the* EU - Information *guide to healthcare professionals,* 29*.*

38 Gavrila et al., "Biostatic, legislative and ethical problems of comparative clinical studies. I. Generic and biosimilar drugs case,"933.

39 *Ibid*.

40 European Medicines Agency and European Commission, *Biosimilars in the EU: Information guide to healthcare professionals*, 12.

41 David Goldsmith et al., "Epoetin biosimilars in the treatment of renal Anemia: What have we learned from a decade of European experience?" *Clinical Drug Investigation* 38 (2018): 481–490, 490.

42 Martina Biggioggero et al., "The challenging definition of naïve patient for biological drug use," *Autoimmunity Reviews* 14 (2015): 543-546, 544.

naïve,' however, is required and should consider both pharmacodynamic and immunogenicity parameters.[43]

3.3.1.2 Switching from originator to biosimilar

This refers to switching a patient from an originator to a biosimilar, which means switching from an option of known response to that of unknown response.[44] Some authors, however, claim that when prescribing a biosimilar the patient is exposed to the same risk as for any other biological medicine.[45] On switching to biosimilars patients may also suffer from the nocebo effect, defined as "a negative effect of a therapeutical treatment (pharmacological or non-pharmacological), which is a result of the patient's perceived expectations,"[46] which may greatly influence patients' adherence to treatment.

The lack of a central decision by the regulator has led to different interpretations among MSs and physicians such that independent studies were undertaken aimed to increase the confidence of physicians in the quality and effectiveness of biosimilars so as to encourage switching.[47] Below is a summary of the outcomes of studies for first generation and second generation biosimilars.

3.3.1.2.1 First Generation Biosimilars

The majority of safety studies for erythropoietin and granulocyte colony-stimulating factor (G-CSF) were limited to short-term studies for switching between innovators or between innovator and biosimilar and did not conclude that switching was free from risk.[48] Studies on switching originator G-CSF to its biosimilar are less common since G-

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43 *Ibid*., 544-545.

44 Paolo Rocco et al., "Biosimilar switching and related medical liability," *Journal of Forensic and Legal Medicine* 55 (2018): 93–94, 94.

45 *Ibid*., 94.

46 Eva Rahman Kabir et al., "The Breakthrough of Biosimilars: A Twist in the Narrative of Biological Therapy," *Biomolecules* 9 No. 410 (2019):1-34, 24, https://doi.org/10.3390/biom9090410.

47 Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement* 19.

48 Hans C. Ebbers et al., "The safety of switching between therapeutic proteins," *Expert Opinion on Biological Therapy* 12, no. 11 (31 July 2012): 1473-1485, 1745.

CSF, such as filgrastim, is given during chemotherapy short cycles; however, there are no reports of safety concerns with switching between G-CSF products.[49] The studies showed no evidence that switching poses a risk to patients or reduced efficacy due to a change in the manufacturing process or immunogenicity.[50] A large scale observational study conducted in Italy in 2019 for switching from originator epoetin alfa to other originator brands and biosimilars in 14,400 patients suffering from chronic kidney disease (CKD) confirmed safety and efficacy of switching.[51] Also, studies on insulin showed that switching is safe and effective with minor cases of hypersensitivity reactions, rashes and reactions at injection sites.[52]

3.3.1.2.2 Second Generation Biosimilars

The NOR-SWITCH study was the first non-inferiority Phase IV double blind clinical study to test interchangeability from infliximab reference product to the biosimilar CT-P13 in six different clinical indications. This study started in October 2014 and was funded by the Swedish government. It resulted in no reports in lack of safety or efficacy or anti-drug antibodies (ADA) formation due to switching.[53]

Further studies were performed to determine the long-term effects of switching to second generation biosimilars which are summarised in Table 6 below. In addition, a systematic review of the literature showed that data collected from 90 studies including 14,225 individuals, covering 14 different diseases and different molecular entities did not report any differences in immunogenicity, safety and efficacy on switching from a reference product to a biosimilar.[54]

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49 Ebbers et al., "The safety of switching between therapeutic proteins 1744.

50 *Ibid*., 1780.

51 Valeria Belleudi et al., "Effectiveness and safety of switching originator and biosimilar epoetins in patients with chronic kidney disease in a large-scale Italian cohort study," *Drug Safety* 42 (2019):1437–1447, 1437, https://doi.org/10.1007/s40264-019-00845-y

52 Ebbers et al., "The safety of switching between therapeutic proteins," 1781.

53 Silvio Danese et al., "ECCO Position statement on the use of biosimilars for inflammatory bowel disease - an update," *Journal of Crohn's and Colitis* 11, no. 1 (2017): 26-34, 30-31, https://doi.org/10.1093/ecco-jcc/jjw198.

54 Hillel P. Cohen et al. "Switching reference medicines to biosimilars: A systematic literature review of clinical outcomes," *Drugs* 03 March 2018, 1, https://doi.org/10.1007/s40265-018-0881-y.

The clinical studies provide increased prescribers' confidence in switching such that since 2015, as reported by Medicines for Europe, switching from a reference product to a biosimilar under the supervision of the prescriber is generally allowed in most European countries.[55]

Table 6: Summary of results of safety, efficacy and immunogenicity studies

Study	Summary of results
Phase IV SIMILAR study	A study between Remicade® and CT-P13 in patients suffering from CD and UC in remission under treatment with infliximab for up to three months showed comparative safety and efficacy data.[56]
PLANETAS study on Ankylosing Spondylitis (AS) patients and PLANETRA study on Rheumatoid Arthritis (RA) patients[57]	(Start date October 2010 and Completion date: July 2012) at 54 weeks and 102 weeks showed no issues with safety, efficacy and immunogenicity. [58]
Danese et al. (2016) study.[59]	It was observed that antibodies usually develop after 2-3 treatments and it was recommended not to switch within six months
A study on Flixabi® (the second biosimilar infliximab) compared to the originator[60]	There were no clinical differences in ADA positive and ADA negative patients.
A follow-up study of 120 weeks following the NOR-SWITCH study	It reported that the nocebo effect that may occur in the initial weeks following the switch fades off, confirming that Remicade® and CT-P13 are identical in terms of efficacy, safety and acceptability in the long term.[61]

[55] "Medicines for Europe – Biosimilar Medicines Group – Position on physician-led switching and pharmacy substitution of Biosimilar Medicines," Posted July 2015, www.medicinesforeurope.com.

[56] Danese et al., "ECCO Position statement on the use of biosimilars for inflammatory bowel disease - an update," 31.

[57] Program evaLuating the Autoimmune Disease iNvEstigational Drug cT-p13 in AS Patients (PLANETAS) https://clinicaltrials.gov/ct2/show/record/NCT01220518 and Program evaLuating the Autoimmune Disease iNvEstigational Drug cT-p13 in RA Patients(PLANETRA), https://clinicaltrials.gov/ct2/show/NCT01217086?term=planetra&draw=2&rank=1.

[58] Tommaso Gabbani et al., "CT-P13 design, development, and place in therapy," *Drug Design, Development and Therapy* 11 (2017): 1653–1661, 1655.

[59] Danese et al., "ECCO Position statement on the use of biosimilars for inflammatory bowel disease - an update," 31.

[60] *Ibid.*

[61] "Long-term follow-up of switching to biosimilar infliximab," GaBi online (Generics and Biosimilars Initiative), posted January, 11, 2019, accessed on January 30, 2019, http://www.gabionline.net/Biosimilars/Research/Long-term-follow-up-of-switching-to-biosimilar-infliximab.

A two-year follow-up study after switching from originator to CT-P13. [62]	It showed that most of the patients maintained the therapy with good profile of safety and efficacy.
ELEMENT 5 non-inferiority 24 weeks randomized control clinical trial of Lilly Insulin glargine versus Lantus in insulin-naïve and insulin-treated adults with type 2 diabetes from December 2014 to July 2016.[63]	The results showed that overall, Lilly insulin glargine Basaglar® in insulin-naïve patients or patients on insulin glargine, alone or with oral anti-glycaemic drugs provided similar glucose control and safety findings in type 2 diabetes population (mainly Asian patients).

Zoltán Kaló claimed that following a review on 41 non-empirical papers, the hypothetical risk to adverse events could not be justified, whilst another 12 empirical studies did not show an increased risk of adverse events or loss of efficacy on switching. This could imply a disproportionate fear to immunogenicity that is negatively impacting improved access and sustainability of healthcare.[64] This raises ethical issues related to patient safety and will be discussed in Section 4.2.

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62 Maria Fernanda Guerra Veloz et al., "Long-term follow up after switching from original infliximab to an infliximab biosimilar: real-world data," *Therapeutic Advances in Gastroenterology* 12 (2019): 1-12, 1.

63 Robyn K. Pollom et al., "Lilly Insulin Glargine versus Lantus in Insulin-Naïve and insulin-treated adults with Type 2 diabetes: A randomized, controlled trial (ELEMENT 5)," *Diabetes Therapy* 10 (2019): 189–203.

64 Zoltán Kaló, "Optimizing the benefits of biosimilars for society," GaBi online (Generics and Biosimilars Initiative), posted February, 28, 2020, accessed June 20, 2020, http://www.gabionline.net/ Reports/Optimizing-the-benefits -of-biosimilars-for-society.

3.3.1.3 Multiple switching

Repeat switching may be associated with increased risk of immunogenicity and adverse reactions.[65] Separate studies with filgrastim,[66] etanercept,[67] and adalimumab[68] showed no differences in efficacy and safety on multiple switching between reference product and biosimilars, whilst Kang and colleagues,[69] and Yazici and colleagues[70] reported loss of efficacy.

Comparative clinical data of different biosimilars with the reference biological product is highly unlikely to exist such that switching between biosimilars presents a high degree of uncertainty.[71] There are no studies on safety, efficacy and immunogenicity on cross switching (i.e. switching between biosimilars), reverse switching (i.e. switching from biosimilar to originator) or multiple/repeated switching for Infliximab.[72] Due to residual uncertainty there is still strong debate on switching patients from originator to biosimilar, or from biosimilar-to-biosimilar or multiple

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65 Lisa Diependaele et al., "Similar or the Same? Why biosimilars are not the solution," *Journal of Law, Medicine and Ethics* 46, no. 3 (2018): 776-790, 779.

66 Blackwell et al., "Comparison of EP2006, a filgrastim biosimilar, to the reference: a randomized, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy," *Annals of Oncology* 26, no. 9 (2015): 1948-53. Cited in Cohen et al., "Switching reference medicines to biosimilars: A systematic literature review of clinical outcomes," 11.

67 Christopher Griffiths et al., "The EGALITY study: a confirmatory, randomized double-blind study comparing efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs the originator product in patients with moderate-to-severe plaque psoriasis: A randomised, double-blind, multicentre, phase III study," *Annals of American Academia of Dermatology* 76, no. 6 (2017): 1093-102. Cited in *Ibid.*

68 Andrew Blauvelt et al., "A phase III confirmatory study comparing GP2017 with reference adalimumab in patients with moderate-to-high severe chronic plaque psoriasis: 51-week results from ADACCESS study," *European Academy of Dermatology and Venereology Annual Congress Geneva Switzerland* (13 -17 September 2017) EADZ-2017. Cited in *Ibid.*

69 Yun-Seong Kang et al., "Clinical experience of the use of CT-P13, a biosimilar to infliximab in patients with inflammatory bowel disease: a case series," *Digestive Diseases and Sciences* 60, no. 4 (2015): 951-6. Cited in in *Ibid.*

70 Yusuf Yazici et al., "A descriptive analysis of real-world treatment patterns in a Turkish rheumatology population that continued innovator infliximab (Remicade) therapy or switched to biosimilar infliximab," *Arthritis and Rheumatology* 68, Suppl. 10 (2016) (abstract 2240). Cited in *Ibid.*13.

71 Rahman Kabir et al., "The Breakthrough of Biosimilars: A Twist in the Narrative of Biological Therapy," 10.

72 Francois-Xavier Frapaise, "The End of Phase 3 Clinical Trials in Biosimilars Development?" *BioDrugs* 32 (2018): 319–324, 322, https://doi.org/10.1007/s40259-018-0287-0.

switching, such that a physician-led clinical decision is required through shared-decision with the individual patient.[73]

3.3.2 Pharmacy substitution

'Substitution' refers to "the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber."[74] The WHO in its Similar Biological Products (SPB) scientific guidance reflects the European Commission's position i.e. pharmacy substitution is to be determined at the national regulatory level.[75] Policies for pharmacy substitution should only be considered in specific circumstances if supported by scientific evidence, and should be such that the prescribing physician is aware and approves the biosimilar being dispensed.[76] This will be discussed in more detail in the Section 3.3.3.

3.3.3 Positions of Member States

The absence of a central decision on interchangeability at European level resulted in different interpretations by the individual MSs of the EU.[77] A number of European countries set their own policies or regulations on switching or substitution.[78] Following the first immunogenicity incident of pure red cell aplasia (PRCA) reported with erythropoietin in 2002, more incidents led to the banning of automatic substitution by fifteen regulatory authorities.[79] There is no consensus among EU countries on switching

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73 Steven Simoens et al. "How to realize the potential of off-patent biologicals and biosimilars in Europe? Guidance to policymakers," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 7, no. 2 (2018): 70-4, 1.

74 *Ibid*.

75 Ivana Knezevic, "Evaluation of Similar Biotherapeutic products: Scientific and Regulatory Challenges, edited by Elwyn Griffiths, Robin Thorpe, Meenu Wadhwa, Yeowon Sohn," *Biologicals* 39, no. 5 (2011): 249-358. Cited in Gustavo Grampp et al., "Policy considerations for originator and similar biotherapeutic products," *Pharmaceuticals Policy and Law* 18 (2016): 121-139, 131.

76 *Ibid*.

77 Evelien Moorkens et al., "Policies for biosimilar uptake in Europe: An overview," *Public Library of Science (PLoS ONE)* 12 (2017): 1-17, 4.

78 Pieter Dylst et al., "Barriers to the uptake of biosimilars and possible solutions: A Belgian case study," *PharmacoEconomics* 32 (2014): 681-691, 686.

79 Paul Cornes, "The economic pressures for biosimilar drug use in cancer medicine," *Oncologie* 13 (2011): 222-233, 229.

of existing patients, though switching from the reference product to a biosimilar became more acceptable with time in principle.[80] A number of national regulatory authorities in the EU, namely the Dutch MEB, Finnish FMEA, Irish HPRA, Scottish Healthcare Improvement Board and German Paul Ehrlich Institute set position statements and endorsed interchangeability under the supervision of the prescriber.[81] In the Italian regulatory agency (AIFA) position paper on biosimilars (updated 2016) biosimilars are not considered to be completely interchangeable, leaving the final decision to the prescribing physician following a clinical assessment on a case by case basis.[82] Twenty of 31 countries in Europe have laws or policies in place that do not allow pharmacy substitution of biologicals.[83] Some European countries allow pharmacy substitution e.g. Estonia, France, Poland, Latvia and Russia but with some differences in policies.[84] More countries are allowing substitution at pharmacy level.[85] In Malta, medicines are generally provided through the national healthcare system and are procured by central government. The next section will provide an overview of the public healthcare systems in Europe also making reference to that in Malta. Before doing so, however, it is important to point out that the 'soft law' set by EMA with respect to interchangeability may lead to two major ethical and medico-legal questions. First, is a re-evaluation of the comparability studies by MSs or clinicians necessary when it was performed by industry and accepted by EMA experts at pre-authorisation stage? Related to this is the question of whether Mss and clinicians have the required expertise to re-evaluate the comparability studies. Second, what are the ethical and medico-legal implications of switching or substitution that are not in line with EC guidelines of physician-led switching? These ethical issues will be discussed in Section 4.2.2 and 4.2.3, respectively.

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80 Moorkens et al., "Policies for biosimilar uptake in Europe: An overview," 12.

81 Pekka Kurki et al., "Interchangeability of biosimilars: A European perspective," *BioDrugs* 31, no. 2 (2017): 83-91, 89, https://doi.org/10.1007/s40259-017-0210-0.

82 Raffaelli and Massimino, "Biosimilars: considerations in light of the Italian legal framework," 5.

83 Roediger et al., "What pricing and reimbursement policies to use for off-patent biologicals? - Results from the EBE 2014 biological medicines policy survey," 19.

84 Moorkens et al., "Policies for biosimilar uptake in Europe: An overview," 9.

85 *Ibid.,* 12.

3.4 Public healthcare system policies

The Constitution of Malta states that every person is:

> entitled to the fundamental rights and freedoms of the individual … subject to respect for the rights and freedoms of others and for the public interest, to each and all of the following, namely: (a) life … [and] (c) respect for his private and family life,[86]

and, furthermore, that:

> No person shall intentionally be deprived of his life save in execution of the sentence of a court in respect of a criminal offence under the law of Malta of which he has been convicted.[87]

The *Universal Declaration of Human Rights* article 25, paragraph 1, confirms human right to health and health care as a fundamental right of every person.[88]

The European Parliament recognised that public health systems must guarantee universal access to health care, which is a fundamental right of European citizens as per Article 35 of the European Charter of Fundamental Rights of the European Union.[89] The basic rights of patients have been adopted into Maltese Law through Article 27 of the Health Act (2013).[90] Where there is no consensus among the Council of Europe MSs, they are afforded a margin of appreciation (based on the principle subsidiarity),[91] with the aim to reach a balance between individual rights with national interests, referred to as the principle of subsidiarity. If patients feel that their rights are threatened, after seeking redress at the national law courts, if they are unsatisfied with the court judgement, they may refer the case to the European Court of Human Rights.

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86 Constitution of Malta, Art. 32; accessed June 20, 2020. https://legislation.mt/eli/const/eng/pdf.

87 *Ibid*., Art. 33;

88 Norman Daniels, *Just Health – Meeting Health Needs Fairly,* (New York: Cambridge University Press, 2008), 316.

89 "Charter of Fundamental Rights of the European Union." *Official Journal of the European Union* C326 (26.10.2012): 391.

90 Laws of Malta, Chapter 528: *Health Act, 2013*, art. 28, https://legislation.mt/eli/cap/528/eng/pdf.

91 Steven Greer, European Convention on Human Rights – The margin of appreciation: interpretation and discretion under the European Convention on human rights, (Strasbourg: Council of Europe, July 2000), https://www.echr.coe.int/LibraryDocs/DG2/HRFILES/DG2-EN-HRFILES-17(2000).pdf

Does the right to life imply a right to healthcare? Does it mean the right to free medical care as a fundamental human right? This was legally challenged at the Maltese law courts through the case of *Katerina Cachia vs Director General, Department of Health and Honourable Minister for Health* (2000).[92] The plaintiff lost the case and the First Hall of the Civil Court (Constitutional Jurisdiction) decision was appealed to the Constitutional Court in 2007,[93] which confirmed the decision taken by the First Hall of the Civil, which had argued that, neither Chapter IV of the Constitution of Malta on the "Fundamental Rights and Freedoms of the Individual" nor the European Convention give the right to free medical care.[94] The First Hall of the Civil Court quoted Sir Thomas Bingham:

> It is common knowledge that health authorities of all kinds are constantly pressed to make ends meet … they cannot provide all the treatments they would like; … Difficult and agonising judgements have to be made as to how a limited budget is best allocated to the maximum advantage of the maximum number of patients. That is not a judgement which the court can make.[95]

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92 Prim' Awla Tal-Qorti Civili (Sede Kostituzzjonali) Imhallef Onor. Vincent Degaetano LL. D., Seduta tal-Gimgha, 11 ta' Awissu, tas-sena elfejn (2000) fil-10.00 a.m. Rikors Nru: 748/00 VDG Katerina Cachia v. Direttur Generali tad-Dipartiment tas-Sahha u Onorevoli Ministru tas-Sahha, 1-54, 10, https://ecourts.gov.mt/onlineservices/Judgements/Details?JudgementId=0&CaseJudgementId=1628; The case law refers to Ms Katerina Cachia who suffered from advanced cancer of the breast and according to medical opinion from foreign consultants, the only alternative therapy was Taxotere, which at the time was not provided through the Maltese National Healthcare System (NHS). Though the treatment may only prolong life by a few weeks, on the recommendation of the Royal Marsden Hospital, UK, the patient purchased the medicine out-of-pocket. The patient claimed in court that the fundamental right to life was seriously negated as per Article 33 of the Constitution of Malta. Also, the case referred to discrimination towards KC as another patient was claimed to have been provided Taxol through the NHS, though the court concluded that that this was a different treatment and therefore the court ruling in this regard is out of scope of this discussion.

93 Qorti Kostituzjonali (Malta), On. Imhallef Joseph D Camilleri, On. Imhallef Joseph D Filletti u On Imhallef Anton Depasquale, Appell Civili Numru 748/2000/1 Seduta 8 ta' Jannar 2007, *Katerina Cachia u b'digriet tat-8 ta' Jannar 2001, stante mewt ta' l-istess Katerina Cachia fil-mori ta' l-appell. Il-gudizzju gie trasfuz f'isem Mary Cachia, Carmelo Cachia u Cynthia Rapa, lkoll ahwa tal-mejta Katerina Cachia v. Direttur Generali tad-Dipartiment tas-Sahha u Onorevoli Ministru tas-Sahha*, 2007: 1-37, https://ecourts.gov.mt/onlineservices/Judgements/Details?JudgementId=0&CaseJudgementId=1628.

94 Katerina Cachia u b'digriet tat-8 ta' Jannar 2001, stante mewt ta' l-istess Katerina Cachia fil-mori ta' l-appell. Il-gudizzju gie trasfuz f'isem Mary Cachia, Carmelo Cachia u Cynthia Rapa, lkoll ahwa tal-mejta *Katerina Cachia v. Direttur Generali tad-Dipartiment tas-Sahha u Onorevoli Ministru tas-Sahha*, 10.

95 *Ibid.,* 14.

In the case of Katerina Cachia, the Constitutional Court claimed that the position taken was purely a legal one without entering into ethical, moral or political grounds.[96]

The right to health and healthcare, in fact, is more than simply a political (or legal) right; it is a moral right.[97] A rights-based approach requires governments to secure the health and well-being of its population, whilst ensuring equity in the allocation and utilization of resources.[98] However, it does not mean that states are obliged to give all medical care for free.

States are therefore responsible towards fair and equitable distribution of scarce medical resources. It is precisely because of this that MSs are free to set their own healthcare policies on prescribing, pricing and reimbursement at MS level (as illustrated in Section 3.3) depending on the availability of medical resources in that state, the finances of that state, the disease distributions in that state, etc.

In 2017, the European Parliament (EP) called on the EC to improve access to medicines through

> measures to guarantee the right of patients to universal, affordable, effective, safe and timely access to essential and innovative therapies, to guarantee the sustainability of EU public healthcare systems, and to ensure future investment in pharmaceutical innovation; stresses that patient access to medicines is a shared responsibility of all actors of the healthcare system.[99]

As a result, European countries have introduced various policies with the aim of increasing competition, reducing medicine prices and increasing biosimilar uptake.[100] An analysis of the various policies is provided below.

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96 *Katerina Cachia v. Direttur Generali tad-Dipartiment tas-Sahha u Onorevoli Ministru tas-Sahha*, 21.

97 Daniels, *Just Health – Meeting Health Needs Fairly*, 316.

98 *Ibid.,* 314.

99 European Parliament, *Options for improving access to medicines – European Parliament resolution of 2 March 2017 on EU options for improving access to medicines,* (Brussels: European Parliament, 2017), No. 52.

100 Alessandra Ferrario et al., "Strategy procurement and international collaboration to improve access to medicines," *Bulletin World Health Organization* 95 (2017): 720-722, 720.

3.4.1 Mandatory switching policies

Mandatory switching mainly refers to 'non-medical switching' or constrained prescribing through tendering systems which favour the cheaper biosimilars and through financial incentives to doctors to prescribe the less expensive biosimilars via 'gain sharing' projects where the hospital department is given some of the money saved.[101] Hospitals may also set quotas to be reached by physicians with the aim that a specific percentage of biosimilar prescriptions is reached as compared to the prescriptions for the originator.[102]

A study in Denmark showed that mandatory switching of etanercept could result in increased risk of the nocebo effect, though more studies are necessary to determine whether a shared physician-patient decision is superior to mandatory switching in terms of nocebo effect, increased efficacy and reduced health care costs.[103]

3.4.1.1 Incentive systems and 'gain sharing'

Biosimilar companies offer financial incentives to hospitals through 'gain sharing' claiming that they are offered to cover expenses related to the switch for engaging more nurses in educating the patient and monitoring closely the patients for any adverse effects. In Belgium, originator biological companies, however, already provide incentives to hospitals through high discount systems resulting in the lack of price transparency, thus making it difficult for biosimilar companies to compete.[104] This shows the lack of transparency that exists within hospital settings which would benefit from discounts at the expense of taxpayers and society.[105]

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[101] Sean Milmo, "A question of quality," *Pharmaceutical Technology Europe* (July 2017), 11-12.

[102] Moorkens et al., "Policies for biosimilar uptake in Europe: An overview," 8.

[103] "Mandatory and non-mandatory switching for biosimilars," GaBi online (Generics and Biosimilars Initiative), posted March 01, 2019, accessed December 11, 2019, http://gabionline.net/Biosimilars/Research/Mandatory-and-non-mandatory-switching-for-biosimilars.

[104] Dylst et al., "Barriers to the uptake of biosimilars and possible solutions: A Belgian case study," 686.

[105] *Ibid.,* 689.

It is interesting to note that Aladul and colleagues report that healthcare professionals (HCPs) favour cost savings through biosimilars only if their department would benefit directly, which raises ethical questions.[106]

3.4.1.2 Procurement policies

Public procurement "refers to the process by which public authorities, such as government departments or local authorities, purchase work, goods or services from companies."[107] The EU law sets out minimum harmonised public procurement rules with the aim of achieving transparency, open competition and equal treatment through standard procedures so as to ensure that public funds are used appropriately. EU law covers tenders whose monetary value exceeds a certain amount and is transposed into national legislation. For tenders of lower value, national rules that respect the general principles of EU law apply.[108] Procurement policies are aimed at increasing competition between biosimilars and originator biologicals of the same therapeutic class.[109] Centralised procurement at national level is reported to result in efficiency gains and to lower prices.[110] Procurement agencies or hospitals should factor in the additional costs involved to implement the switch as the biosimilar may end up not being the economic choice.

3.4.1.2.1 Reference Pricing

This refers to External Reference Pricing (ERP) and Internal Reference Pricing (IRP) where the benchmark prices are set by government based on the prices of medicines in other countries (for ERP) or other medicines on the national market (for IRP).[111] IRP is

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[106] Mohammed Ibrahim Aladul et al., "Healthcare professionals' perceptions and perspectives on biosimilar medicines and the barriers and facilitators to their prescribing in UK: a qualitative study," *British Medical Journal* (2018), 1, https://doi.org/10.1136/bmjopen-2018-023603.

[107] "Internal Market, Industry, Entrepreneurship and SMEs – Public Procurement," European Commission, last accessed June 28, 2020, https://ec.europa.eu/growth/single-market/public-procurement_en.

[108] *Ibid.*

[109] Bocquet et al., "Competition between biosimilars and patented biologics: Learning from European and Japanese experience," *PharmacoEconomics* 34 (2016): 1173-1186, 1174.

[110] Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* 18.

[111] Moorkens et al., "Policies for biosimilar uptake in Europe: An overview," 5.

implemented in two thirds of European countries allowing open competition between originator biologicals and biosimilars.[112] In Malta, ERP is implemented only for originator products and no IRP system is in place since a national reference pricing system exists. If biosimilars are included in ERP and IRP systems, this would imply that the biosimilars are considered as interchangeable with those products in the same reference group which would mean that biologicals are automatically substituted to biosimilars.[113] In Malta generics and biosimilars are not included in the ERP system but may be procured through open tendering systems.

3.4.1.2.2 Negotiated procedures

Another system is the negotiated procedure, which is used for patented medicines, as is the case in Malta. The procedure may also be used for non-patented biologicals, where on expiry of the patent of an originator biological, a new negotiated procedure is launched for the corresponding biosimilars, with the aim to achieve price reduction.[114]

3.4.1.2.3 Tendering systems

Tendering systems are aimed at achieving lower prices through competition and can be implemented at hospital, regional and national level.[115] Netherlands reported that the procurement process for adalimumab biosimilars resulted in an 89% discount by AbbVie, the MAH for the originator adalimumab (Humira®), such that at least 70% of Dutch patients remained on Humira.[116] Norway reported an 80% discount for biosimilars through the tendering system, leading to significant cost savings.[117] It is argued that tendering systems where 'the winner takes all' should be avoided due to the risk of

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[112] Moorkens et al., "Policies for biosimilar uptake in Europe: An overview," 5

[113] *Ibid.,* 12.

[114] *Ibid.,* 5.

[115] Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* 18.

[116] Eric Sagonowsky, "AbbVie's massive Humira discounts are stifling Netherlands biosimilars: report," April 2, 2019, accessed March 28, 2020, "https://www.fiercepharma.com/pharma/abbvie-stifling-humira-biosim-competition-massive-discounting-dutch-report

[117] Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* 19.

withdrawal of products which do not have any market share from the market, which could result in shortages.[118] They may also lead to multiple switches which could increase the risk of adverse effects.[119]

In Malta, an open tendering system is implemented in line with procurement regulations. There is no official policy specifically for the procurement of biologicals but generally prior agreement is reached with the clinical department within the Health Department on a case-by-case basis. If the specifications are 'open,' i.e. they do not specify a specific brand, biosimilars would be considered as interchangeable, which could mean that patients may be automatically switched to biosimilars, as for generics, at pharmacy level.

This was the case with epoetin, human growth hormone and filgrastim and the system could result in multiple switches between different brands or biosimilars, but tenders are generally awarded on a time-based principle for a minimum of 24 months, thus avoiding frequent multiple switching between products, which is recommended by clinicians.

A different approach is in place for the more complex mAbs where the switch is considered on a case-by-case basis in agreement with clinicians as will be discussed in Section 3.4.2 below. Generally, a tender is initiated prior to the expiry of the patent and the first cheapest biological or biosimilar is awarded via tender. The branded originator would continue to be purchased via the negotiated procedure for those patients who are retained on the originator until there is a complete switchover to the biosimilar, unless otherwise stipulated in the policy.

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[118] Simoens et al., "How to realize the potential of off-patent biologicals and biosimilars in Europe? Guidance to policymakers."

[119] Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* 18.

3.4.1.2.4 Alternative funding mechanisms

Some European countries obtain funding on a national level through different funding systems. [120] These include:

- Managed-entry agreements (MEAs) with the aim to obtain favourable prices, where a confidential agreement is reached between the MAH and the government on, for example, price discounts, price-volume agreements, or utilisation capping.[121] In 2019 the Department of Health and Social Care (DHSC) representing the governments of Scotland, Wales and Northern Ireland introduced the Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) with the Association of the British Pharmaceutical Industry (ABPI) aimed to support innovation by industry whilst introducing new medicines for specific clinical areas where the increase in expenditure is capped.[122] Malta also used similar agreements, as was the case with Hepatitis C treatment, which was introduced in 2018 through confidential agreement with the company, as otherwise this was unaffordable to the NHS.[123]
- Amortization (i.e. paying by making a number of smaller payments over a period of time) is being proposed and piloted as an alternative for medicines with extremely high price tags.
- Value-based pricing where expensive medicines are accepted even if benefits are low, but may be of 'value,' for example for orphan diseases and cancer treatment.

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120 Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* 13.

121 *Ibid.*, 14.

122 "What is the new Voluntary Scheme on branded medicines?" Association of the British Pharmaceutical Industry (ABPI), accessed March 28, 2020 https://www.abpi.org.uk/new-medicines/medicine-pricing-in-the-uk/what-is-the-new-voluntary-scheme-on-branded-medicines/.

123 Ivan Martin, "All Hep C patients to start receiving free treatment," *Times of Malta*, published February 14, 2018, https://timesofmalta.com/articles/view/free-treatment-to-all-hep-c-patients-to-be-made-available.670655.

These arrangements are generally confidential agreements resulting in a lack of transparency in prices, which would raise ethical questions on appropriate allocation of resources and fair competition which will be discussed in Section 4.3.1.

3.4.2 Reimbursement and hospital formulary systems

3.4.2.1 Reimbursement system

Health Technology Assessment (HTA) for medicines is applied in many European countries as part of the reimbursement system and is mainly used as a decision tool by expert groups, such as the EUNETHTA (European Network Health Technology Assessment), which provides practical application of tools and approaches to cross-border HTA collaboration to MSs.[124] Some expert groups such as Institute for Health and Care Excellence (NICE) in the UK, the European League Against Rheumatism (EULAR) and the French Society of Rheumatology recognised biosimilars for rheumatoid arthritis in the same therapeutic level as the corresponding originator biologicals.[125] In Malta, HTAs are used only for innovative originator medicines.

The transparency of pricing and reimbursement decisions may contribute towards the identification of solutions that could lead to fair pricing, i.e. the right balance between affordability and innovation, and ultimately guarantee accessibility to patients.[126] The Transparency Directive 89/105/EEC dating back to 1989 is aimed towards transparency on the duration of national decisions on pricing and reimbursement for medicines. A draft proposal to streamline and reduce the timing of national decisions was withdrawn due to objections by MSs as no agreement could be reached.[127] The EC proposed alternative ways to ensure the transparency of pricing and

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[124] "European Network Health Technology Assessments (EUNetHTA)," accessed June 29, 2020, https://eunethta.eu/about-eunethta/history-of-eunethta/.

[125] Baumgart et al., "Biologic therapies in immune-mediated inflammatory diseases: Can biosimilars reduce access inequities?" 9.

[126] Allison Colbert et al., "Can affordability and innovation coexist for medicines?" *British Medical Journal* 368, no. 7058 (2020): 115, https://doi.org/10.1136/bmj.l7058.

[127] "Transparency Directive," European Commission, accessed February 29, 2020, https://ec.europa.eu/growth/sectors/healthcare/competitiveness/products-pricing-reimbursement_en.

reimbursement measures for medicinal products with the aim of guaranteeing timely entry into the market of generics and biosimilars.[128] A number of Councils under different European presidencies, including the Maltese Presidency in 2017, tried to promote sharing of information on national pricing and reimbursement policies, including pricing agreements between MSs, but this remains through voluntary collaborations.[129]

3.4.2.2 Hospital formulary system

The new biologicals are mainly dispensed from the hospital setting, which in most European countries does not form part of the reimbursement system. It is reported that hospital pharmaceutical expenditure constitutes a significant share of the overall pharmaceutical expenditure.[130] For the hospital setting, the Pharmacy & Therapeutic Committee (P&T Committee) selects which medicines are included on the Formulary based on a number of factors, i.e. clinical, quality of life, safety and pharmacoeconomic outcomes.[131] The evaluation checklist for biosimilars by Krämer and colleagues considered other factors, namely, the manufacturing process, clinical comparability data, batch consistency, reliability of supply, data on good handling practice and pharmacovigilance data.[132] An improved version by Boone and colleagues limits the checklist to a set of 10 clinically relevant criteria.[133] The P&T Committee assigns a % score to the biosimilar in comparison with the reference product and those biosimilars meeting the set % score may be considered for introduction on the Formulary based on price.[134] A more specific tool for the evaluation of biosimilars of Low Molecular Weight

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[128] "Commission initiatives in pricing and reimbursement," European Commission, accessed March 28, 2020, https://ec.europa.eu/growth/sectors/healthcare/competitiveness/products-pricing-reimbursement/initiatives_en.

[129] Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* 10.

[130] *Ibid.,* 8.

[131] Irene Krämer et al., "Points to consider in the evaluation of biopharmaceuticals," *European Journal of Hospital Pharmacy* 14, no. 1 (2008): 73-76, 73.

[132] *Ibid*., 76.

[133] Niels Boone et al., "How to select a biosimilar," *European Journal of Hospital Pharmacy* 20 (2013): 275–286, 277.

[134] *Ibid*.

Heparin (LMWH) is the 'System of Objectified Judgement Analysis / Informatix model' (SOJA), which takes into consideration a number of factors, for example, the heparin source and production process together with weighted factors by P & T members prior to recommending for formulary uptake.[135]

3.4.2.3 Switching to biosimilars in Malta

Within the Maltese national healthcare system, generic substitution is automatic, as medicines are listed on the Government Formulary List in their international non-proprietary name (INN) and are prescribed and dispensed as non-proprietary. This is not the case if the product is listed by brand name, as in the case with biological medicines, some anti-epileptic medicines and narrow therapeutic index drugs, or if the patient is approved for the branded product through the Exceptional Medicinal Treatment Committee.[136]

Cassar and colleagues reported that only 27% of 942 clinicians within the Maltese NHS agreed with switching to biosimilars, with 46% considering the physician's "sole authority to prescribe a reference product or biosimilar … as very important or critical."[137] There is no over-arching policy on switching to biosimilars within the Maltese NHS, but consensus is reached at clinical departmental level, which means that medicines are automatically substituted when a new brand is awarded through open tendering system. Healthcare professionals are generally notified of the switch from one brand to another. For mAbs, specific switching policies were issued by the Department of Health in agreement with clinicians at clinical department level. The different policies are listed in Table 7.

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[135] Jacobus R.B.J. Brouwers et al., "Biosimilars of low molecular weight heparins: Relevant background information for your drug formulary," *British Journal of Pharmacology* (2019) 1-8, 6-7.

[136] Ministry for Health, Malta, *Amendments to Legal Notice 58/2018 regarding the Exceptional Medicinal Treatment Committee, Regulations DH Circular 22/2019, accessed May 11, 2020,* https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/Circulars/2019/circular_22_2019.pdf.

[137] Kathleen Cassar et al., "Biosimilars: The perception among Maltese clinicians," *Annals of the Rheumatic Diseases*, suppl. 2; London 75 (June 2016): 1294, https://doi.org/10.1136/annrheumdis-2016-eular.1061SAT0637-HPR.

Table 7: Policies for switching to biosimilars in Malta

Name	Date of Implementation
Human growth hormone, Filgrastim	n/a
Erythropoietin[138]	2015 & 2019
Infliximab[139]	October 2016
Etanercept[140]	November 2017
Adalimumab[141]	September 2019

3.4.3 Funding by non-profit organisations

Other specific funding systems, such as the UK Cancer drug fund, have also been set up.[142] In Malta, the Malta Community Chest Fund Foundation (MCCFF) chaired by the President of Malta provides financial assistance for treatment not provided by the National Health Service. In June 2019, it was reported that over €1.2 million per month were being spent by the MCCFF on cancer drugs.[143] This scheme was strongly criticised as such arrangements could lead to "wastage of resources, as patients would be maintained on expensive treatments which are of no benefit to them."[144] In 2019, the

[138] Ministry for Health, Malta, *Erythropoietin ALL doses (2000IU; 3000IU and 4000IU) – Change in Brand for Adult Patients,* July 22, 2019, accessed May 11, 2020, https://deputyprimeminister.gov.mt/en/cpsu/Documents/News/CPSU%20Medicine%20Alerts%20%20Internal/2019/MFH%5E12%5E2019.pdf.

[139] Ministry for Health, Malta, *Switchover Implementation Plan from Remicade® to Biosimilar Infliximab (Inflectra®/Remsima®*), October, 07, 2016, accessed May 11, 2020, https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/Circulars/2016/circular_428_2016.pdf

[140] Ministry for Health, Malta, *Biosimilar Etanercept 50mg Pre-Filled Pen,* November 21, 2017, accessed May 11, 2020, https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/Circulars/2017/circular_96_2017.pdf.

[141] Ministry for Health, Malta, *Biosimilar Adalimumab 40mg Pre-filled Syringes*, September 16, 2019, accessed May 11, 2020, https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/Circulars/2019/circular_95_2019.pdf

[142] Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* 17.

[143] Kurt Sansone, "Government to step in and offer cancer drugs currently funded by President's charity," *Malta Today,* June 23, 2019, https://www.maltatoday.com.mt/news/ national/95830/government_to_step_in_and_offer_cancer_drugs_currently_funded_by_presidents_charity_#.XsLmTWgzbcc.

[144] "Drugs for Cancer and rare diseases should be provided by government – Chamber," *Times of Malta*, March 23, 2017, https://timesofmalta.com/articles/view/drugs-for-cancer-and-rare-diseases-should-be-provided-by-government.648814.

new chair of the MCCFF, the Hon. President of Malta, Dr George Vella, called for procurement to be taken over by the government, with a proper means testing and more control on funding and a just allocation system.[145] This would ensure proper allocation of resources and purchase of medicines through the appropriate procurement procedures to ensure fair prices.[146]

3.4.4 Conclusion on public healthcare system policies

Overall, biosimilar uptake in most developed countries where switching was imposed remains moderate as a result of price reduction by originator companies and refusal by patients to accept a biosimilar such that they are switched to an alternative branded biological.[147] In some European countries, however, drug procurement and national healthcare systems are leading to biosimilar switching which goes beyond the recommendation of national regulatory authorities of physician-led prescribing.[148] The different policies being implemented in EU countries could lead to inequity in accessibility across European countries and also at national and regional levels.

Various ethical issues arise with mandatory switching policies which will be discussed in Chapter 4, namely:

- Ethical concerns related to safety (Section 4.2)
- The lack of pricing transparency that results from financial incentives may lead to unfair competition and inappropriate allocation of resources (Section 4.3);
- Financial incentives to healthcare professionals could lead to conflict of interest (Section 4.1);

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[145] David Hudson, "George Vella wants more control over presidential charity's funds," *Malta Today*, June 20, 2019, https://www.maltatoday.com.mt/news/xtra/95798/watch_george_vella_wants_more_control_over_presidential_charitys_funds#.Xn9QoG5Fx5s.

[146] Kurt Sansone, "Government to step in and offer cancer drugs currently funded by President's charity," *Malta Today*, June 23, 2019.

[147] Marc Scherlinger et al., "Acceptance rate and sociological factors involved in the switch from originator to biosimilar etanercept (SB4)," *Seminars in Arthritis and Rheumatism* 00 (2018): 1-6, 5.

[148] Grampp et al., "Policy considerations for originator and similar biotherapeutic products," 130.

- Whether procurement and reimbursement policies aimed at cost savings to the NHS justify switching stabilised patients to a biosimilar, exposing them to new risks and even additional risks resulting from multiple switching (Section 4.3);
- On the other hand, not switching patients means inappropriate allocation of resources (Section 4.3);
- Switching by non-government organisations could lead to lack of transparency in prices (Section 4.3)
- Different policies across Europe means inequity to accessibility of medicines between EU countries (Section 4.3).

3.5 Accessibility to biologicals

As discussed above, the availability of biologicals differs greatly between European countries and depends on the level of funding by governments.[149] Substitution may sustain affordability of healthcare and product access to healthcare to a larger number of patients.[150] The problem of affordability for low-income countries and financial sustainability of health care systems, even in high-income countries, have been a priority on the agenda of policy makers.[151]

3.5.1 Economic impact of biosimilars

The OECD claimed that healthcare systems stand to benefit from competition of off-patent biologicals and biosimilars.[152] Medicines for Europe, the organisation representing the generic pharmaceutical industry, reported savings to EU governments

[149] Moorkens et al., "Policies for biosimilar uptake in Europe: An overview," 4.

[150] Steven Simeons, "Generic and therapeutic substitution: ethics meets health economics," *International Journal of Clinical Pharmacy* 33 (2011): 469-470, 469.

[151] Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* 8.

[152] Simoens et al., "How to realize the potential of off-patent biologicals and biosimilars in Europe? Guidance to policymakers."

of €100 billion in 2014 through generics.[153] Considering these savings for generics, significant savings should be achieved with biosimilars. According to Quintiles IMS (previously IMS Health), €50 to €100 billion in aggregated savings over a five-year period were projected to be achieved by 2020.[154] A campaign by the UK NHS to doctors and patients to use generics and biosimilars led to over €700 million savings over the period 2018 - 2019.[155] Higher cost savings were projected to be achieved with mAbs. For example, etanercept was envisaged to result in cost savings of £81.6 million/year (€96.4million) based on 70% biosimilar uptake and a price reduction of 20% on Enbrel (originator brand) considering UK sales in 2015 of £408 million/year (€482 million).[156] In 2018 etanercept biosimilars were projected to bring cost savings of €90 million over 5 years to the Italian NHS.[157] In 2015, the potential cost savings on infliximab biosimilars were between €25.79 million and €77.37 million (assuming price reduction of 10% and 30%) in Belgium, Germany, Italy, Netherlands and UK.[158] In Eastern countries, potential cost savings on infliximab biosimilars for CD over three years were between €8 million and €16.9 million.[159] Adalimumab biosimilars were predicted to take over 19% of RA & Gastroenterology market by 2020.[160]

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153 Jean-Baptiste Reiland, "What pricing and reimbursement policies to use for off-patent biologicals in Europe? - results from the second EBE biological medicines policy survey," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 6, no. 2 (2017): 61-78, 61.

154 *Ibid*., 61.

155 "NHS cuts medicines costs by three quarters of a billion pounds," *Long Term Plan,* 31 August 2019, https://www.longermplan.nhs.uk.

156 Scherlinger et al., "Acceptance rate and sociological factors involved in the switch from originator to biosimilar etanercept (SB4),", 5.

157 Roberto Ravasio et al., "Analisi di budget impact del biosimilare di etanercept: lo scenario italiano," *Global & Regional Health Technology Assessment* 5, no.1 (2018): 1–12. Cited in Baumgart et al., "Biologic therapies in immune-mediated inflammatory diseases: Can biosimilars reduce access inequities?" 8.

158 Ashok Jha et al., *Advances in Therapy* 32, (2015): 742–756. Cited in *Ibid.*

159 Bradowski et al., *Expert Review of Pharmacoeconomics & Outcomes Research* 16, no. 1, (2016): 119.125. Cited in Baumgart et al., "Biologic therapies in immune-mediated inflammatory diseases: Can biosimilars reduce access inequities?" 8.

160 Baumgart et al., "Biologic therapies in immune-mediated inflammatory diseases: Can biosimilars reduce access inequities?" 8.

Biosimilars indicated for the treatment of RA (for example infliximab, adalimumab and etanercept), resulted in significant cost-savings to the UK NHS.[161] Another study showed that biosimilars for immune-mediated inflammatory diseases (IMIDs), resulted in price reduction as a result of competition, which lead to reduced healthcare expenditure on IMIDs.[162] Cost savings could be utilised to provide treatment for other diseases or to other patients who qualified for treatment, which would translate in long-term cost savings, as more hospitalisations and surgeries may be avoided, thus positively impacting the health economy.[163]

3.5.2. Outcomes of biosimilar uptake

Generally, once a biosimilar product is authorised, volumes of biosimilar sales increase gradually as prices are lowered. Biosimilar uptake, however, is influenced by new indications, economy and changes in diagnosis and prevalence of disease.[164] According to Quintiles IMS, in Europe alone, sales of biosimilars tripled over five years.[165] The average uptake rate across European countries in 2019 was 43% for complex biosimilars, such as mAbs, which were first approved in 2013, and 91% for the older first-generation biosimilars which were authorised earlier.[166] The biosimilar market in 2018, however, accounted for only 2% of the global sales of biologicals (and 4.6% of European sales).[167] By 2019 Europe accounted for 60% of the global biosimilar market, which is constantly on the increase.[168] It was also reported that by 2020, biosimilars would be on the market for 12 blockbuster drugs with global sales of over US$67 billion, bringing potential savings of between €11.8 and €33.4 billion in Europe between 2007 and

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161 Aladul et al., "Healthcare professionals' perceptions and perspectives on biosimilar medicines and the barriers and facilitators to their prescribing in UK: a qualitative study," 533.

162 Baumgart et al., "Biologic therapies in immune-mediated inflammatory diseases: Can biosimilars reduce access inequities?" 1.

163 *Ibid*., 9.

164 IMS Health, *Impact of Biosimilar competition*, (United States: IMS Health, June 2016), 7.

165 Milmo, "A question of quality," 11.

166 Pharmaceutical Technology, "The top-selling prescription drugs by revenue: Ranking the top ten."

167 Derbyshire and Shina, "Patent expiry dates for biologicals: 2018 update."

168 Reilly and Schneider, "The evolution of the European biosimilars market."

2020.[169] There is a wide variation in biosimilar uptake across European countries depending on culture;[170] local regulatory frameworks and different national pricing policies adopted by European governments;[171] variations between therapeutic classes and market sectors i.e. hospital or retail;[172] and variations across European countries in prescriber and patient confidence.[173]

3.5.3 Biosimilar uptake strategies

The penetration of biosimilars on the European market is expected to intensify competition leading to lower prices, even if biosimilars remain unsold or biosimilar uptake is low, as they impact the price of the whole therapeutic class including that of the reference product and biosimilar.[174] Biosimilars therefore may contribute towards improving accessibility for all, with the ultimate goal of achieving universal health coverage.[175]

For generics, the higher the consumption of generics, the lower the price, but this is not so for biosimilars, showing that pricing policies alone are not sufficient to increase biosimilar uptake.[176] Price reductions of 50-70% have been reported with some biosimilars, but there is a poor correlation between the biosimilar market share and

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169 "67 billion worth of biosimilar patents expiring before 2020," GaBi online (Generics and Biosimilars Initiative), posted January 20, 2014, accessed December 11, 2019, 683, http://www.gabionline.net/Biosimilars/General/US-67-billion-worth-of-biosimilar-patents-expiring-before-2020.

170 Roediger et al., "What pricing and reimbursement policies to use for off-patent biologicals? - Results from the EBE 2014 biological medicines policy survey," 21.

171 Francois Bocquet et al., "Biosimilar granulocyte colony-stimulating factor uptakes in the EU-5 markets," *Applied Health Economics and Health Policy* 12, no.3 (2014): 315-26. Cited in Dylst et al., "Barriers to the uptake of biosimilars and possible solutions: A Belgian case study," 688.

172 Bocquet et al., "Competition between biosimilars and patented biologics: Learning from European and Japanese experience,"1173.

173 Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* 7.

174 IMS Health, *Impact of Biosimilar competition,* 4-5.

175 Ferrario et al., "Strategy procurement and international collaboration to improve access to medicines," 720.

176 Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* 19.

price reduction.[177] In fact, price reduction was not always achieved with the introduction of biosimilars, for example with erythropoietin (EPO) and G-CSFs biosimilars, as patients were switched to second-generation products, namely mAbs.[178]

There are various barriers to biosimilar uptake, including the perception of inferior quality, lack of incentives to prescribers, lack of clear regulation and reluctance by prescribers to switch brands.[179] These barriers result from a lack of knowledge on biosimilars, a lack of a central regulatory decision on 'interchangeability' and increased burden on physicians during switching.[180] A 2014 survey in the EU and US on a sample of the general population showed that only 6% - 30% reported at least a general impression of biosimilars and more than 70% reported that they never heard of biosimilars.[181] This could be a deterrent to their acceptance on switching, emphasizing the need for patient education about biosimilars.[182] Cassar and colleagues reported that 59% of 942 clinicians within the Maltese NHS were not familiar with biosimilars.[183] Various strategies were implemented to address these barriers as detailed in Table 8 below.

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177 IMS Health, *Impact of Biosimilar competition,* 4-5.

178 Bocquet et al., "Competition between biosimilars and patented biologics: Learning from European and Japanese experience," 1182.

179 Dylst et al., *"Barriers to the uptake of biosimilars and possible solutions: A Belgian case study,"* 686.

180 *Ibid*.

181 Ira Jacobs et al., "Patient attitudes and understanding about biosimilars: an international cross-sectional survey," *Patient Preference and Adherence* 10 (2016): 937-948, 942.

182 *Ibid.,* 943.

183 Cassar et al., "Biosimilars: The perception among Maltese clinicians."

Table 8: Strategies that addressed barriers to biosimilar uptake

Barriers to biosimilar uptake	Implemented strategies
Lack of knowledge on biosimilars. Lack of knowledge on biosimilars resulted in the lack of stakeholder confidence in prescribing biosimilars.[184] Patients' reluctance to switch on the basis of cost alone due to safety & efficacy concerns especially in view of lack of long-term safety data on biosimilars.[185] Also lack of data on comparative efficacy. Negative perception by patients who tend to compare biosimilars to generics, which are considered of poor quality due to cheap price such that patients are likely to switch back to the branded biological.[186]	Strategies to provide information.[187] International initiatives to promote the use of biosimilars in various countries, including: A. Specific education programmes to healthcare professionals in Germany, France, Norway and the Netherlands. [188] B. The EMA issued various information documents including:[189] - A consensus information paper was issued in 2013. - Information document for HCPs in 2016. - Guide to HCPs in 2016. - Q & A to HCPs and patients that has been translated in several languages, with the aim to increase knowledge; - Animated video for patients. C. The Danish Council for the use of expensive medicines in Denmark issued recommendations on switching patients to biosimilars. [190] D. In Norway annual conferences were held for physicians aimed at providing a platform for open discussion on their concerns.[191] E. The NHS England issued a guidance document, "What is a Biosimilar Medicine?" in 2015 which was updated in 2019 which recommends that switching must be made

184 Dylst et al., "Barriers to the uptake of biosimilars and possible solutions: A Belgian case study," 681.

185 Mohammed Aladul et al., "Impact of Infliximab and Etanercept Biosimilars on Biological Disease-Modifying Antirheumatic Drugs Utilisation and NHS Budget in the UK," *BioDrugs* 31 (2017): 533–544, https//:doi.org/10.1007/s40259-017-0252-3.

186 Scherlinger et al., "Acceptance rate and sociological factors involved in the switch from originator to biosimilar etanercept (SB4)," 4.

187 Moorkens et al., "Policies for biosimilar uptake in Europe: An overview," 10 – 11.

188 "International promotion and education for biosimilars," GaBi online (Generics and Biosimilars Initiative), posted, December 14, 2018, accessed December 11, 2019, http://www.gabionline.net/Reports/International-promotion-and-education-for-biosimilars.

189 *Ibid*.

190 Alessandra Ferrario et al., "Strategy procurement and international collaboration to improve access to medicines," 720.

191 *Ibid*.

	by the prescriber in consultation with the patient in line with the principles of shared decision making.[192]
Lack of a clear regulatory decision on interchangeability Concerns on switching or substitution and interchangeability result in lack of confidence by physicians and patients.[193]	1. Studies performed by independent institutions for example the NOR-SWITCH study which was funded by the Norwegian government and other studies detailed in Table 6; 2. Different professional associations have issued their own position statements to guide their professionals. For example, the European Society of Medical Oncology (ESMO) considers the involvement of clinicians and nurses and informing the patients about the biosimilar as crucial when switching patients and therefore does not endorse substitution at pharmacy level.[194]
Burden of switching	**Strategies to reduce burden of switching**
Monitoring of patients on switching to biosimilars may be very resource intensive.[195]	Gain sharing where part of the savings goes to the hospital or prescribing physician

The above shows that the strategies implemented so far still show a slow biosimilar uptake. The key drivers for biosimilar uptake are incentives to physicians to prescribe, to pharmacists to dispense and to patients to accept biosimilars.[196]

Professor Zoltán Kaló, Professor of Health Economics at the Centre for Health Technology Assessment, Semmelweis University and Syreon Research Institute, presented a case study on trastuzumab at the EC fifth workshop in October 2019, which showed that the uptake of trastuzumab for the treatment of breast cancer "indicates access restrictions in lower income countries in Europe and that the five-year survival is

[192] NHS England and NHS Improvement, *What is a Biosimilar Medicine?* June 2019, 1-20, 10, https://www.england.nhs.uk/publication/what-is-a-biosimilar-medicine/.

[193] *Ibid*.

[194] Emilio Bria and Pierfranco Conte, "Biosimilars as a strategy to improve sustainability," *European Society for Medical Oncology* 2 (2017): 1-2, 2.

[195] Moorkens et al., "Policies for biosimilar uptake in Europe: An overview," 10.

[196] Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* 19.

indicative of a greater unmet need in lower income countries, confirming that biosimilars are a game changer for both healthcare and increased patient access."[197]

A long-term ethical and sustainable policy framework is needed based on a multi-stakeholder approach with the aim of achieving an equitable, competitive and sustainable market for off-patent biologicals and biosimilars in Europe.[198] Pharmacists can act as 'catalyst(s) of change' in their respective roles in regulatory affairs, in industry and patient care so as to increase the use of biosimilars.[199] Physicians, academia and patients should be involved in the development of policies for prescribing and switching to biosimilars.[200] The switching policy should be based on scientific evidence, including real-world data, pharmacovigilance data, switching data and outcome data.[201] In addition, an IT infrastructure could be a useful tool for physicians in the monitoring of patients being switched to biosimilars.[202] The ethical issues related to inequitable access to medicines in Europe will be discussed in Section 4.3.2.

3.5.4 Accessibility on a global level

The issue of accessibility is considered to be a global issue as over 2 billion people worldwide are reported as not having access to medicines, which is equivalent to one third of the world population. [203] The same authors reported that there is inequality between developed and underdeveloped countries. A significant percentage of the 1.3 billion population in India suffers from chronic diseases, generally low to medium

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[197] Kaló, "Optimizing the benefits of biosimilars for society," 1.

[198] Simoens et al., "How to realize the potential of off-patent biologicals and biosimilars in Europe? Guidance to policymakers."

[199] "Pharmacists must be ready to take the lead on biosimilars," GaBi online (Generics and Biosimilars Initiative), posted December, 13, 2019, accessed December 30, 2019, http://www.gabionline.net/Biosimilars/Research/Pharmacists-must-be-ready-to-take-the-lead-on-biosimilars.

[200] Simoens et al., "How to realize the potential of off-patent biologicals and biosimilars in Europe? Guidance to policymakers."

[201] *Ibid*.

[202] Moorkens et al., "Policies for biosimilar uptake in Europe: An overview," 10.

[203] Lee and Kohler, "Benchmarking and Transparency: Incentives for the Pharmaceutical Industry's Corporate Social Responsibility," 641.

income groups.[204] The United Nations aimed to increase accessibility to medicines by making them more affordable and developing new medicines.[205]

On a global level, the WHO has also recognised that high prices of medicines are impeding the achievement of Universal Health Coverage within and among countries and noted that 'confidentiality agreements' between manufacturing companies and governments are used as a tool to restrict transparency.[206] At the 72nd World Health Assembly in May 2019, governments agreed to share information on the official prices and improve price transparency and data on clinical trial results among other factors.[207] Unfortunately, however, confidentiality agreements are resulting in unfair competition and inequity to accessibility of innovative high-priced biologicals between countries, and these will be discussed further in Section 4.3.3.

3.6 Conclusion

The high cost of biologicals is responsible for a significant share of healthcare costs which negatively impacts on the economy. In line with the EU Treaty, MSs are free to set their own prescribing, pricing and reimbursement policies for biosimilars based on their resources, priorities and health needs. The decision by EMA to leave the decision of interchangeability to MSs may raise ethical questions as this requires further analysis and that MSs have the required expertise. Moreover, this has to be seen in the context of the European Charter of Fundamental Rights of the European Union which states that universal access to health care is a fundamental human right (article 35). Public healthcare systems, therefore, must guarantee universal access to health care, even though from a legal perspective, this does not mean that patients have the right to free medical care, even though health authorities need to ensure the maximisation of allocation of resources. Some states set up mandatory switching policies aimed to

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[204] GR Soni, "Overview of non-innovator biological products in India," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 9, no.1 (2020): 1-10, 1.

[205] Lee and Kohler, "Benchmarking and Transparency: Incentives for the Pharmaceutical Industry's Corporate Social Responsibility," 641.

[206] World Health Organization, *Improving the transparency of markets for medicines, vaccines and other health products*, World Health Organization Seventy-second World Health Assembly 28 May 2019, 1.

[207] *Ibid.*

increase access to biosimilars, for prescribing, procurements, reimbursement and hospital formularies, which could raise ethical and medico-legal questions to prescribers and expose patients to new risks so as to achieve cost savings. On the other hand, leaving the decision to the prescriber could lead to inappropriate allocation of resources. The different policies across Europe could also raise inequity in accessibility to treatment across countries, regions and hospitals. Sharing of information on pricing and reimbursement policies, including pricing agreements between states remains through voluntary collaboration. Data shows that significant cost savings were achieved but despite the various strategies that were implemented biosimilar uptake remains slow. A holistic multi-stakeholder policy framework is required to achieve equitable access to these medicines. Accessibility to medicines is a global issue which needs to be addressed at a global level. This should first take into consideration the ethical issues identified and that will be discussed in the next chapter.

Chapter 4: Ethical issues related to biosimilars

In previous chapters, the regulatory aspects in relation to IP rights, authorisation, and prescribing regulations of biologicals and biosimilars within the public healthcare systems were discussed and ethical issues were identified. This chapter considers the various ethical aspects identified in the previous chapters.

By way of introduction, the Beauchamp and Childress principles of biomedical ethics, which were set in the 1970's in the US context, refer to respect for autonomy, beneficence, non-maleficence and justice and are generally referred to in the medical field for treating patients, which also involves prescribing of medicines. Respect for autonomy implies recognising that patients have the right to make their own decisions, and therefore requires that the benefit-risk ratio for each treatment option is to be discussed with the patient and informed consent obtained prior to treating them.[1] The ethical principle of beneficence is the duty to act in the best interest of the patient whilst non-maleficence is the duty to never harm the patient and is the fundamental principle of the Hippocratic Oath.[2]

In Europe, however, alternative principles to those of Beauchamp and Childress were presented in 2000 by Rendtorff and Kemp, namely, autonomy, dignity, integrity and vulnerability, as the four central principles of the bioethics and biolaw which were endorsed by the European Commission (EC).[3] These principles are useful to national legislation and legal practice and provide a foundation of a European policy on human

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1 Michael Payette and Jane M. Grant-Kels, "Brand name versus generic drugs: The ethical quandary in caring for our sophisticated patients while trying to reduce health-care costs: Facts and controversies," *Clinics in Dermatology* 31 (2013): 772-776, 772.

2 *Ibid.,* 773.

3 J. D. Rendtorff, J.D. and P. Kemp, "Basic Ethical Principles in European Bioethics and Biolaw, Vol I–II. Barcelona and Copenhagen: Institut Borja di bioètica and Centre for Ethics and Law (2000) Cited in Jacob Dahl Rendtorff, "Basic ethical principles in European bioethics and biolaw: Autonomy, dignity, integrity and vulnerability – Towards a foundation of bioethics and biolaw," *Medicine, Health Care and Philosophy* no. 5 (2002): 235-244, 242.

rights to protect humanity and the human person, and may in fact be applied in the various fields of biomedicine and also serve as guidelines for medical clinical practice.[4]

In the field of medical practice, in Europe, "autonomy" refers to the capacity for self-legislation and self-determination of rational human beings, and therefore it is closely linked to integrity, in the sense of the wholeness of the personal sphere of self-determination.[5] This requires that the patient is well informed which is built on the physician-patient relationship.[6] Autonomy and dignity of the person however may be threatened resulting in vulnerability, which needs to be protected.

These four ethical principles should be considered in the frame of justice.[7] They are essential in the 20th century culture of rights, where dignity forms the basis of equality of all human beings.[8] They are applied in the context of biomedicine, economy and culture in Europe, where the principle of autonomy refers to the care for others, and is closely linked with other principles, namely, solidarity, responsibility and fairness or justice.[9] In the context of biomedicine, where one deals in a highly competitive business sector, the principles of autonomy (not being coerced or deceived) and integrity, here understood as uprightness, honesty and having a good moral character, are critical.[10] Matti Häyry argued that the Beauchamps and Childress principles lack virtue ethics which is a fundamental European value.[11] Häyry further presented the principles of dignity, precaution and solidarity as the foundation for national and international

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4 Rendtorff, "Basic ethical principles in European bioethics and biolaw: Autonomy, dignity, integrity and vulnerability – Towards a foundation of bioethics and biolaw," 235.

5 *Ibid.*, 237.

6 *Ibid*.

7 *Ibid*., 241.

8 *Ibid*., 237.

9 *Ibid.,* 242.

10 *Ibid*., 237.

11 Matti Häyry, "European values in bioethics: Why, What, and How to be used?" *Theoretical Medicine* 24 (2003): 199-214, 201.

regulations concerning biomedicine and biotechnology.[12] In addition Häyry considered prudence, communality and sensitivity as essential in ethical decisions.[13]

The above ethical principles will be useful in the following discussion on the issues related to biosimilars that emerged from previous chapters. The first ethical issue that will be discussed is that related to conflicts of interests, seen in terms of the principles of autonomy and beneficence. First identified in Section 1.5, this contributes to the abuse of the dominant position by originator companies. The issue also presented itself in Section 3.4.1.1, mainly through agreements with hospitals and healthcare professionals.

Since Chapter 2 highlighted the residual uncertainties related to biosimilars, the next ethical issue to be discussed will be that related to their safety, which needs to be seen in the context of the precautionary principle at regulatory level and in the context of beneficence and (bodily) integrity at prescribing level. This will include a discussion about EMA's decision to leave interchangeability to the physician, which raises further ethical issues related to switching. Considering that prescribing is made within public healthcare systems, leads to the third ethical issue, that of equitable access at national level. As explained in Chapter 3, the mandatory switching policies lead to significant ethical issues related to procurement of biologicals and biosimilars and these need to be elucidated over here.

In chapter 3, it was found that the lack of sharing of information related to pricing and reimbursement between European Member States (MSs) is contributing to unfair competition and higher prices which leads to inequity among states, which is another ethical issue that will be discussed.

As discussed in Section 3.5, accessibility to medicines is a global concern and considering that the pharmaceutical industry is operating on a global level, harmonisation and convergence of regulation were recommended in Section 2.6 to improve accessibility. Within the global market, the needs of others cannot be

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[12] Häyry, "European values in bioethics: Why, What, and How to be used?" 208.

[13] *Ibid*.

neglected, such that ethical principles need to be identified to achieve equitable access to biological medicines with the aim to achieve universal health coverage. Solidarity may respond to the needs of societies towards achieving equitable access at national, European and global level and will be explored in this chapter.

4.1 Ethical issues related to conflicts of interest

Various public and private organisations involved in decisions related to biological medicines are prone to potential conflicts of interest, including regulatory authorities, competent authorities involved in reimbursement and pricing policies, patient organisations and non-profit organisations. The Organisation for Economic Co-operation and Development (OECD) reported that "conflicts of interest in both the public and private sectors have become a major matter of public concern worldwide."[14] The OECD guidelines for the public service defines a "conflict of interest" as "a conflict between the public duty and private interests of public officials, in which public officials have private-capacity interests which could improperly influence the performance of their official duties and responsibilities."[15] Potential conflicts of interest in decision-taking could lead to unfair business competition, calling for good governance by both the private and public sector.

4.1.1 Decision-taking by competent authorities

Rachel Tansey recommended that processes for policy-setting should be safeguarded from the strong influence of the pharmaceutical industry.[16] This may be achieved through the proper management of any declaration of interests at all stages of the process, especially when engaging consultancies and participation in discussion fora related to pharmaceuticals.

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[14] Organisation for Economic Co-operation and Development (OECD), *Managing Conflict of Interest in the Public Service OECD Guidelines and Overview* (France: OECD, 2003): 1-249, 15.

[15] *Ibid.*

[16] Rachel Tansey*, High prices, poor access: What is Big Pharma fighting for in Brussels?* ed. Katharine Ainger, (Brussels: Corporate Europe Observatory, May 2019), Chapter 1, Box 2, 11, https://corporateeurope.org/en/2019/05/high-prices-poor-access-eu-medicines-market-and-big-pharma.

The EC, through Article 63 of Regulation (EC) 726/2004, introduced safeguards for impartiality and for full transparency of the decisions of the technical committees of the EMA related to authorisations or the supervision of medicinal products and make these decisions public at EMA and on the Internet.[17] This article provided the basis for the EMA to set up a Code of Conduct with particular reference to acceptance of gifts.[18] Regulatory authorities must have a transparent process that provides the necessary guarantees to ensure impartiality in the granting of authorisations and surveillance of medicines, including biologicals and biosimilars. This will provide public confidence in the medicines that are authorised by the regulatory authority, not only to patients but also to other regulatory authorities, especially with regards to the authorisation of innovative complex biological medicines. This is essential to counteract the 'nocebo' effect related to biosimilars (see Section 3.4.1).

4.1.2 Incentives to clinicians

Apart from 'gain sharing' (Section 3.4.1.1), it is a known fact that originator companies offer grants and speaker honoraria and sponsor professional organisations. A literature review on conflict of interest and the pharmaceutical industry showed that physician-industry interactions affect professional behaviour and prescribing.[19] This means that healthcare professionals do not retain their autonomy in decision-taking to the detriment of beneficence towards their patients and society. There should be

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17 "Regulation (EC) No 726/2004 of the European Parliament and of The Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency," *Official Journal of the European Union*, L136 (30.04.2004), Article 63.

18 "Handling competing interests," *European Medicines Agency,* accessed May 27, 2020, https://www.ema.europa.eu/en/about-us/how-we-work/handling-competing-interests.

19 Ashley Wazana, "Physicians and the pharmaceutical industry: is a gift ever just a gift?" *Journal of the American Medical Association* no.2 (2000): 373–380. Cited in Julie Allard and Marie-Chantal Fortin, "Is it ethical to prescribe generic immunosuppressive drugs to renal transplant patients?" *Journal of Kidney Health and Disease* 1 no. 23 (2014): 1-7, 5.

transparency which means public disclosure of relationships and potential conflicts of interest.[20]

4.1.3 Funding to patient organisations

Patient organisations tend to benefit from funding from manufacturing companies.[21] As nowadays patients are getting more involved in discussions on accessibility of medicines, the pharmaceutical industry could buy their silence through funding.[22] In order to safeguard patients' autonomy in decision-taking, funding from industry should be made public to avoid any conflicts.[23]

4.1.4 Concluding remarks on conflicting interests

Generally, the pharmaceutical industry is in a dominant position and stakeholders (the member on the decision-taking committee, healthcare professional or patient) are in a vulnerable position such that their autonomy in taking decisions is threatened. This requires integrity of the individuals operating within the pharmaceutical sector, that is, their uprightness and good moral character. Transparency, which means disclosure of relationships and agreements and declaration of interests, is essential in order to protect the autonomy of the vulnerable person or group. This aims to increase confidence among the general public in institutions that are involved in decision-taking in the best interest of public health.

4.2 Ethical issues related to safety of biosimilars

As discussed in Chapter 1, the risk of lack of efficacy or safety or immunogenicity related to biologicals is primarily due to biological drift as a result of changes to the manufacturing process for the biological. These are of a greater concern for biosimilars, where patients are exposed to an unknown level of risk. In fact, Carlo Petrini, the

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[20] "List of Guiding Principles Promoting Good Governance in the Pharmaceutical Sector," *European Commission Corporate responsibility in the pharmaceutical industry*, last accessed May 27, 2020, 1-5, 2, https://ec.europa.eu/growth/sectors/healthcare/competitiveness/corporate-responsibility_en.

[21] *Ibid*.

[22] Tansey, *High prices, poor access: What is Big Pharma fighting for in Brussels*? Chapter 1, Box 2, 11.

[23] *Ibid*.

Director of the Bioethics Unit of the Italian National Institute of Health (Istituto Superiore di Sanità), has stated that from the ethical point of view, the most important issue raised by biosimilars is that of safety.[24] The renowned bioethicist, who is not to be confused with the founder of the International Slow Food Movement who holds the same name, explained: "Risk is a technical matter but it is also a social problem and scientific data is not always helpful and it is difficult to quantify the entity and probability of a given risk."[25] Risk may hinder access to biosimilars but not specifically of under resourced populations.

Risk is defined as the possibility or probability of harm.[26] Matti Häyry claims that "we cannot always predict all the outcomes of our actions, nor agree on the most important moral values and we should not pretend that we have scientific grounds for our ethical and political choices."[27] The precautionary principle, therefore, should be based on prudence and the 'maximin' principle.[28] In practice, it involves considering the different options based on the assessment of risk or harm.[29] According to the precautionary principle, risk creates a degree of uncertainty which may be used as an argument against technological development and for protective regulation.[30] In the case of biosimilars, patients may be protected from harm at regulatory and prescribing levels and the emerging ethical issues will be discussed below.

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[24] Carlo Petrini, "A bioethicist's view of the use of biosimilars," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 1, no. 3-4 (2012): 110-111, 110.

[25] *Ibid*.

[26] Häyry, "European values in bioethics: Why, What, and How to be used?" 205.

[27] *Ibid*.

[28] The Maximin Principle is "a principle of decision theory, that counsels that at least in some circumstance, the right decision is that which maximizes the minimum outcome: i.e., that which makes the worst outcome as good as can be. The principle is often described as risk-aversive. It is a key component in the influential work A Theory of Justice (1971) by Rawls." https://www.oxfordreference.com/view/10.1093/oi/authority.20110803100141723

[29] Häyry, "European values in bioethics: Why, What, and How to be used?" 206.

[30] *Ibid*.

4.2.1 Ethical issues related to the regulation of biosimilars

Petrini claimed that the marketing authorisation procedure for biosimilars, on a collective level is based on the principle of distributive justice as biosimilars were introduced to increase access to biologicals, whilst for the individual biosimilar medicine, it is based on the benefit-to-risk assessment during the authorisation process.[31] In fact, Schneider questioned whether biosimilars should be authorised when there is an originator with a huge safety database and experience from practical clinical use.[32] The author claimed that whilst a new active substance (through positive benefit-risk balance) in the same therapeutic class could present advantages over the already authorised product, it is difficult to ethically justify a biosimilar due to unknown safety risks.[33] Witts, however, has argued that "the final test of safety of a drug is in fact its release for general use."[34] Also, Gavrila and colleagues claimed that the risk related to switching to biosimilars is lower than the risk from the lack of access to the originator biological due to lack of adequate finances.[35]

It may be concluded that patient safety should not hinder the accessibility to biologicals through biosimilars as long as the necessary regulatory safeguards are in place through a step-wise Biosimilar Regulatory Pathway (illustrated in Section 2.2) and a robust pharmacovigilance system, (illustrated in Section 2.5). The requirement for additional comparability studies as part of the regulatory process has been strongly debated, which will be discussed below.

4.2.1.1 Ethical issues of clinical comparability studies

The EMA Biosimilar Regulatory Pathway involves expensive and intensive clinical trials also on human subjects, exposing patients to unnecessary risks related to

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31 Petrini, "A bioethicist's view of the use of biosimilars," 110.

32 Christian K. Schneider, "The ethics of biosimilars," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 2, no. 1 (2013): 6-7, 7.

33 *Ibid*., 7.

34 Leslie John Witts, "Adverse reactions to drugs," *The British Medical Journal* 2, no. 5470 (1965): 1081-6. Cited in Petrini, "A bioethicist's view of the use of biosimilars," 111.

35 Raluca Gavrila et al., "Biostatic, legislative and ethical problems of comparative clinical studies. I. Generic and biosimilar drugs case," *Farmacia* 66, no. 6 (2018): 930-937, 936.

biological treatment.[36] Kurki (see Section 2.3), however, questioned the requirement of comparability data for biosimilars when these are not required for variations between batches of originator biologicals.[37] Schneider, in fact, confirmed that originator biologicals are required to perform in vitro assays only when there are changes to the manufacturing process.[38] This raises the question as to whether clinical studies in the case of biosimilars are ethically justified. In view of Article 33 of the World Medical Association (WMA) Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, research on biosimilars would be unethical as there is already established medical treatment available.[39] It is further claimed that medical research should aim to generate knowledge that contributes to improve health and wellbeing of patients and unnecessary duplication of clinical trials is prohibited by the Oviedo Convention (article 16) which states that research may only be undertaken where "there is no alternative of comparable effectiveness to research on humans."[40]

Yaniv Heled further claimed that such trials are unethical as such resources would have been better used on other research projects.[41] In fact, Leintz and Dedhia argued that redundant research which offers the human subjects little or no benefit, but which is aimed to advance a biosimilar to commercialisation, is a direct violation of the Declaration of Helsinki.[42] The authors claimed that giving a research subject, generally a sick patient in need of treatment, a biosimilar is unethical when a known and proven treatment for the stated indication is already available via the reference medicine.[43] The

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36 Gavrila et al., "Biostatic, legislative and ethical problems of comparative clinical studies. I. Generic and biosimilar drugs case," 936.

37 Pekka Kurki, "Physicians, Hippocrates and biosimilars: applying ancient principles in a modern society," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 5, no. 4 (2016): 149-150.

38 Schneider, "The ethics of biosimilars," 6.

39 Gavrila et al. "Biostatic, legislative and ethical problems of comparative clinical studies. I. Generic," 936.

40 Lisa Diependaele et al, "Why biosimilars are not the solution," *Journal of Law, Medicine and Ethics* Fall (2018): 776-790, 780.

41 Yaniv Heled, "The case for disclosure of biologics manufacturing information," *Journal of Law, Medicine and Ethics* 4784 (2019): 54-78, 58.

42 Christopher J. Leintz and Riddhi Dedhia, "Biosimilars and emerging markets: historical and bioethical considerations," *Journal of Clinical Research and Bioethics* 6, no. 5 (2015): 1-4, 2.

43 *Ibid*.

authors argued, however, that if this standard were to be applied universally much of the clinical research as part of development of drugs and biologicals would go against this principle since clinical research does not benefit the research subjects but those who will benefit from treatment.[44] In fact, Gavrila and colleagues confirmed that healthy volunteers do not have a therapeutic benefit from participating in such studies, which would be justified as future patients will benefit as for all clinical studies.[45] Considering the immunogenicity risk with biologicals, due to product drift, comparability studies are considered to be ethically justified.

4.2.1.2 Clinical studies for new indications

As discussed in Section 2.4, for biosimilars additional clinical studies are required for new clinical indications, except where extrapolation is allowed by EMA. The decision on extrapolation should be based on scientific evidence in line with the principle of non-maleficence and not on the principle of distributive justice.[46] This would imply that clinical studies are necessary so as to safeguard patient safety. For cancer treatment, a biological medicine may be indicated for different types of cancer with different end-points for the different cancers.[47] It is arguable whether extrapolation is justified or whether cancer patients should be exposed to biosimilars undergoing clinical trials when this is the only possibility of obtaining cancer treatment which would otherwise be unaffordable. For cancer treatment, European Society of Medical Oncology (ESMO) accepts extrapolation of the clinical indication, provided there is solid scientific information and a clear justification.[48]

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44 Leintz and Dedhia, "Biosimilars and emerging markets: historical and bioethical considerations."

45 Gavrila et al., "Biostatic, legislative and ethical problems of comparative clinical studies. I. Generic and biosimilar drugs case," 936.

46 Zoran Todorovic and Dragana Protic, "Bioethical issues in the development of biopharmaceuticals," *Filozofija Drustvo* XXIII 4, (2012): 49-56, 53.

47 Emilio Bria and Pierfranco Conte. "Biosimilars as a strategy to improve sustainability." *European Society for Medical Oncology* 2, (2017): 1-2, 1.

48 Josep Tabernero et al., "Biosimilars: a position paper of the European Society of Medical Oncology, with particular reference to oncology prescribers," *European Society for Medical Oncology* 2, (2016): 1-5, 2.

4.2.1.3 Clinical studies for new formulations

Alternative formulations (illustrated in Section 2.2,) for example, sub-cutaneous instead of intravenous injection, would present benefits to the patient, for example they would not need to go to hospital. In such cases animal studies are not able to exclude adverse effects, such that safety clinical studies on humans would be ethically justified.[49] Professor Zoltán Kaló, during the EC's fifth workshop on biosimilars held on 30 October 2019, however, claimed that originator companies could be creating a 'hype' with regards to new formulations, as was the case with SC trastuzumab, so as to achieve product differentiation since a review of 41 studies on trastuzumab IV compared to SC found that the studies lacked the appropriate validation methods.[50]

4.2.1.4 Conclusion on clinical studies

Whilst it is acknowledged that biosimilars could present a degree of risk to patients, based on the precautionary principle, clinical comparability studies would be considered to be ethically justified. However, where data on safety is available, the need for clinical comparability should be reviewed such that comparability studies would be reserved only for complex molecules. Also, once analytical methods are available, they should replace clinical studies, thus minimising unnecessary costs on clinical studies whilst bringing biosimilars to the market at a faster rate. Extrapolation would contribute to faster accessibility to new clinical indications and therefore is ethically justified. With regards to new formulations, from the precautionary perspective, the decision of extrapolation should also be based on scientific grounds.

4.2.2 Ethical issues related to interchangeability

As discussed in Section 2.3, EMA left the decision of interchangeability to the clinical level, i.e. to the prescribing physician through their national regulations and guidelines with regard to reimbursement and prescribing. This position resulted in apprehension by physicians to switch patients as they do not have the same level of expertise as EMA

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[49] Leintz and Dedhia, "Biosimilars and emerging markets: historical and bioethical considerations," 2.

[50] Zoltán Kaló, "Optimizing the benefits of biosimilars for society," GaBi online (Generics and Biosimilars Initiative), posted February, 28, 2020, accessed May 11, 2020, http://www.gabionline.net/Reports/Optimizing-the-benefits-of-biosimilars-for-society.

experts in the field, which led to delays in biosimilar uptake. In order to increase physicians' confidence in biosimilars, additional independent switching studies, such as the NORSWTICH study, were performed at additional expense. Zoltán Kaló asked "why policy makers and/or regulators in some countries still question what has been answered in other countries?" in a global industry.[51] Professor Kaló further questioned the need for additional studies when there is sufficient evidence generated through the European Public Assessment Reports (EPARs) and EPAR summaries which are readily available through the EMA website.[52] De Mora and colleagues claimed that these studies would question the credibility of the comparability studies at pre-authorisation stage.[53] Whilst some investigators considered such trials to be ethical as they provide alternative treatment and enhance competition, others considered that they do not offer any advantage to patients which goes against patient-centred ethic, placing economic and financial interests above the clinical interest.[54] Others claimed that these clinical studies would be contentious as they promote switching.[55] It is concluded that expensive switching studies are not ethically justified based on the Oviedo Convention (discussed in Section 4.2.1.1).

Prima facie, from the precautionary principle perspective, EMA's position to leave the decision of interchangeability to Member States appears to be justified, as patients are protected through safe regulation, where switching is performed by the physician at a clinical level and the patient is educated and monitored for any adverse effects on the biosimilar. Switching at physician level could however raise ethical questions which will be discussed in Section 4.2.3 below. In addition, since interchangeability also depends on national prescribing and reimbursement policies, the issue should also be considered from the perspective of equitable access, which will be discussed in Section 4.3.

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51 Kaló, "Optimizing the benefits of biosimilars for society."

52 *Ibid*.

53 Fernando de Mora et al., "Biosimilar and interchangeable: Inseparable scientific concepts?" *British Journal of Clinical Pharmacology* 85 (2019): 2460-2463, 2461.

54 Mubarak AlAmeri et al., "Generic and therapeutic substitutions: are they always ethical in their own terms?" *Pharmacy World and Science* 32 (2010): 691-695, 692.

55 *Ibid.,* 693.

4.2.3 Ethical issues related to prescribing biosimilars

The ethical principles in relation to prescribing of medicines and substitution from branded to generic medicines have been debated extensively. The concept of substitution to biosimilars is more recent and a number of ethical principles that were identified with generic substitution would apply to biosimilars.

4.2.3.1 Medical liability on switching to biosimilars

The Hippocratic oath of '*primum non nocere,'* i.e. 'first do no harm', based on the principle of non-maleficence and beneficence, requires doctors to be informed on the efficacy and safety of biosimilars and present the different treatment options to their patients.[56] The law usually assigns the final decision over which treatment is administered to the prescriber, who is completely liable for the choice of treatment adopted. When switching to a biosimilar, the doctor may be liable if a patient were to experience an adverse event or loss of efficacy.[57] Under tort legislation, malpractice refers to "an act of professional incompetence that results in harm to a patient" where generally the specific individual is liable where "allegations of medical negligence are made against the physician."[58] Tort is defined "as an act deemed unlawful and capable of triggering a civil action; the wrongdoer (tortfeasor) may be held liable in damages."[59] In practice, it means that on switching a patient to a biosimilar the doctor should present the various options to the patient and seek informed consent.[60]

The WMA at its 69th General Assembly of October 2018 on biosimilars recommended that the decision to switch should be made by the physician and not the health insurance company and advised towards safe regulation for interchanging

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[56] AlAmeri et al., "Generic and therapeutic substitutions: are they always ethical in their own terms?"

[57] Paolo Rocco et al, "Biosimilar switching and related medical liability," *Journal of Forensic and Legal Medicine* 55 (2018): 93–94, 93.

[58] W. Lahey and R. Currie, "Regulatory and medico-legal barriers to interprofessional practice," Journal of Interprofessional Care Supplement 1 (May 2005): 197-223. Cited in Josette Sciberras, "Effectiveness of Communication on Physician-Pharmacist Collaboration - The Case of a State Hospital in Malta," Masters Business Management diss., Henley Management College, UK 2006, 33.

[59] Definition "Tort law" https://medical-dictionary.thefreedictionary.com/Tort+law

[60] Rocco et al., "Biosimilar switching and related medical liability," 94.

biosimilars.[61] This is in line with the principle of beneficence, where the prescribing physician performs a clinical assessment on an individual patient level. Any guidelines, concept papers or recommendations could influence the prescriber's decision, but ultimately he remains liable in case of harm to the patient as the documents are non-binding.[62] Schneider argued, however, that if the doctor does not follow established guidelines, he would be liable and it would be difficult for him to defend his decision at law especially if the indication is not supported by scientific literature.[63]

Within the national healthcare system in Malta, consultants are medico-legally responsible for the care of the patient. The Maltese physicians are aware of the 'tort' system such that a conservative approach is preferred by physicians in clinical decision-taking, where the final decision is taken by the physician.[64] This reflects the findings by Cassar and colleagues where Maltese clinicians showed preference to retaining "sole authority" on prescribing biologicals or biosimilars.[65] As discussed in Section 3.4.2.3, in Malta, switching of biologicals is mandatory as the decision is taken at policy level by government, which will be discussed in Section 4.2.3.3.

4.2.3.2 Patient's autonomy

As explained in the introduction to this Chapter, respect for autonomy in the European context refers to respect for the patient and respect for the other. In prescribing practice, this means that the patient understands the illness and treatment and retains the right to consent and refuse treatment through informed consent. The Barcelona Declaration Policy Proposals recommended that a Patients' Charter, is

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61 "WMA Statement on biosimilar medicinal products - Adopted by the 69th World Medical Association General Assembly, Reykjavik, Iceland, October 2018.," *World Medical Association*, accessed May 29, 2020. https://www.wma.net/policies-post/wma-statement-on-biosimilar-medicinal-products/.

62 Rocco et al., "Biosimilar switching and related medical liability," 94.

63 Schneider, "The ethics of biosimilars," 1.

64 Sciberras, "Effectiveness of Communication on Physician-Pharmacist Collaboration - The Case of a State Hospital in Malta," 57.

65 Kathleen Cassar et al., "Biosimilars: The perception among Maltese clinicians," *Annals of the Rheumatic Diseases*, suppl. 2; London 75 (June 2016): 1294, https://doi.org/10.1136/annrheumdis-2016-eular.1061SAT0637-HPR.

"enshrined in the legislation of all European countries."[66] Patients benefiting from the UK NHS have the right to easily accessible information to allow patients to participate fully in making informed decisions and make the right choices.[67] In Malta, Article 27 of the Health Care Act lists patients' rights,[68] including to information and involvement in decisions, and article 29 requires the setting up of a Charter of Patient Rights and Responsibilities which require confidentially, participation in decision-making and understanding that are built on communication and trust between the patient and physician.[69] Switching could raise ethical conflicts between the choices of the patients in need of the treatment and the expense of the NHS, which will be discussed next.

4.2.3.3 Switching to biosimilars

Generics played a pivotal role in promoting distributive justice in health care by making more medicines available to more people at lower cost. Norman Daniels's theory of fair equality of opportunity has been used in the context of generic substitution and would apply to mandatory switching to biosimilars. Daniels's theory of fair equality of opportunity provides the opportunity for all to access treatment, while allowing patients the liberty to purchase a branded drug.[70] This theory aims at a fair process for critical resource allocation decisions in healthcare, extending Rawls theory of justice as fairness which requires fair distribution of primary goods which are allocated based on "fair equality of opportunity,"[71] and applying it to a distributive theory for healthcare. In the UK NHS, patients would have to cover the difference between the generic and branded

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66 Rendtorff, "Basic ethical principles in European bioethics and biolaw: Autonomy, dignity, integrity and vulnerability – Towards a foundation of bioethics and biolaw," 243.

67 AlAmeri et al., "Generic and therapeutic substitutions: are they always ethical in their own terms?" 693.

68 Laws of Malta, Chapter 528: *Health Act*, https://legislation.mt/eli/cap/528/eng/pdf.

69 Ministry for Health, Malta, *Patient's Charter - Charter of Patient's Rights and Responsibilities*, 21 November, 2016, accessed May 11, 2020. http://deputyprimeminister.gov.mt/en/hcs/Pages/patients-charter.aspx.

70 Norman Daniels, "Justice, health, and healthcare," *American Journal of Bioethics* 1, no.2 (2001): 2-16. Cited in Allard and Fortin, "Is it ethical to prescribe generic immunosuppressive drugs to renal transplant patients?" 6.

71 Jennifer Prah Ruger, "Ethics of the social determinants of health," *The Lancet* 18, no. 364 (September 2004): 1092-1097, 1092.

medicine which, however, depends on their income and their affordability of the branded medicine.[72] In Malta, if the patient is to be prescribed a specific brand, the treating clinician would need to submit a justification to the Exceptional Medicinal Treatment Committee. Alternatively, the patient would need to buy the medicine out-of-pocket if the patient can afford it, in which case it is difficult to achieve in practice and questions of social justice would arise.

The ethics of prescribing generic immunosuppressive drugs to renal transplant patients was strongly debated as the risk of substitution could lead to organ rejection.[73] The benefits of substitution are to other patients who would benefit from the additional available resources.[74] The authors argued, however, that the duty of the physician is to act beneficently towards their patients and no degree of risk is acceptable as this would lead to organ rejection. The Hippocratic Oath, in fact, binds physicians to their duties to the individual patient and to other physicians, while making no reference to their responsibility towards society and the public healthcare system. They ought to consider, therefore, what is most appropriate for their patients.[75]

Physicians, however, are seen to have dual responsibilities: both to their patients and to society,[76] considering that it is society which grants them a licence to practice medicine. This would imply that doctors should persuade patients to use generics so as to achieve savings, thus releasing funds for the benefit of more patients.[77] It could be argued, therefore, that if policies are implemented to minimise risks it would be ethical to use generic immunosuppressants as the benefits to society would be greater than the risks to individual patients.[78] It would be ethical to prescribe generic

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72 Prah Ruger, "Ethics of the social determinants of health," 7.

73 Allard and Fortin, "Is it ethical to prescribe generic immunosuppressive drugs to renal transplant patients?" 1.

74 *Ibid*.

75 *Ibid*., 4.

76 I*bid*., 5.

77 Christopher Newdick, "Using generic medicines: a UK view on legal rights and duties," *European Journal of Hospital Pharmacy* 20, no. 5 (2013): 287–291, 287.

78 Allard and Fortin, "Is it ethical to prescribe generic immunosuppressive drugs to renal transplant patients?" 6.

immunosuppressants provided that patients are educated and the regulatory safeguards are in place to minimise the risk of 'generic drift.'[79] This is in line with the ethical principles of precaution, justice and solidarity, which are implied.

In the case of biosimilars, the major difference from generics is that switching of biologicals entails switching patients from a stable biological to another which is not considered to be therapeutically equivalent.[80] As discussed in Section 2.5, switching to biosimilars may expose patients to the risk of immunogenicity, due to 'product drift,' and therefore patients are to be monitored for any adverse effects. As yet, safety with multiple switching is not supported scientifically for biologicals. As for the case of generic immunosuppressants, mandatory switching to biosimilars would be ethically justified based on the same ethical principles provided that safe regulation i.e. switching is retained in the remit of the prescribing physician, so as to protect the patient from harm that may occur due to 'product drift,' which may be more pronounced with multiple switching. For the same reason, automatic substitution is not ethically justified.

In Malta, the decision of switching is taken by government following agreement with the Clinical Chairman of the specific clinical department. As for generics, promoting switching on financial grounds could, however, be incompatible with patient-centred ethics.[81] On the other hand, if patients' right to health is ranked higher than societal health, there would be huge losses to the health system as financial savings could be used either to provide effective treatment to more patients or for new medicines.[82] Though patients have a right to health, this does not mean that they can refuse to be switched to biosimilars. In practice, government can make its own choices of allocation of resources, whilst respecting patients by informing them of the switch, as patients

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79 Generic drift i.e., a generic at one end of the acceptable range of the area under the curve (AUC) might not be bioequivalent to another generic at the other end of the acceptable range" Allard and Fortin, "Is it ethical to prescribe generic immunosuppressive drugs to renal transplant patients?" 3.

80 Allard and Fortin, "Is it ethical to prescribe generic immunosuppressive drugs to renal transplant patients?" 7.

81 AlAmeri et al., "Generic and therapeutic substitutions: are they always ethical in their own terms?" 694.

82 Schneider, "The ethics of biosimilars," 6.

have the right to receive all available information concerning potential consequences of switching and of multiple switching.[83]

As for generics, biosimilars are perceived by patients to be of poor quality due to their much cheaper prices. It is of course imperative that generics provide the same efficacy as their branded counterparts.[84] AlAmeri and colleagues claimed that any substitution to a generic medicine which is less effective or with unknown risks is considered to be unethical and patients cannot be expected to accept the cheaper medicine.[85] Patients' perception of the poor quality of biosimilars, led to the 'nocebo' effect (as illustrated in Section 3.4.1.), which is resulting in patients' discontinuation of treatment. It is therefore imperative from the ethical perspective that the prescriber should provide the patient with the correct and complete information so as to come to a shared decision.[86] Patients are automatically switched to biosimilars in the case of the first generation biosimilars. This means that patients' right for information (patients' integrity) is being compromised. It is only with the monoclonal antibody (mAb) biosimilars that patient informed consent is being sought on switching to biosimilars, following consideration of the various choices. In practice, however, the patient's level of understanding of biological medicines and any possible adverse effects on switching to biosimilars is questionable, such that patients are reliant on the doctor's decision. However, there is insufficient evidence to confirm that shared decision-taking addresses the risk of the 'nocebo' effect (Section 3.4.1), despite the educational strategies elicited in Table 3.5. Therefore, patient safety must be a question of regulation, not a question of patient's autonomy and informed consent.

4.2.3.4 Concluding remarks on prescribing biosimilars

As discussed in this Section, within the frame of justice, switching to biosimilars by the prescriber is ethically justified based on the principles of justice, precaution,

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83 Raffaelli and Massimino, "Biosimilars: considerations in light of the Italian legal framework."

84 Payette and Grant-Kels, "Brand name versus generic drugs: The ethical quandary in caring for our sophisticated patients while trying to reduce health-care costs: Facts and controversies," 775.

85 AlAmeri et al., "Generic and therapeutic substitutions: are they always ethical in their own terms?" 691.

86 Rocco et al, "Biosimilar switching and related medical liability," 94.

solidarity and integrity, provided that safe regulation is implemented to protect the patient from harm. In view of the risk to harm with multiple switching, automatic substitution is not recommended unless this is supported scientifically. Doctors are medically liable as per 'tort' legislation and their decision is aimed towards beneficence and non-maleficence which requires patient-shared decisions through informed consent. This also aims to meet patients' rights for complete information. However, patient safety is achieved through the regulation of biosimilars rather than informed consent. In Malta, as for some other European countries, mandatory switching is being introduced to improve access and the ethical issues related to equitable access will be debated in the next Section.

4.3 Ethical issues related to equitable access

According to Morgan and colleagues, equitable access to new medicines is a fundamental human right.[87] This requires that healthcare resources are distributed fairly and equally and, in this context, the choice between brand-name and generic or biosimilar medicines is of specific importance.[88] Where healthcare systems are aimed at cost-containment, the principle of distributive justice is used to argue in favour of switching to more cost-effective treatment, whereas for flourishing economies, the principle of beneficence, non-maleficence and autonomy is used to argue in favour of patients' choice.[89] Overall, however, there is a general consensus that patient's rights are not compromised.[90] In the light of the European ethical principles, patients' integrity and vulnerability should be protected in the framework of distributive justice, as discussed in Section 4.2.3. In view of this, the demands of distributive justice become paramount, that is, the central question should revolve around the right of patients to

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87 Steven Morgan et al., "Pricing of pharmaceuticals is becoming a major challenge for health systems," *British Medical Journal* 368 no. 4627 (2020): 1-4, 1. https://doi.org/10.1136/bmj.l4627

88 Payette and Grant-Kels, "Brand name versus generic drugs: The ethical quandary in caring for our sophisticated patients while trying to reduce health-care costs: Facts and controversies," 774.

89 Häyry, "European values in bioethics: Why, What, and How to be used?" 200.

90 AlAmeri et al., "Generic and therapeutic substitutions: are they always ethical in their own terms?" 692.

have access to reasonable care. This should be based on the principles of equity and solidarity.[91]

Solidarity may contribute to improving accessibility. Though the principle of solidarity is discussed in the literature of European Welfare states,[92] and also as an ethical principle guiding the EU, solidarity has been strongly on the bioethical agenda through the work of UNESCO. Article 13 of the *Universal Declaration on Bioethics and Human Rights* (UDBHR), in fact, states that solidarity among human beings and international cooperation toward that end are to be encouraged within the field of bioethics, which is translated to freedom of action within nations and cooperation between nations.[93] An important achievement was reached as all states signed the UDBHR in 2005 showing their commitment to achieve global minimum standards in biomedical research and clinical practice with the ultimate goal to protect human dignity and human rights.[94] The aim to promote human dignity (Article 3.1) is intimately related to solidarity. Articles 5 and 6 on autonomy and consent and respect for vulnerability in Article 8 as fundamental principles of the framework are inherently solidaristic. The principles of equality, justice, and equity (article 10) assumes that solidarity supports justice, and non-discrimination and non-stigmatisation (article 11) with regards to equality. Cultural diversity and pluralism (article 12) are also solidaristic as taking "the Other" seriously. Access to healthcare and essential medicines (article 14) and benefit sharing (article 15) are implicitly solidaristic as they aim to achieve justice. Even though the UDBHR hardly mentions 'solidarity' in its principles, this is implied and plays a central role.[95] Solidarity aims to achieve justice i.e. reducing economic and health inequalities.[96]

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91 Häyry, "European values in bioethics: Why, What, and How to be used?" 200.

92 *Ibid*., 207.

93 Alphonse Elungu, "Chapter 15 - Article 13: Solidarity and Cooperation," in The UNESCO Universal Declaration on Bioethics and Human Rights: background, principles and application, ed. Henk A.M.J. ten Have and Michèle S. Jean, (Paris, France: UNESCO, 2009), 211-217.

94 Roberto Andorno, "Global bioethics at UNESCO: In defence of the Universal Declaration on Bioethics and Human Rights," *Journal of Medical Ethics* 33 (2007): 150-44. Cited in Darryl Gunson, "Solidarity and the Universal Declaration on Bioethics and Human Rights," *Journal of Medicine and Philosophy* 34 (2009): 241-260. 242.

95 *Ibid.* 258.

96 Gunson, "Solidarity and the Universal Declaration on Bioethics and Human Rights." 249.

The equity of access to biological medicines through biosimilars will now be analysed at three levels, that is, at the national, European and global level.

4.3.1 Equitable access at national level

4.3.1.1 Subsidiarity

As discussed in Section 3.2, governments are free to set their own prescribing, pricing and reimbursement policies. This is in line with the principle of subsidiarity discussed in Section 3.4. Resource allocation is important in public policy especially with regards to pharmaco-economics in the light of the ever-increasing healthcare costs, rising pharmaceutical expenditure and ageing population.[97]

Public healthcare systems were originally based on the principle of solidarity, which, for Europeans is an expression of "togetherness and commitment to the common good."[98] Germany first introduced enforcement of solidarity by the state in 1880 to compensate workers for disabilities, accidents and illness.[99] It was later introduced in a number of European countries for compulsory health insurance systems managed by the state as part of the social security system to guarantee equal access to health and social care services especially for those who are not able to pay for it.[100] Prainsack and Buyx refers to 'tier 3' solidarity which is the legal or contractual norm of 'tier 2' solidarity described as "manifestations of a collective commitment to carry costs to assist others."[101] The Barcelona Declaration Policy recommends that "each country should have a national health service based on the principle of social insurance."[102] In most European countries, the state carries costs to assist others e.g. collect taxes from the

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97 Rego Guilhermina et al. "Distributive justice and the introduction of generic medicines," *Health Care Analysis* 10 (2002): 221-229, 223.

98 Ruud Ter Meulen, "Solidarity, justice, and recognition of the other," Theoretical Medicine and Bioethics (2016): 1-13, 3, https://doi.org/10.1007/s1107-016-9187-3.

99 *Ibid*., 2.

100 *Ibid*.

101 Barbara Prainsack and Alena Buyx, "Solidarity in contemporary bioethics: Towards a new approach," *Bioethics* 26, no. 7 (2012): 343-350, 347.

102 Rendtorff, "Basic ethical principles in European bioethics and biolaw: Autonomy, dignity, integrity and vulnerability – Towards a foundation of bioethics and biolaw," 242.

population to fund the services provided to those in need of healthcare.[103] The Malta national healthcare system is also funded through taxation. Nevertheless, in view of the problem of the limitation of health care resources, the focus seems to have shifted on cost containment rather than solidarity.[104] The individualistic and heterogeneity culture is also making it more difficult to justify solidarity with other members of society, such that the definition of solidarity has shifted to 'interest solidarity,' i.e. an investment in the health care system expecting to be helped when needed. The rising healthcare costs of solidarity, however, have become unsustainable and individuals may not receive a 'safe' return on their 'investment'. When seen as a personal interest only, "it becomes difficult to differentiate it from the liberal idea of justice in which individual interests are balanced against one another in the context of a social contract."[105]

4.3.1.2 Procurement of biologicals and biosimilars

Procurement policies (as illustrated in Section 3.4.1), play a critical role in maximising resources and different procurement strategies are implemented which raise ethical questions as to the fairness and allocation of resources.

4.3.1.2.1 Confidential agreements

As discussed in Section 3.4, pharmaceutical companies take advantage of confidentiality agreements with procurement agencies and hospitals (incentives and gain sharing agreements Section 3.4.1.1), alternative funding mechanisms (Section 3.4.1.3.4) and also non-profit organisations, such as the Malta Community Chest Fund (MCCFF) (Section 3.4.3). The 'gain sharing' projects (Section 3.4.1.1) implemented by hospitals through confidential high discount agreements lack price transparency, making it difficult for biosimilar companies to compete whilst prices remain high.[106]

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[103] Prainsack and Buyx, "Solidarity in contemporary bioethics: Towards a new approach," 347.

[104] *Ibid*., 350.

[105] Ter Meulen, "Solidarity, justice, and recognition of the other," 3

[106] Dylst et al., "Barriers to the uptake of biosimilars and possible solutions: A Belgian case study," *PharmacoEconomics* 32 (2014): 681-691, 686.

Healthcare professionals (HCPs) tend to favour switching only if their department is likely to benefit, which goes against the principle of distributive justice.

The lack of transparency in pricing may result in higher prices. In addition, as discussed in Section 3.4.1, these confidential agreements are used to access more innovative patented medicines which are not provided through the NHS as they are unaffordable. This is leading to inappropriate allocation of resources, such that resources are allocated to certain diseases and not others which may be of higher priority to the NHS. This is contrary to the principle of distributive justice leading to inequality. Competent authorities at EU, regional and national level involved in healthcare policy decision-making, (i.e. procurement, pricing and reimbursement) should provide adequate access to relevant information to all stakeholders whilst respecting principles and laws, taking into account commercial confidentiality and data privacy.[107] Good governance based on the fundamental principles of integrity, mutual respect, responsiveness, accountability, collaboration and transparency is recommended by the EC. [108]

4.3.1.2.3 Tendering systems

As discussed in Section 3.4.1.2 procurement should aim to achieve transparency, open competition and equal treatment through the tendering system. As discussed in Section 3.4.1.3.3, however, in Malta, procurement of unpatented medicines, including biosimilars, is mainly through a tendering system where the winner takes all which could lead to shortages. It also means that stabilised patients will be switched over to biosimilars that could raise ethical issues related to safety. This is especially the case if more biosimilars for the same originator reach the market, when there is insufficient scientific evidence to support multiple switching that may compromise patients' safety.

Procurement policies and switching policies should be aligned and should be based on the principle of justice, equity, solidarity and integrity. The design of tenders should be such as to enable more than one product to be chosen in the adjudication process so

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[107] "List of Guiding Principles Promoting Good Governance in the Pharmaceutical Sector," 3.

[108] *Ibid*., 1.

as to maintain a 'healthy market', which would allow different products to be available to protect from shortages and at the same time the physician is free to act in the best interests of the patient.[109] Competition through the tendering system may still be achieved through lots based on therapeutic indications, whilst ensuring therapeutic continuity of patients, and considerable savings may be achieved if the tender is launched immediately once the specific biosimilar is authorised.[110] This is already done in Italy, for example, where open competition is implemented through tender lots based on therapeutic indications whilst ensuring therapeutic continuity of patients already being treated, with the aim to protect the patient from the potential risk of substitution.[111]

4.3.2 Ethics related to equitable access at European level

As reported in Chapter 3, governments maintain confidentiality on pricing and reimbursement information. This means not only that the pharmaceutical industry continues to benefit from high prices, but it could also result in high price variations between Member States leading to inequitable access of medicines across the EU. This is resulting in inequity to access of biologicals between European countries.

The European Parliament (EP) encouraged voluntary collaboration among Member States on pricing and reimbursement systems, with the aim to protect patients' rights to access to medicines and ensure sustainability of the healthcare systems.[112] Based on the solidarity principle with a view to increasing access in low-income countries, Vogler and colleagues recommended differential pricing, or equity pricing, where the

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[109] Steven Simoens et al. "How to realize the potential of off-patent biologicals and biosimilars in Europe? Guidance to policymakers," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 7, no. 2 (2018): 70-4.

[110] Enrico Adriano Raffaelli and Fausto Massimino, "Biosimilars: considerations in light of the Italian legal framework," *Generics and Biosimilars Initiative Journal* (GaBi Journal) 8, no. 1 (2018): 5-23, 8.

[111] *Ibid*.

[112] European Parliament, *Options for improving access to medicines – European Parliament resolution of 2 March 2017 on EU options for improving access to medicines,* (2016/2057(INI) No. P8_TA (2017)0061, (Brussels: European Parliament, 2017), Recommendation No. 39.

Marketing Authorisation Holder (MAH) agrees on different prices with different countries based on their income level and ability to pay.[113]

4.3.3 Equitable access to biologicals at a global level

Accessibility to essential medicines is, however, a global concern. The WHO Constitution states that "the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being."[114] Indeed, the WHO explains that "accessibility to essential medicines as part of the highest attainable standard of health ('right to health') is well-founded in international law."[115] The WHO refers to the WHO Constitution (1946) where the right to health is a social right, the *Universal Declaration of Human Rights* (1948); the *International Covenant on Economic, Social, and Cultural Rights* (ICESCR) of 1966 which identifies access to healthcare facilities, goods and services to achieve the right to health; the General Comment 14 (2000) which applies the principles of accessibility, availability, appropriateness and assured quality to goods and services, which include essential medicines "as defined by the WHO Action Programme on Essential Drugs" and the WHO Strategic Objective 11 (Improved access, quality and use of medical products and technologies) of the WHO Medium Term Strategic Plan for 2008-2013, where access to medical products and technologies is recognised as part of the right to health in countries constitutions or national legislation.[116]

Globalisation, however, presents ethical implications which were analysed by the EC through an international consortium Project – BIG (Bioethical Implications of

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[113] Sabine Vogler et al., *Ensuring access to medicines: How to redesign pricing, reimbursement and procurement?* (World Health Organisation Regional Office for Europe, 2018), 14, https://www.euro.who.int/en/about-us/partners/observatory/publications/policy-briefs-and-summaries/ensuring-access-to-medicines-how-to-redesign-pricing,-reimbursement-and-procurement.

[114] World Health Organisation Constitution. Cited in WHO, *Health 2020 – A European policy framework and strategy for the 21st century* (Denmark: WHO Regional Office for Europe, 2013,) 11.

[115] "Access to essential medicines as part of the right to health," *World Health Organisation,* accessed June 28, 2020, https://www.who.int/medicines/areas/human_rights/en/.

[116] *Ibid*.

Globalisation).[117] Future developments should be in line with the core principles of ethics, i.e. beneficence, non-maleficence, integrity, human dignity, equity and social justice.[118]

The care for others has no boundaries and is the baseline of the main European ethical principles not only at European level but within the global market. This is especially important in the globalised industry of biotechnology. This means that the interests of others especially those in developing countries cannot be neglected.[119] In fact, in the context of global health many authors believe that global solidarity would result in better distribution of resources and more equal access to healthcare.[120] At a global level, health equality or justice may only be achieved through solidarity.[121] This requires action by "institutions with the ability to *enforce* conduct which is *globally* utilitarian and therefore better capable of actively enhancing the health and human dignity of everyone."[122]

In order to assess whether global solidarity exists and its meaning, Eckenwiler and colleagues applied the concept to migrant nurses, which involves prudent interdependence between the sending and the host country, where the latter should cover for education costs, provision of better wages and conditions of work without depriving the sending country of nursing resources.[123] The SARS pandemic between November 2002 and July 2003 affected the international community at large, which

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[117] Thomas E. Novotny et al., "Bioethical implications of globalization: An International Consortium Project of the European Commission," *PLoS Medicine* 3, No. 2 (February 2006): 0173-0176; www.plosmedicine.org.0173.

[118] *Ibid*.

[119] Rendtorff, "Basic ethical principles in European bioethics and biolaw: Autonomy, dignity, integrity and vulnerability – Towards a foundation of bioethics and biolaw," 242.

[120] Prainsack and Buyx, "Solidarity in contemporary bioethics: Towards a new approach," 345.

[121] Lisa Eckenwiler, et al., "Global solidarity, migration and global health inequity," Bioethics 26, no. 7 (2012): 382–390, 390.

[122] Shawn Harmon, "Solidarity: A (new) ethic for global health policy," *Health Care Analysis* 14 (2006): 215 – 36. Cited in Gunson, "Solidarity and the Universal Declaration on Bioethics and Human Rights," 249.

[123] Eckenwiler et al., "Global solidarity, migration and global health inequity," 390.

needed to be addressed at global level through global solidarity for health equity.[124] Solidarity needs to be seen as a universal health care provision, which also refers to access to medicines and therefore allocation of resources for the development of new medicines, such as for HIV and Hepatitis C infections, which should be free from encroachment on autonomy such as coerced medical interventions, for example forced sterilisation.[125] The WHO claimed that the global ethical approaches should cover research, advances in science and technology, apply international codes of ethics, and ensure assessment and promotion of the quality of health systems and services.[126]

4.3.3.1 Trade secrets

As discussed in Section 1.5.1, trade secrets of cell lines over and above the patent protection and other regulatory mechanisms that are used to protect intellectual property of biologicals created a 'knowledge gap' perpetually. Trade secrets and intellectual property (IP) protection rights are covered by complex legal systems placing manufacturing companies at a disadvantage when producing follow-on biologicals. Various authors have therefore concluded that the trade secrets of cell lines are unethical on the basis of distributive justice and have thus called for disclosure of information.

However, the issue of patency and intellectual property rights is more complex and was strongly debated with respect to HIV drugs, which strongly impact the poorer countries. As discussed in Section 1.5.5, Trade-Released Intellectual Property (TRIPS) agreements related to patent protection are linked with trade policy between countries, at the risk that countries which need cheaper medicines and are not conforming to patent rules would suffer from trade retaliation, which is unethical on the basis of distributive justice, non-maleficence and beneficence.[127] The implementation of the General Agreement on Trade in Services should be based on the principles of social

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[124] Eckenwiler et al., "Global solidarity, migration and global health inequity," 390.

[125] Samuel A. Butler, "A dialectic of cooperation and competition: Solidarity and universal health care provision," *Bioethics* 26, no. 7 (2012): 351-360, 357.

[126] Prainsack and Buyx, "Solidarity in contemporary bioethics: Towards a new approach," 345.

[127] Novotny et al., "Bioethical implications of globalization: An International Consortium Project of the European Commission," 176.

justice, equity, beneficence and non-maleficence.[128] Globalisation would bring about liberalisation of trade and therefore remove trade sanctions on patency. Those who argue against liberalisation claim that this would lead to social injustice as it would result in a wider wealth gap between rich and poor countries. It is also argued that biomedical research in developing countries could bring about the dual-use technology development for health benefits and for possible biological weapons such that disclosure of information should be restricted. However, the benefits of biomedical research in developing countries outweigh the risk of misuse.[129] The principle of solidarity is not mentioned but should be considered so as to achieve equity and justice. This was implemented in medical research as will be illustrated below.

4.3.3.2 Medical Research in biosimilars

Solidarity is "the basis for a 'global ethic' uniting states and individuals aimed to reduce healthcare inequalities through the regulations on medical research as agreed by the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects."[130]

As discussed in Section 3.5.5, accessibility to medicines, especially innovative biological medicines, is a great concern to developed and less developed countries. Biosimilars may provide a solution to the problem of accessibility, and the harmonisation of regulations between states would ensure that biosimilars of acceptable quality, safety and efficacy may be authorised. The development and authorisation of high quality biosimilars in the emerging markets may contribute to equity in the access of life-saving biologicals and may be achieved through solidarity between governments, research sponsors, biotechnology industry and the patient, ensuring universal health coverage.[131]

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[128] Novotny et al., "Bioethical implications of globalization: An International Consortium Project of the European Commission," 176.

[129] *Ibid*.

[130] Gunson, "Solidarity and the Universal Declaration on Bioethics and Human Rights," 245.

[131] Leintz and Dedhia, "Biosimilars and emerging markets: historical and bioethical considerations," 3.

Research in emerging markets makes it possible to ensure that the universal medical imperative of treating those in need is being met.[132] As explained in Section 1.2.1, however, clinical trials must comply with the principles of Good Clinical Practice (GCP), which is an international standard for conducting clinical trials aimed at ensuring that clinical trials on human subjects are consistent with the principles set out in the Declaration of Helsinki.[133]

The R&D of biosimilars in emerging markets may be seen as providing accessibility to biological medicines in these developing countries.[134] The participation in clinical studies on biosimilars are considered to be ethically acceptable for public health reasons as they aim to increase the overall well-being of the population.[135] There is the risk, however, that the biosimilars developed in emerging markets do not meet the international quality standards and are not assessed according to acceptable regulatory standards. It is, of course, not ethical to provide substandard products to patients who need biologicals.[136] For example, a number of deficiencies were reported by the committee of clinical trials in India and also in the authorisation procedure by the regulatory authority in that country, raising doubts on the quality, safety and efficacy of biologicals and biosimilars manufactured and authorised in India.[137] The Indian regulatory authority, which is responsible for promoting and protecting the health of its citizens, should ensure that high quality biosimilars are made available whilst non-innovative biologicals which did not follow an internationally recognised regulatory procedure and are currently being used in the country are phased out.[138] In addition, high-quality biosimilars should be introduced in the public healthcare system as part of

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132 Leintz and Dedhia, "Biosimilars and emerging markets: historical and bioethical considerations," 2.

133 European Medicines Agency - Committee for Human Medicinal Products, *ICH E6 (R2) Good clinical practice,* EMA/CHMP/ICH/135/1995, (European Medicines Agency, 1 December 2016).

134 Leintz and Dedhia, "Biosimilars and emerging markets: historical and bioethical considerations," 3.

135 *Ibid*.

136 *Ibid*.

137 GR Soni, "Overview of non-innovator biological products in India," *Generics and Biosimilars Initiative Journal (GaBi Journal)* 9, no.1 (2020): 1-10, 4, http://gabi-journal.net/overview-of-non-innovator-biological-products-in-india.html.

138 *Ibid*., 10.

the commitment of the Government of India to achieve universal health coverage.[139] Thus, it is recommended to promote the development of high quality biosimilars in order to increase access to life-saving biologicals.

4.3.3.3 Regulatory harmonisation or convergence

The success being achieved with medical research in emerging markets with biosimilars through solidarity may be used as a model for governments in the harmonization and convergence of regulations so as to further increase equitable access to biological medicines through biosimilars. Positive results are being achieved with the WHO pre-qualification pilot system (Section 2.6), but inconsistencies still exist. So far, states retain control through their national regulatory systems, which in the globalised industry would need to be revisited. Another area of concern is related to regulation, where mutual recognition agreements on regulation are part of trade agreements which are negotiated by trade representatives and not by the regulators, which could have public health implications.[140] Solidarity in regulatory harmonisation and convergence may be the key towards equitable access to biologicals on a global level. As discussed in Section 4.1.1, regulatory authorities should set transparent processes that are based on good governance so as to provide public confidence in the medicines that are authorised by the regulatory authority.

4.4 Conclusion

This chapter has discussed the various ethical issues related to biosimilars which were identified in the previous chapters. Conflicts of interest and lack of transparency between the pharmaceutical industry and competent authorities including regulators, pricing and reimbursement authorities, hospitals, physicians and patient organisations, are considered to be unethical, as they could influence decision-taking on pharmaceuticals, which would not be in the interests of public health. Transparency and

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[139] Soni, "Overview of non-innovator biological products in India," 10.

[140] Lawrence O. Gostin et al. "Regulating medicines in a globalized world with increased recognition and reliance among regulators," *Journal of the American Medical Association* March 5 (2020): E1-E2, E2, https://doi.org/10.1001/jama.2019.21793.

impartiality in decision-taking are therefore of paramount importance to achieve confidence in decisions taken in the best interests of patients.

The second ethical issue is that related to safety of biosimilars, due to the 'residual uncertainties' involved, where the Biosimilars Regulatory Pathway and robust pharmacovigilance systems are justified to capture ADR's in real time so as to safeguard patient safety. The requirement of comparability clinical studies as part of the authorisation process, could also lead to ethical issues, which results in delays and high expense to authorise biosimilars, and therefore should be limited only to complex molecules, where analytical tests are insufficient.

From the ethical aspect, the position by the EMA to leave the decision of interchangeability to MSs, is ethically justified as it promotes 'safe regulation' i.e. through physician-led prescribing, based on the precautionary principle rather than patient-physician shared decision and informed consent. In practice the lack of a clear position by EMA on interchangeability is resulting in delays in biosimilar market entry, a waste of resources for 'non-inferiority' studies, a lack of confidence in the EMA authorisation process, and conflicting positions between MSs and professional associations. In the light of the above, physicians and Member States need to be supported by EMA who has the expertise and knowledge of biosimilars.

The third ethical issue is that of equitable access, at national, European and global level. The national healthcare system in Malta which is based on taxation is based on the solidarity principle. As universal healthcare has become increasingly unsustainable and governments are resorting to cost containment measures based on the principle of distributive justice. This is implemented through open tendering systems for non-patented biologicals. In parallel, governments are entering in confidentiality agreements with pharmaceutical companies for innovative highly priced medicines may lead to higher prices and inequity in allocation of resources. The confidentiality agreements and open tendering system seem to be contradictory in equity in allocation of resources and a coherent procurement policy is required.

Tendering systems are resulting in mandatory switching which could lead to multiple switches, that are not scientifically supported and therefore could result in patient harm,

such that physician-led switching is ethically justified. This is aimed towards safe regulation, through a robust pharmacovigilance system. Automatic substitution should therefore be avoided. For first generation biosimilars, where patients are automatically switched, patient's right to information is neglected whilst patient's consent is only sought for mAbs. It is recommended that procurement policies are aligned to switching policies which should be based on the principles of justice, solidarity, precaution and integrity.

The different interpretations of interchangeability by Member States contributes to inequity between European countries, which is exacerbated by different pricing and reimbursement systems and lack of price sharing. Solidarity between countries on price sharing and alternative procurement methods, such as differential pricing may contribute to better accessibility to innovative medicines.

Health equality may only be achieved at a global level through solidarity, which could bring governments, pharmaceutical industry and patients together towards achieving universal health coverage, as illustrated in the case of medical research in emerging markets, which follows the principles of UDBHR. This could be used as a model for regulatory harmonisation and convergence.

Conclusion

Biotechnology revolutionised the medical field and led to the development of biological medicines, which are much more expensive to produce than chemically-synthesised products due to their complex manufacturing processes.

From the analysis on the pricing of biologicals it was found that the top ten 'blockbuster' drugs are biologicals. The exorbitant prices of biologicals result in a problem of accessibility and affordability to patients as well as governments. The pharmaceutical industry justifies the high prices of biological medicines and attributes it to the cost of development and high risk in investment.

Biosimilars may be produced by pharmaceutical companies but these are not exact copies of originators and are seen as a possible solution to provide accessibility to patients. Manufacturing companies may produce biosimilars through reverse engineering and set up their own cell lines and manufacturing processes.

Summary of findings

The main findings of this dissertation are listed below:

Intellectual property protection

The pharmaceutical industry benefits from the monopoly status of originator biologicals during the patent period of twenty years. Biological medicines do not face the 'patent cliff' as for other types of medicines due to the complexity in the development process of similar biologicals (biosimilars) as a result of trade secrets. The EC introduced other regulatory mechanisms to extend the patent period in order to protect innovation. These include supplementary protection certificates (SPCs), data exclusivity rights, paediatric regulation, orphan drug data exclusivity rights, etc., such that a complex system is in place. An investigation carried out by the EC found that the prices of biologicals are disproportionate to the cost of development, and the pharmaceutical industry is abusing of its dominant position, through 'evergreening' strategies. These strategies involve hidden agreements with other companies,

professionals or patient organisations, which are unethical, as they lead to unfair competition and high prices.

Prior to the signing of the TRIPS agreement in 1995, manufacturing companies had taken advantage from the lack of patent law in Eastern countries, like China and India and transferred R&D and production of medicines including biologicals to developing countries. This led to the globalisation of the pharmaceutical industry.

Conflicting interests

The EC implemented recommendations to improve accessibility but with limited success, which could be attributed to the strong influence by pharmaceutical industry. It was also reported that the participation of pharmaceutical industry on boards and the relationships with committees involved in decision-taking on pharmaceutical issues could influence decisions and behaviours of professionals, at the expense of public health interest. Stakeholders autonomy in decision taking should be protected.

Regulation of biosimilars

As the first originator biologicals were placed on the market in the 1980's it was envisaged that their patents would expire in the early 2000. The EMA was at the fore front to set up new regulation for biosimilars in 2003 and the first biosimilar was authorised in 2006. The authorisation of biosimilars was questioned from the ethical aspect, but appears to be justified on the principle of distributive justice. An analysis of the authorisations by the EMA showed that since 2006, there were only 54 biosimilars authorised in Europe for 16 unique biological molecules compared to 481 authorised biologicals by end of December 2019. The low number of authorised biosimilars and their delay in reaching the market was investigated through the literature review. A critical analysis of the regulatory procedure showed that the delay in authorisation is partly due to clinical comparability studies that are required as part of the Biosimilar Regulatory Pathway to demonstrate similarity in efficacy and safety to the originator. For reference biologicals, there is no need for clinical studies to be performed for batch variations provided this is within acceptable limits. However, biosimilars undergo quality testing and comparability studies to ensure similarity in clinical efficacy and safety. Extrapolation of clinical indications is ethically justified based on scientific information

and would avoid unnecessary delays in treating patients and wastage of resources. For new formulations, based on the report of Professor Zalton, additional comparability studies are not ethically justified and new formulations are introduced by pharmaceutical industry to benefit from product differentiation.

Safety

Biologicals are associated with immunogenicity due to their complex molecular structure which could generate anti-drug antibodies (ADA's) that could result in ADRs which could be life threatening. There's a high risk of immunogenicity with switching to biosimilars. In view of this, safety has been identified as the main ethical issue with biosimilars. More rigorous pharmacovigilance is required, especially to capture adverse effects on switching to biosimilars.

In addition, the residual uncertainties on safety and efficacy of biosimilars raised questions on their interchangeability. EMA left the decision on switching to MSs, to the prescriber and according to reimbursement and prescribing policies, which is referred to as a 'soft' law. From the legal aspect, the position of EMA to leave the decision of interchangeability to Member States is justified, as it is in line with European regulation to issue a positive opinion and marketing authorisation for the biosimilar product. This follows the subsidiarity principle, where states decide on the allocation of resources. Also, in order to safeguard patients' safety, the EMA recommended safe regulation, i.e. physician-led prescribing which involves patient participation and patient education.

The need for additional 'non-inferiority' clinical studies, however, though aimed to increase confidence, is not ethically justified and results in waste of resources and it is arguable whether the clinical switching studies are ethically justified. Though all product information on biosimilars on EMA website is accessible to all physicians, they may not have the expertise and time and resources to review all the literature to come to a decision on a case by case basis as advised by the EMA when implementing the switch. This means that they would rely on guidance issued by professional associations, which could be influenced by pharmaceutical industry, and may be conflicting to the switching policy issued by the MSs, leading to an ethical quagmire.

Interchangeability is implemented through various models, including starting naïve patients on biosimilars, switching patients from originator to biosimilar, multiple switching and automated substitution. It has been concluded that prescribing biosimilars to naïve patients is ethically justified. Different product classes of biologicals and biosimilars exist and due to the differences in complexity, clinical indications and whether they are intended for acute or chronic treatment, specific product data is required with regard to safety of switching. First generation biosimilars have been authorised for several years and there is experience with switching and safety data is available. Second generation biosimilars are more complex molecules and overall, there was no major difference in efficacy, safety or immunogenicity related with switching, though discontinuations were reported which could be attributed to the nocebo effect. Multiple switching as yet is not scientifically supported and therefore prudence should be used in such decisions. Prescribing should follow safe regulation, i.e. physician-led, which means that pharmacy (automatic) substitution is not ethically justified. However, biologicals are prescribed within the framework of the public healthcare systems which are based on government policies.

Public healthcare systems

The universal access to health care has been recognised as a fundamental right of European citizens, which is difficult to be guaranteed by governments. From the legal aspect, according to the Maltese case law Katerina Cachia vs Director General, Department of Health and Honourable Minister for Health, patients do not have an absolute right to medical care in Malta but public health care systems should maximise allocation of resources.

Public health care systems are based on the principle of solidarity, which are enforced through health insurance systems and taxation but which shifted to the distributive justice, as cost containment measures. In the light of the above, in Malta procurement for non-patented biologicals are generally through the tendering system with the aim to increase competition, where the 'the winner takes it all.' This is based on the principle of distributive justice to maximise resources and achieve cost savings as it is government's responsibility to provide access to medicines to the maximum number of patients. The benefits include treating new patients or other diseases, and less

hospitalisations. Open tenders led to mandatory switching to biosimilars which is considered to be ethically justified based on the principle of distributive justice provided that switching is physician-led so as to ensure that patient safety is protected through safe regulation, i.e. robust pharmacovigilance systems in place and avoidance of multiple switches. In addition, patients' right to information should be safeguarded. In Malta, where mandatory switching is implemented for first generation biologicals without patient informed consent, patients' right to information is not protected. For second generation biosimilars (mAbs), patients are notified through informed consent.

At the same time, patented medicines are procured through confidentiality agreements between government and manufacturing companies, resulting in lack of price transparency, that could lead to inequity in allocation of resources.

As more biosimilars will reach the market, this could result in multiple switching, where the safety of multiple switching is not supported scientifically and could result in patient harm. It is therefore important that procurement policies are aligned to prescribing policies which are based on the principles of justice, solidarity, beneficence and integrity.

Equitable access of biologicals

The different interpretations of interchangeability by Member States, contributes to inequitable access to medicines across European countries, regions and hospitals, as this is implemented through different switching policies by MSs which are implemented through different pricing and reimbursement systems.

Pricing of biologicals and biosimilars is one of the major causes of inequality among European countries. It is accepted at European level that prices should not be shared as these are considered to be confidential information. Sharing of prices and reimbursement policies between states remains through voluntary collaboration.

The WHO has also recognised that high prices of medicines are impeding the achievement of Universal Health Coverage within and among countries and noted that 'confidentiality agreements' between manufacturing companies and governments are used as a tool to restrict transparency. At the 72nd World Health Assembly in May 2019, governments agreed to share information on the official prices and improve price

transparency and data on clinical trial results among other factors, which requires more commitment by governments. The principle of solidarity could play a critical role towards equitable access to biologicals on European and global level.

Globalisation

The globalisation of the pharmaceutical industry and the inconsistencies across different regulatory authorities have led to the need of regulatory harmonization and convergence for biosimilars, which could provide advantages as repetitive clinical studies will be minimised, thus increasing patients' accessibility to biologicals.

It also raises questions, however, related to the level of standards set by different regulatory authorities, which present challenges to the harmonisation of the regulatory framework. The WHO is also working on harmonisation of regulatory standards for biologicals and biosimilars. In 2017, a prequalification system for biosimilars was piloted by WHO and the first trastuzumab biosimilar was listed in December 2019 followed by rituximab in May 2020, which could lead to better access to life-saving medicines globally. There are still inconsistencies in the regulatory standards between countries. The model of medical research which is implemented based on the principles of UDBHR where solidarity was identified as the global ethical principle, should be used as a model for the implementation of harmonisation and convergence of regulations for biosimilars.

Recommendations

A number of recommendations are presented based on the above findings:

Good governance

Transparency and disclosure of agreements and relationships with pharmaceutical industry are key to achieve fair competition and safeguard public health interests. Good governance is required in the pharmaceutical sector at all levels, from patient organisations, to healthcare professionals, to professional organisations, procurement and reimbursement committees, regulatory authorities, governments, political level and institutions at European and global level, to ensure impartiality in decision-taking that impact on public health.

Intellectual property protection

In view of the problem of accessibility resulting from IP protection, the EC should consider revision of the various IP protection regulatory mechanisms, namely SPC manufacturing waiver, review of orphan drugs designation and the prioritisation system of unmet needs as proposed by EP and revisit the '8+2+1' regime for data exclusivity. In addition, it should consider changes in regulation to allow governments to introduce compulsory license for centrally authorised products which remain inaccessible to patients due to their exorbitant prices. As recommended by Dzintars Gotham, depositing cell lines at the regulatory authority seems to be a possible solution, such that 'biogenerics' may be produced, which have better safety profile and which will reach the market at a faster rate and lower prices contributing to better access of such medicines. This requires that the legal and regulatory aspects of trade secrets of cell lines in Europe be analysed further.

Improvements to the regulation of biosimilars

Clinical comparability studies are not justified where new analytical testing is available. Biosimilar companies should set robust pharmacovigilance systems that may capture efficacy or safety issues that may occur on switching. They are required to ensure that risk minimisation measures are in place to mitigate the risk of adverse effect / nocebo effect on switching. Biosimilar companies should support hospitals to set up an IT infrastructure to better capture ADRs on switching to biosimilars. A universal naming system is recommended to clearly distinguish between original biologicals and biosimilars.

It is recommended that all national regulatory authorities are committed towards harmonisation and MRA's based on the principle of solidarity, which is a 21st century best regulatory practice in the globalised world.

Switching to biosimilars (Procurement and prescribing)

As proposed by De Mora and colleagues, EMA should support MSs by drawing a list of biosimilars which may be substituted. This should form the basis for states to switch to biosimilars without the need for additional switching studies, whilst increasing

confidence in biosimilars both by physicians and patients, as a strategy to minimise the nocebo effect, thus increasing trust between patient and physician.

Physicians, academia and patients should be involved in the development of policies for prescribing and switching to biosimilars. The switching policy should be based on scientific evidence including real-world data, pharmacovigilance data, switching data and outcome data. This should be based on ethical principles of solidarity, justice, beneficence (non-maleficence) and integrity.

Hospitals and procurement agencies should consider additional costs of switching when determining the most economic choice. In addition, hospital Pharmaceutical and Therapeutics (P&T) committees should consider checklists for assessment of biosimilars as proposed by Boone and colleagues and System of Objectified Judgement Analysis (SOJA), which should be used as evaluating criteria when considering which biosimilars are to be introduced on the Hospital Formulary List. This should safeguard against multiple switching of biosimilars.

Governments should set procurement policies for patented and non-patented medicines, based on the principle of distributive justice and solidarity, which should be aligned with prescribing policies that are based on principles of beneficence and non-maleficence, justice, integrity so as to safeguard patient safety. This is important since open tendering systems could lead to multiple switches which so far is not supported by scientific evidence.

Collaboration at the European level

The EC and European governments should be committed to set up the structures to actively investigate the high prices of pharmaceuticals. In addition, as reported, the EC should ensure more transparency on costs of R&D and marketing for biologicals. More collaboration between countries on pricing and reimbursement systems is required, based on the principle of solidarity and equity.

Towards universal health coverage

Health equality may only be achieved at a global level through solidarity, which could bring governments, pharmaceutical industry and patients together towards achieving

universal health coverage, as illustrated in the case of medical research in emerging markets, which follows the principles of UDBHR.

Conclusion

This literature review has shown that biosimilars may contribute to provide equitable accessibility to treatment. Various regulatory and ethical factors have been identified related to biosimilars through this literature review, which led to a number of recommendations that may be implemented to achieve equitable access to biological medicines at local, regional, national, European and global level.

The findings and recommendations presented in this chapter confirm that the thesis question in the Introduction has been adequately answered and therefore the objectives of this thesis have been met through the extensive literature review on the various areas of this topic. The study allowed the author to identify the regulatory and ethical issues related to biosimilars and to critically analyse the theories and concepts related to regulation and ethics and apply them to the biosimilars.

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Appendix A: Definitions of key terminology

Term	Definition
Active substance	"The substance responsible for the activity of a medicine," accessed May 03, 2020, https://www.ema.europa.eu/en/glossary/active-substance.
Advanced therapeutic medicinal products (ATMP's)	"medicines for human use that are based on genes, tissues or cells. They offer ground breaking new opportunities for the treatment of disease and injury," accessed May 03,2020 https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview.
Biological medicine	"a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physicochemical-biological testing, together with the production process and its control."[1]
Biosimilar medicine	A biological medicine highly similar to another already approved biological medicine (the 'reference medicine') whose IP and / or regulatory data protection has expired. Biological medicines contain active substances from a biological source, such as living cells or organisms.[2]

[1] "Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use," *Official Journal of the European Union*, L159 (27.6.2003): 62.

[2] European Commission, *Fact Sheet Supplementary protection certificate for medicinal products: Frequently Asked Questions (FAQs)* (Brussels: European Commission, 28 May 2018), accessed on May 11, 2020, https://ec.europa.eu/commission/presscorner/detail/en/MEMO_18_3908.

Decentralised procedure	"The procedure for authorising medicines in more than one European Union Member State in parallel. It can be used for medicines that do not need to be authorised via the centralised procedure and have not already been authorised in any Member State," accessed May 03, 2020, https://www.ema.europa.eu/en/glossary/decentralised-procedure.
Economic accessibility, or affordability	"is a measure of people's ability to pay for services without financial hardship. It takes into account not only the price of the health services but also indirect and opportunity costs (e.g. the costs of transportation to and from facilities and of taking time away from work)." Affordability is influenced by the wider health financing system and by household income.[3]
Intellectual property rights	Rights awarded by society to individuals or organisations over inventions, literary and artistic works, symbols, names, images, and designs used in commerce. They give the titleholder the right to prevent others from making unauthorised use of their property for a limited period.[4]
Interchangeability	Refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect.[5]

[3] "Universal Health Coverage and Universal Access," *Bulletin of the World Health Organization (*2013): 91:546-546A, https://www.who.int/gender-equity-rights/understanding/accessibility-definition/en/.

[4] Sisule Musungu, "Intellectual property and access to medicines," in *Management Sciences for Health*, ed. Marian Ryan (Virginia: Management Sciences for Health, Inc 2012), 3.6, accessed on May 11, 2020, https://www.msh.org/sites/default/files/mds3-jan2014.pdf

[5] European Medicines Agency and the European Commission, *Biosimilars in the EU – Information guide to healthcare professionals,* posted October 02, 2019, accessed on December 30, 2019, https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf, 1-36, 29.

Substitution	Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber.[6]
Switching	When the prescriber decides to exchange one medicine for another medicine with the same therapeutic intent.[7]
Universal health coverage	"Ensuring that all people have access to health services, (including prevention, promotion, treatment, rehabilitation and palliation) of sufficient quality to be effective while also ensuring that the use of these services do not expose the user the financial hardship."[8]

[6] European Medicines Agency and European Commission, *Biosimilars in the* EU, *Biosimilars in the EU – Information guide to healthcare professionals,* 29.

[7] *Ibid*.

[8] "Universal health coverage," *World Health Organisation,* last accessed 8th February 2020, https://www.who.int/healthsystems/universal_health_coverage/en/