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

COMPULSORY LICENSING FOR EXPENSIVE MEDICINES

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COMPULSORY LICENSING FOR EXPENSIVE MEDICINES

LEGAL STUDY

ESTHER VAN ZIMMEREN, TIMO MINSSEN, LIESBET PAEMEN

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AI	Artificial Intelligence
API	Active Pharmaceutical Ingredient
BCEL	Belgian Code Economic Law
CJEU	Court of Justice of the EU
CL	Compulsory License
CSR	Clinical Studies Report
CTD	Clinical Trials Data
CTIS	Clinical Trials Information System
EMA	European Medicines Agency
EPO	European Patent Office
EPOrg	European Patent Organization
EU	European Union
FDA	US Food and Drug Administration
FTA	Free Trade Agreement
GDPR	General Data Protection Regulation
ICT	Information and Communication Technologies
IP	Intellectual Property
LDC	Least Developed Countries
LMIC	Low- or Middle Income Countries
MA	Market Approval
MPP	Medicines Patent Pool
NCE	New Chemical Entity
NME	New Molecular Entity

OECD	Organization for Economic Co-operation and Development
R&D	Research & Development
RPS	Reference Product Sponsor
SPC	Supplementary Protection Certificate
TRIPs	Agreement on Trade-Related Aspects of Intellectual Property Rights
UPC	Unified Patent Court
WTO	World Trade Organization

GLOSSARY

- **Compulsory licensing**: when the authorities license companies or individuals other than the patent owner to use the rights of the patent — to make, use, sell or import a product covered by patent protection (i.e. a patented product or a product made by a patented process) — without the permission of the patent owner.
- **Government use (also called "public non-commercial use"):** when the government itself uses or authorizes other persons to use the rights over a patented product or process, for government purposes, without the permission of the patent owner.
- **Failure to work**: official term in the Paris Convention referring to the situation where the patent holder is not exploiting the invention (in French: "faute d'exploitation").
- **Clinical study report (CSR):** a report of an individual study of an investigational medicinal product conducted in trial subjects, in which the clinical and statistical description, presentations, and analyses are integrated.
- **Clinical trials**: a study performed to investigate the safety and efficacy of a medicine.
- **Data exclusivity**: period of time during which the originators' pre-clinical and clinical trials data may not be referenced in the regulatory filings of another company (typically a biosimilar or generic company) for the same or similar product. However, applicants could still base their application for a marketing authorization (MA) on their own and independently generated data.
- **Market exclusivity**: period of time during which a generic or biosimilar company may not market an equivalent generic version of the originator's pharmaceutical product. However, once the data exclusivity period has expired, their application for a MA may be processed and they may rely on the originator's pre-clinical and clinical trials data. This helps generic and biosimilar producers to be in a position that allows them to market their product on the expiry of this additional 2 year period.
- **Know-how**: any confidential business information resulting from research or experience which provides an enterprise a competitive edge and is unknown to others. Know-how encompasses technical information, such as information concerning manufacturing processes, pharmaceutical test data, formulas and recipes, designs and drawings of computer programs and source codes. This information can be recorded in any form or even just held in the memory of an inventor or employee. Know-how can be protected as a trade secret.
- **Patent**: an exclusive intellectual property (IP) right granted for an invention, which is a product or a process that provides a new way of doing something, or a new technical solution to a problem. In order to get patent protection for an invention, the applicant needs to disclose information about the invention by way of a patent application.
- **Trade secrets**: know-how and commercial information, such as distribution methods, list of suppliers and clients, and advertising strategies and financial information can be protected as trade secrets. To qualify as a

trade secret, the information must be: (1) commercially valuable because it is secret, (2) be known only to a limited group of persons, and (3) be subject to reasonable steps taken by the rightful holder of the information to keep it secret, including the use of confidentiality agreements for business partners and employees.

- **Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs):** international convention between all the countries that are members of the World Trade Organization (WTO). It establishes minimum standards for the regulation by national governments of different intellectual property rights (IPRs). Unlike other agreements on intellectual property, TRIPs can rely on a potentially powerful enforcement and dispute settlement mechanism established within the context of the WTO, the dispute settlement body.

1 INTRODUCTION

Globally major concerns exist regarding the increased prices for medicines putting intense pressures on health budgets. Existing medicines are in some cases extremely expensive and prices may increase further for new innovative treatment options. Incentivising innovation in the pharmaceutical sector while ensuring access, availability and affordability of medicines is essential. The affordability and access to life-saving medicines is a key issue in health policies of many countries. Even in the US, home to many of the world's largest pharmaceutical companies and traditionally a fierce defender of medicine patents on the global stage, criticism of drug pricing practices is on the rise. As expenditures for medicines are skyrocketing, calls for a drug pricing reform have been moving to a next phase in the US as well.[1] It is often assumed that at least in a number of cases the excessive price setting is linked to the exclusivity generated by patent protection.

National, European and international law already provide a basis for price-reducing options, including **compulsory licenses** (CLs). CLs offer a legal mechanism that allows an institution (i.e. government or court) to grant a license to a third-party without the authorization of the patent owner. Normally, patent owners can determine freely to license out or not and to determine the licensing conditions, including the license fee or royalties; the CL limits that prerogative of the patent owner.

In line with international intellectual property (IP) law requirements, the national patent acts of most countries provide a legal basis to grant CLs for various reasons (e.g. abuse, including failure to work[2], public interest/public health, interdependence, anti-competitive practices, for more details see Chapter 5). Apart from the possibility to grant CLs to a third-party, patent legislation often also allows for so-called 'government use', enabling governments to use or authorize other persons to use the rights over a patented product or process, for government purposes, without the permission of the patent owner. **Government use** is a particular form of CL for government purposes (reflected by the fact that CLs and government use are covered by the same article in the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs), but the legal grounding and procedures are slightly different.[3] In this report, we refer generally to CLs, but at some instances we will examine in more detail the implications of government use.

In practice stakeholders and countries tend to be quite reluctant to actually apply for and to issue CLs. CLs are typically used as a bargaining tool in negotiations, as a defence in patent litigation and as an exceptional mechanism which is only rarely invoked explicitly. Whereas a considerable number of CLs has been granted in developing and least-developed countries, only a relatively limited number of examples exist where courts or governments in high income countries have granted CLs.[4]

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1 A.M. Olstein, 'A massive step forward': Democrats clinch drug pricing deal', POLITICO, 2 November 2021, available at https://www.politico.com/news/2021/11/02/dems-drug-pricing-518554. Whereas the current debate on drug pricing reform tends to focus on pricing negotiations, proposals similar to the use of CLs have been made in the US as well, see for instance H. Brennan et al. (2017), 'A Prescription for Excessive Drug Pricing: Leveraging Government Patent Use for Health', 18 *Yale J.L. & Tech*, available at: https://digitalcommons.law.yale.edu/yjolt/vol18/iss1/7 (referring to 28 U.S.C. § 1498, which permits the government to "use" patents under its responsibility (even if the government involves a contractor to perform the work) at any time without permission of the patent holder, as long as reasonable compensation is provided).

2 For more information on the concept of 'failure to work', see Section 5.2.1.3.

3 For more information on the concept of 'government use', see Section 5.2.1.3.

4 See e.g. E.F.M. 't Hoen et al. (2018), 'Medicine procurement and the use of flexibilities in the Agreement on Trade-Related Aspects of Intellectual Property Rights, 2001-2016', 96 *Bull World Health Organ,* 185-193, who convincingly show that the use of the flexibilities included in the WTO TRIPs Agreement to access lower-priced generic medicines, including CLs, is much more frequent then is commonly assumed. They identify 100 CLs/public non-commercial use licenses, including 2 granted by developed countries. A well-known rather recent case (2017) is a CL granted by the German Federal Court of Justice. In its ruling on August 31st 2016, the Federal Patent Court granted a 'preliminary' CL (Bundes Patent Gericht (BPatG), judgement 31 August 2016, 3 LiQ 1/16 (EP), available in German at

The Belgian patent law framework also contains various provisions regarding CLs but does not include government use provisions. However, until now no cases of applications for CLs have been reported in Belgium. Yet, a proposal was introduced to revise one of the current CL mechanisms and to introduce a mechanism that allows the government to take the initiative to license without the authorization of the patent owner concerned in case of excessively priced medicines.

The sub-group of parliamentary members in charge of examining this proposal (Federal 'Commission de la Santé et de l'Egalité des chances/Commissie voor gezondheid en gelijkheid van kansen'[5]) requested the KCE to investigate the proposed mechanism of for cases where pharmaceutical companies ask excessive prices for essential drugs.

The **overall objective** of this KCE study is to assess the feasibility and effectiveness of CLs for medicines and treatments sold at excessive prices. In this study we do not aim to define a specific threshold above which a price can be considered as excessive, but we rather refer to the methods used and elements taken into consideration in case law and theoretical economic models. Moreover, when we use the term "excessive" it should generally not be understood only specifically in the context and according to the definition developed in competition law, but rather in a broader and more general sense unless indicated differently in the text (e.g. Sections of the report and Appendix 1 focused on competition law).

Several research questions have been identified by KCE. These research questions have been addressed by a legal and an economic study.

The five research questions identified for the entire project are:

1. What is the legal framework surrounding patents and CLs?
2. What are the (possible) consequences for the medicines market (economic)?
3. What are the obstacles for the implementation of CLs and how can they be overcome?
4. What is the proportionality of the instrument (when is the use 'justified'/how to select a drug that may be subject to CLs)?
5. What are the pro's and con's when considering CLs for (medico-) economic purposes in Belgium?

This **legal report aims** to provide a good understanding of the CL mechanism by clarifying the application of patent law principles in the pharmaceutical sector, detailing the legal basis of CL and considering the implications of CLs in terms of data and market exclusivity to feed into the important debate as to the role that CLs can effectively play in case of excessively priced medicines. In this respect, we also take into consideration key developments in related legal fields, recent societal and legal developments and the interests of various stakeholders in the way legal rules and principles are applied.

Excessive pricing concerns have been raised for medicines that vary considerably in terms of the specific factual circumstances, innovation and legal contexts. In some cases these are new innovative drugs covered by

http://www.rechtsprechung-im-internet.de/jportal/portal/t/19ke/page/bsjrsprod.psml?pid=Dokumentanzeige&showdoccase=1&js_peid=Trefferliste&documentnumber=1&numberofresults=10908&fromdoctodoc=yes&doc.id=MPRE135990964&doc.part=L&doc.price=0.0&doc.hl=1#focuspoint), which was confirmed by the Federal Court of Justice on July 11th 2017 (Bundesgerichtshof (BGH), judgement 11 July 2017, X ZB 2/17, available in German at http://www.rechtsprechung-im-internet.de/jportal/portal/t/19ke/page/bsjrsprod.psml?pid=Dokumentanzeige&showdoccase=1&js_peid=Trefferliste&documentnumber=1&numberofresults=10908&fromdoctodoc=yes&doc.id=KORE313612017&doc.part=L&doc.price=0.0&doc.hl=1#focuspoint. For an English translation of the case, see: https://unctad.org/ippcaselaw/sites/default/files/ippcaselaw/2020-12/MSD%20v%20Shionogi%20%282017%29%2C%20German%20Federal%20Court%20of%20Justice_0.pdf. We note, however, that some countries, such as the US, have used the mechanism of 'government use' more often.

5 This Commission is a specific sub-group of parliament members which are represented according to the proportion between the different political groups in the Chamber of Representatives.

patent protection, trade secrets and regulatory exclusivities with potential for extended protection for the treatment of rare diseases and/or paediatric use. In particular, the public concern is high when patients do not have any alternative options. For instance, in the case of Zolgensma, a gene therapy for the rare disease spinal muscular atrophy is only available at a price of 1.9 million euro. Other cases relate to older medicines which have received additional patent protection and regulatory exclusivities for newly identified indications. While patent protection for these cases may lie at the basis of the dominant position, we will show in this report that the grant of a CL can, in case of abuse of this exclusivity, only be part of the solution, as data and market exclusivities, complementary trade secret protection and lack of access to the active ingredients may still block generic manufacturers with a CL from producing the medicines. Moreover, excessive pricing is also observed for old, off-patent drugs (generics) where prices are sometimes raised over time by hundreds or sometimes even thousands of percent. One would expect that, for generics, the absence of exclusive rights would allow competition such that the market would gradually "self-correct" once new generics enter the market. However, for various reasons (i.e. small patient group, nature of the disease, regulatory framework, high entry barriers) a limited number of players may enter the market in such a way that those generic producers also get a strong, even dominant market position and are able to set excessive prices. In these cases, CLs will not be of help as the relevant patents have already expired. Competition law enforcement may provide a complementary mechanism for dealing with such cases (see Section 5.2.2.5). It is an open question to what extent, in cases where patent protection or other applicable exclusivities are still in force, competition authorities can and should interfere in pricing situations that could be considered "excessive" according to competition law (see also Section 5.2.2.5).

The COVID-19 crisis has reinvigorated the public and political attention for the role that IP law is playing in the pharmaceutical sector. At the national level, many countries have adopted new rules on CLs to respond to the need for diagnostic kits, medical masks, other personal protective equipment and ventilators, as well as vaccines and medicines for the prevention and treatment of patients in emergency situations. The fierce international debate on the need for an IP waiver for COVID-19 reflects the many diverging views as to the implications that restrictions on exclusive patent rights may have on the availability of those products and incentives to innovate. In addition, the developments show the complexity of the pharmaceutical and biotechnology market, its highly competitive nature and the difficulty of negotiating contract clauses to safeguard the availability and affordability of vaccines, medicines and diagnostics despite considerable public funding. Moreover, the COVID-19 crisis has also revealed the flaws of the current CL mechanisms in terms of the speed and feasibility of applying the mechanisms in emergency situations. **The current report does not focus on CLs in emergency situations, but on the potential to use CLs for excessively priced medicines outside of emergency situations.** Therefore, while we do touch upon some new CL provisions that were introduced in a number of countries in response to the pandemic in Section 5.4, this is not the focus of the current report.

Against this background it is important to briefly describe the characteristics and trends in the pharmaceutical sector as far as relevant for CLs (Chapter 2) and the current national, European and international patent law context for CL mechanisms (Chapter 3). As the IP system works in tandem with the system of regulatory exclusivities, trade secrets and transparency rules, for carefully delineating the potential role of CLs in case of excessive pricing those exclusivities need to be taken into consideration in this evaluation (Chapter 4). However, Chapter 4 focuses primarily on the implications of regulatory exclusivities. In Chapter 5 we then describe the concept, rationale, criteria, procedure and governance framework for CLs at the national, European and international level and we evaluate the role that CLs could play to safeguard access to and the affordability of innovative medicines in Belgium. In Chapter 6 we explore a number of complementary mechanisms followed by provisional conclusions and recommendations in Chapter 7.

The present report also emphasizes the increasing importance of data and access thereto both for the development of innovative and generic medicines. Throughout this report we will highlight this and we will point out to what extent this may also cause challenges within the context of granting CLs and ensuring that they are effective, but it is clear that this topic by itself would warrant a separate report.

The **research methodology** used for this chapter is primarily based on classical, doctrinal legal research, which entails a systematic collection and

analysis of national, European and international law and policy, legal and non-legal literature (e.g. handbooks European patent law, health and medicines law, competition law, international trade law, legal/social sciences/scientific journals, policy reports, working papers) and case-law. For this purpose, we use various databases and search tools, including WestLaw, LexisNexis, HeinOnline, Google Scholar, JSTOR, SSRN, Jura, Stradalex and Jurisquare. We use relatively simply search strings based on combinations of keywords, including for instance compulsory license/licensing, government use, excessive pricing/prices, very high prices, exorbitant prices, reasonable terms, adequate remuneration, competition law, data exclusivity, data transparency, market exclusivity, failure to work, abuse, emergency/urgency. After collecting and analysing key sources, the so-called "snowball method" was used, checking for additional essential references in the footnotes of those key sources. CL cases in different jurisdictions were identified on the basis of secondary sources. For the descriptive section on patent law, patent law handbooks, patent conventions and legislation and recent articles were used.

The legal literature on CLs is very extensive. This report is not aimed at proving an exhaustive overview but focuses on the providing a balanced and accessible account of the most important sources in the context of CLs and excessive pricing of medicines. In this respect, we highlight that this report does not specifically deal with medical devices or the combination of medicines and devices.

2 THE PHARMACEUTICAL SECTOR: TRENDS, PRACTICES AND CHARACTERISTICS OF THE LEGAL AND GOVERNANCE FRAMEWORK

2.1 Introduction

We first provide a description of the environment in which the pharmaceutical industry operates, innovates and protects its innovations, but only as far as relevant to position the problem of excessive pricing in the relevant economic, societal and legal context. The following sections focus on key stakeholders and innovation trends (see Section 2.2), characteristics of the relevant legal framework going beyond patent law and regulatory exclusivities (see Section 2.3) and the costs of R&D and relevant business and IP strategies (see Section 2.4) that feed into the discussion on the potential role of CLs for excessively priced mechanisms.[6]

2.2 Key Stakeholders & Innovation Trends in the Pharmaceutical Sector

There is a wide variety of key stakeholders in the sector, such as patients, hospitals, healthcare professionals, pharmacies, pharmaceutical companies, biotech start-ups, clinical trial companies, research organizations, generic companies, health insurers, universities, international organizations, governments, medical agencies, patent offices, researchers etc. All these actors have different responsibilities, interests and stakes in the process, which ultimately need to be channelled through an effective, safe and affordable R&D process starting from the fundamental research to the patients. This wide diversity of interests cannot be ignored when

[6] These sections were partially inspired by T. Minssen (2012), Assessing the Inventiveness of Bio-Pharmaceuticals under European and US Patent Law, Ph.D. dissertation, Lund University Faculty of Law, but were significantly modified, updated and complemented by other information and sources.

examining the use of CLs to improve access to and affordability of medicines.

Fundamental research underlying the development of drugs is traditionally for a large part carried out by universities and public research institutes and funded through public funding. However, biotechnology companies are also important actors in fundamental research. As universities and research institutes are generally not so well-equipped to turn fundamental research into products, they typically license out or sell patented inventions to industry for further development. The costs of further R&D and for the clinical trials is born by the industry often aided by government and EU support or charitable foundations. Increasingly universities and research institutes are collaborating with pharmaceutical companies, biotech-start-ups and clinical trial companies in public private partnerships to ensure that products are moving more quickly from the “bench to the bedside”, also referred to as ‘translational medicine’. Such consortia tend to be partially publicly funded (i.e. national funding or EU funding such as Horizon2020 and the Innovative Medicines Initiative (IMI)) and partially supported by private investments.

Large multinational pharmaceutical companies, often referred to as “Big Pharma”, traditionally develop small molecule drugs i.e. new chemical entities (NCEs) or new molecular entities (NMEs) produced by chemical synthesis. However, in recent years traditional "Big Pharma" has become increasingly engaged with biotechnology companies and start-ups developing research tools and biologics. Biologics are most often highly complex large-molecule drugs such as proteins (e.g. antibodies or hormones) or polynucleotides (DNA or RNA) that are produced in living organisms. The development of biologics has revolutionized the treatment of various severe and chronic diseases.[7] The evolution of these drugs has been instrumental for developing treatment strategies regarding cancer, autoimmune conditions, diabetes and anaemia.[8] Cell and gene therapies, which manipulate human cells and genomes to correct gene defects or to produce molecules endogenously, are another booming area of biotechnology. The US Food and Drug Administration (FDA) approved the first-ever gene therapy, a drug called Kymriah, in 2017 followed by the European Medicines Agency (EMA) in 2018. The therapy uses a patient’s own genetically modified white blood cells to treat acute lymphatic leukaemia. Despite challenges related to capacity and the ability to scale production, since then, this area of biotechnological research has doubled in growth with promising outcomes in oncology, regenerative medicine, and rare diseases. Pharmaceutical and biotechnology companies are research-based industries and invest heavily in the development of these new and innovative drugs. However, these new types of drugs tend to be very high-priced, which has prompted the need for more cost-effective solutions to enter the market.

Generic companies are companies that develop copies, generic versions, of the originator products when they are no longer protected by patents or otherwise. Traditionally, the term "generic drugs" refers to small molecule drugs. As it is very difficult to make identical reproductions of biologics, only similar products can be produced; these are referred to as “biosimilars”. With recent scientific advances and an evolving regulatory legislation allowing the marketing of “biosimilars” in Europe, the US and other jurisdictions, some experts believe that an advanced generic industry may also emerge for biosimilars comparable to the one for traditional chemical compounds.[9] However, as there are more parameters to control and specific expertise is required for producing biologics, it is generally more difficult and costly to develop these. So, there are still some significant hurdles to overcome for biosimilars to become a success, even though in recent years more biosimilars have been entering the market and increased regulatory experience is gained.[10]

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7 M.J. Espiritu et al. (2014), *A 21st Century Appraoch to Age-Old Problems : The Ascension of Biologics in Clinical Therapeutics*, Amsterdam, Elsevier.

8 E.R. Kabir et al. (2019), ‘The Breakthrough of Biosimilars: A Twist in the Narrative of Biological Therapy’, 9 *Biomolecules* 410 and H.I. Miller (2007), ‘Biotech’s defining moments’, 25 *Trends Biotechnol.*, 56-59.

9 E.R. Kabir et al. (2019), ‘The Breakthrough of Biosimilars: A Twist in the Narrative of Biological Therapy’, 9 *Biomolecules*, 410.

10 See for instance also: L. Diependaele et al. (2018), ‘Similar or the Same? Why Biosimilars are not the Solution’, 46 *Journal of Law, Medicine an Ethics*, 776-790.

Another, increasingly significant trend concerns the emergence of big data and tech players, such as Google, Amazon and Microsoft, in the pharma sector.[11] Although this is not the focus of this study, rapid advances in big data analysis and artificial intelligence (AI) in drug development are changing the processes of how drugmakers find and develop new medicines. These developments and the dynamic competition stimulated by the emergence of new players in the sector, press large pharmaceutical companies to prepare for a new technological race and to enter into new collaborations with big tech, AI and software companies.[12]

2.3 Characteristics Relevant Legal Framework Pharmaceutical Sector

The pharmaceutical sector is one of the largest, but also one of the most heavily regulated sectors in the world; it is controlled and influenced by various areas of law, such as IP law, trade secret law, competition law, internal market law (free movement), human rights law, data protection law and regulation concerning research and development (R&D) and market approval. This results in a complex legal landscape that is rather difficult to navigate and where modifications in legislation in one field may lead to unforeseen consequences in other fields. Recent policy initiatives regarding clinical trial data transparency[13] are a noteworthy example, which requires more consideration within the context of CLs as well (see Chapter 3).[14] The current report focuses on patent law and market regulation and includes some aspects of trade secrets protection,[15] transparency rules, data protection[16] (see Chapter 4) and competition law (see Chapter 5).

The legal framework constantly needs to adapt to new socioeconomic trends and events, such as new technological developments (e.g. digitalisation, big data and AI), aging populations, the personalisation of medicine, open innovation and open science, a push for more transparency of clinical trial data and disease outbreaks. While the patent system is still of vital importance to the industry, this also means that other forms of protection such as regulatory exclusivities, trade secrets, database protection and copyright law are becoming more relevant.

In Europe new harmonizing legislative instruments or policies are often adopted at the European level but require implementation at the national level. In addition, some harmonization happens at the international level. This complex multilevel governance framework will often lead to questions and concerns about tensions that exist between different areas of the law and different stakeholders. Moreover, measures at the national level may often be less effective, but the only option when EU competences are limited

11 See. e.g. A. Schuhmacher et al. (2021), 'Big Techs and start-ups in pharmaceutical R&D – A 2020 perspective on artificial intelligence', 26 *Drug Discovery Today*, 2226-2231.

12 M.B.M.A. Rashid (2021), 'Artificial Intelligence Effecting a Paradigm Shift in Drug Development', 26(1) *SLAS Technol.: Translating Life Sciences Innovation*., 3-15.

13 See EMA policy on publication of clinical data for medicinal products for human use, POLICY/0070, EMA/240910/2013, 2014, London, UK; available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf and EMA's Clinical data publication (Policy 0070) report Oct 2016-Oct 2017, EMA/630246/2017 London, UK, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2018/07/WC500252071.pdf; Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC [2014], *OJ* L158, 1–76.

14 For more information, see e.g.: T. Minssen et al. (2020), 'Clinical trial data transparency and GDPR compliance: Implications for data sharing and open innovation', 47(5) *Science and Public Policy*, 616–626.

15 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, [2016], *OJ* L 157, 1–18.

16 Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation or GDPR), [2016] *OJ* L119, 1–88.

or lacking. To a certain extent coordination and collaboration between groups of Member States could also fill this gap (e.g. BeNeLuxA[17]). However, such initiatives will generally not involve the harmonization of legislation.

2.4 Costs of R&D, Business and IP Strategies

The regulatory approval process, requiring pre-clinical testing in e.g. animal models and costly clinical trials/studies in humans to prove safety, efficacy and an acceptable cost-effectiveness ratio for an NCE/potential drug, constitutes the lion's share of the cost that is incurred before new drugs can be put on the market. Additionally, pharmaceutical industry expenditures on sales and advertising tend to be very large, and for some companies they may even exceed their investments in R&D.[18]

Although the numbers are being contested,[19] DiMasi et al. reported a sharp increase of the cost of developing a new drug in the mean cost of developing a single new therapeutic agent from $1.1 billion in 2003 to $2.8 billion in 2013 (in 2018 US dollars).[20] Since success rates are relatively low, companies also include amortization of the many failures as part of the true costs of making successful drugs. For a long time, evidence suggested that the failure rate for new drugs in clinical trials was increasing: in the 90s, the number of drug approvals reached a peak followed by a steep decline of the success rate.

However, there is now some evidence of a revival in the rate of approval of new drugs.[21] Various papers suggest that this may be related to a more focused and strategic approach by pharmaceutical companies[22], on the one hand, and developments towards more collaboration by pharmaceutical

17 BeNeLuxA is an initiative of Belgium, the Netherlands, Luxembourg, Austria and Ireland focused on joint horizon scanning of important pharmaceutical innovations, health technology assessments and joint price negotiations

18 On the one hand: A. Swanson (2015), 'Big pharmaceutical companies are spending far more on marketing than research, Washington Post,' 11 February 2015, available at: http://www.washingtonpost.com/news/wonkblog/wp/2015/02/11/big-pharmaceutical-companies-are-spending-far-more-on-marketing-than-research/; on the other hand, see: Z. Brennan, 'Do Biopharma Companies Really Spend More on Marketing Than R&D?', Regulatory Affairs Professionals Society, New Articles, 24 July 2019, available at: https://www.raps.org/news-and-articles/news-articles/2019/7/do-biopharma-companies-really-spend-more-on-market.

19 See for instance: O.J. Wouters et al. (2020), 'Estimated research and development investment needed to bring a new medicine to market', 2009-2018, 323(9) *JAMA*, 844-853; D.M. Cutler (2020), 'Are pharmaceutical companies earning too much?', 323(9) *JAMA*, 829-830.

20 J.A. DiMasi et al. (2016), 'Innovation in the pharmaceutical industry: new estimates of R&D costs', 47 *J. Health Econ.* 20-33 (see also: J.A. DiMasi & H.G. Grabowski (2007), 'The Cost of Biopharmaceutical R&D: Is Biotech Different?', 28 *Manage & Decis. Econ.*, 469-79007) and J.A. DiMasi et al. (2003), 'The price of innovation: new estimates of drug development costs,' 22(2) *J. Health Econ.*, 151-185. As these numbers are heavily contested, it is important to also consider other data, such as for instance this WHO report which focuses specifically on cancer drugs pricing: WHO (2018), 'Pricing of cancer medicines and its impacts', available at: https://apps.who.int/iris/bitstream/handle/10665/277190/9789241515115-eng.pdf?sequence=1&isAllowed=y.

21 A. Mullard (2018), 'FDA drug approvals', 18 *Nature Reviews Drugs Discovery*, 85–89. Nonetheless, a substantial number of those approvals tends to offer therapeutic qualities similar to an already approved drug.

22 H. Dowden & J. Munro (2019), 'Trends in clinical success rates and therapeutic focus', 18(7) *Nature Reviews Drugs Discovery*, 495-496. The choice of which therapy area to focus on can also affect success rates, see e.g. cardiovascular and nervous system disorders with the lowest probability of success over the 2010–2017 time period. The authors also observe a growth in the number of drugs for orphan indications or rare diseases in company pipelines; this is likely the result of concerted efforts of patient advocacy groups to raise disease awareness and develop patient registries, as well as the introduction of additional regulatory support mechanisms. Interestingly, the reduced scale of the clinical programmes associated with rare disease therapies have attracted investment from new, small biopharma companies, which may be able to compete more effectively with larger companies in this field.

companies, biotechnology companies, not for profits, universities and research institutes, on the other hand (i.e. acquisitions, strategic alliances, open innovation models, public-private partnerships, grants for targets)[23]. Another explanation could be seen in the rapidly evolving possibilities provided by AI augmented data analysis and the capabilities offered by new platform technologies, such as mRNA, CAR-T or genome editing technologies, as well as the evolving skills on how to use such platforms in more targeted drug development. Moreover, globally research funders have recognized the growing need and opportunities of investing more in translational medicine (e.g. EU Horizon2020, US NIH, UK Medical Research Council and the Wellcome Trust).[24]

A further trend demonstrates that, drug 'repurposing', i.e. the development of a previously marketed drug for a new use – also known as repositioning, reusing, or rediscovery – provides an increasingly attractive option for pharmaceutical companies, as it is much faster, involves lower development costs and has higher success rates than traditional drug development.[25] Many of the drugs have already passed costly preclinical and early clinical testing. This is especially attractive for companies if they face expiring patents on the drug itself, high costs and low productivity, particularly if patent protection is still available for the new use. For non-profit organizations, universities and research institutions, the low cost of repurposing is an opportunity to focus on neglected diseases or address other unmet medical needs.

Another common practice in the sector relates to so-called 'follow-on' or 'me-too strategies'; the development of similar drugs employing the same mechanism but with a different molecule. The actual effects of this practice in terms of the therapeutic benefits are disputed. [26] Therefore, it is important to be cautious of indeterminate claims made about new or added therapeutic benefits. Moreover, the impact of regulatory changes aimed at limiting the use of these practices that have been proposed in the past should be carefully contemplated as they may have unintended side-effects in view of the distinct therapeutic benefits for (some) patients.[27]

It has been reported that only 10% of the new medicinal products are a notable therapeutic advance.[28] Those results seem to be in line with a recent KCE report on 40 new oncology drugs introduced over the past 15 years in 12 advanced cancer types. When outcomes were assessed using linked national cancer registry data and the literature no detectable impact on survival was found for half of the tumour types and only a small effect was found for the other half.[29]

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23 I. Khanna (2012), 'Drug discovery in pharmaceutical industry: productivity challenges and trends', *Drug Discov Today*,17, 1088–1102 and A. Schuhmacher et al. (2016), Changing R&D models in research-based pharmaceutical companies, 14 *J Transl Med.*, 105–115.

24 J.S. Bryans (2019), 'Are academic drug discovery efforts receiving more recognition with declining industry efficiency?', 14(7) *Expert Opinion on Drugs Discovery*, 605–607.

25 S.F. Halabi (2018), 'The Drug Repurposing Ecosystem: Intellectual Property Incentives, Market Exclusivity, and the Future of "New" Medicines', 20 *Yale J. Law Tech.*, 9.

26 See e.g. H.-G. Eichler et al. (2019), 'Added therapeutic benefit and drug licensing', 18 *Nature Reviews Drug Discovery* 18, 651-652. Me-too innovation may, in fact, provide distinct benefits from the perspective of patients and physicians. First, although several clusters of 'me-too' drugs appeared to be almost interchangeable at the time of launch, as more treatment experience accumulated during routine use, they proved to have different safety profiles, different drug–drug or different efficacy profiles or effect sizes. Second, even when average or median effect sizes of products appear similar, treatment responses in individual patients may differ from one drug to the next due to known or unknown individual patient characteristics. Third, patients have different preferences; some are focused on maximizing efficacy while others prefer to minimize adverse effects.

27 *Ibid*.

28 S. Garattini et al. (2021), 'Pharmaceutical Strategy for Europe: Reflections on Public Health-Driven Drug Development, Regulation and Policies', *Front Pharmacol.*, 12, 685604.

29 M.D. Neyt et al. (2021), *Benefits And Costs Of Innovative Oncology Drugs In Belgium (2004-2017)*, KCE Reports 343, available at:

The pharmaceutical industry has a particular interest in extending the lifetime of block-buster drugs – i.e. drugs with annual revenues in excess of $ 1 billion. An important moment of concern is when patents covering the drug are getting closer to their expiration date (the "patent cliff") potentially resulting in significant reductions of annual revenues. The ability to be able to continue profiting from a block-buster drug creates a substantial economic incentive to secure additional indications, rather than pursuing an entirely new R&D program, even if those indications offer only marginal improvements.[30]

In a challenging climate with rapidly increasing global competition from emerging economies in Asia and South America, US and European pharmaceutical companies generally develop a wide range of strategies to anticipate this situation and avoid a sudden loss in revenue when a blockbuster drug becomes off-patent. These strategies include the development of new strategic alliances and collaborations, differentiating product portfolios and making clinical trials and the R&D process more effective by using new technologies, such as AI. Modern-day data collection combined with the use of digital technology will amplify the magnitude and dimensionality of data dramatically.[31] This will increase the opportunities for AI/machine learning techniques to deepen the understanding of biological systems, which will not only help to repurpose drugs for new indications, but also to identify new drug candidates and to inform study design and analysis of clinical trials in drug development. [32]

Various business strategies are combined with legal strategies devised to maximize and prolong the lifecycles of existing products. This “toolbox” of legal strategies that may be used by some companies to delay or block the entry of competing generic products or biosimilars on the market consists of patenting strategies (see Section 3.4), litigation strategies,[33] settlement agreements, strategies aimed at procedures for marketing authorizations, pricing and reimbursement and “life cycle management strategies” for follow-on products. Although most of these strategies *as such* do not violate any legal requirements, the combination of strategies used has become the topic of fierce public debates and competition law scrutiny in various jurisdictions. We will mention this briefly in Section 5.2.2 regarding competition cases on excessive pricing.

In the EU, pharmaceutical law is harmonized to a large extent. However, some important regulatory areas that are very relevant for the current study are not harmonized, such as drug pricing and reimbursement, and fall within the competence of the EU Member States. Therefore, legislative differences between EU countries exist.[34] Nonetheless, coordination and collaboration between EU countries in pricing and reimbursement is increasing, such as for instance the BeNeLuxA initiative, an initiative of Belgium, the

https://kce.fgov.be/sites/default/files/atoms/files/KCE_343_Innovative_oncology_drugs_in_Belgium_Report.pdf.

30 Fojo T et al. (2014), ‘Unintended consequences of expensive cancer therapeutics – the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity’, 140(12) *JAMA Otolaryngology Head and Neck Surgery*, 1225-1236.

31 S. Kolluri et al. (2022), ’Machine Learning and Artificial Intelligence in Pharmaceutical Research and Development: a Review’. 24 *AAPS J.* 19.

32 *Ibid.*

33 Pharmaceuticals and biotechnology patents have the highest litigation intensity across all technical sectors (3 patent cases for every 1 000 patents filed in the aggregate EU-6 (Belgium, Germany, Spain, France, UK and the Netherlands)). (S.J. Graham & N. Van Zeebroeck (2013). ‘Comparing patent litigation across Europe: a first look’, 17 *Stanford Technology Law Review*, 655).

34 J. Espin & J. Rovira (2007), *Analysis of differences and commonalities in pricing and reimbursement systems in Europe*, A study funded by DG Enterprise and Industry of the European Commission, 2007 and see also Federaal Kenniscentrum voor de Gezondheidszorg (KCE), Drug reimbursement systems: international comparison and policy recommendations, KCE reports 147C, 2010, available at https://kce.fgov.be/sites/default/files/atoms/files/KCE_147C_Drug_reimbursement_systems_4.pdf. In the Pharmaceutical Sector Inquiry report the pharmaceutical industry has been blamed by the European Commission to use/abuse these gaps and differences. European Commission, *Pharmaceutical Sector Inquiry - Final Report*, available at https://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf.

Netherlands, Luxembourg, Austria and Ireland focused on joint horizon scanning of important pharmaceutical innovations, health technology assessments and joint price negotiations. Such initiatives may contribute to streamlining procedures in the EU Member States and strengthening the position of health authorities in price negotiations with the pharmaceutical industry. It would be desirable if the EU would adopt a more active role in stimulating and coordinating such initiatives to address gaps and weakness in national procedures. This may be particularly important in dealing with excessively priced medicines. Though likely to be difficult in view of differences in the healthcare systems and the number of industrial players in the contracting states, this type of coordination would complement the implementation of instruments, such as CLs, to ensure access and affordability (see Section 6.6).

Despite laudable efforts to engage in open innovation and more collaboration, an erosion of public trust in the pharmaceutical industry can be observed.[35] The overall secrecy and general reluctance against creating more transparency regarding data and R&D costs, scandals related to safety issues, physician's conflicts of interests, increasing prices for new drugs and limited access to certain treatments have contributed to this. This has resulted in calls for more accountability, transparency and respect for human rights such as the right to health.[36] Debates regarding proposals for regulatory reform, pharmaceutical policies and in particular the use of CLs, fit within this environment characterized by a decrease of trust and lack of transparency and accountability.

Key points

- **The legal framework constantly needs to be adapted to new socio-economic trends and events, including technological developments, such as digitalisation, big data and AI, aging populations, peronalized medicine, open innovation and open science and disease outbreaks.**
- **While the patent system is still of vital importance to the industry, other forms of protection such as regulatory exclusivities, trade secrets, data base protection and copyright law are relevant as well.**
- **The relevant legal and policy framework is rather complex, multilevel and fragmented. Although significant international and European harmonization has taken place, still considerable differences exist between EU countries also beyond patent law (e.g. pricing and reimbursement). Nonetheless, coordination and collaboration in such areas is increasing, such as for instance the BeNeLuxA initiative. It is particularly important in dealing with excessively priced medicines for the EU to adopt a more active role in stimulating such initiatives to address gaps and weakness in national procedures. Therefore, this type of coordination is an essential corollary to instruments such as CLs in ensuring access and affordability.**

35 See for instance: L. Pahus et al. (2014), 'Patient distrust in pharmaceutical companies: an explanation for women under-representation in respiratory clinical trials?', 21 *BMC Med Ethics*, 72; R.J. Blendon et al. (2014), 'Public trust in physicians--U.S. medicine in international perspective', 371 *N Engl J Med.*, 1570–1572; PWC, *Recapturing the vision: Restoring trust in the pharmaceutical industry by translating expectations into actions*, 2006, available at https://www.pwc.com/gx/en/pharma-life-sciences/pdf/recapturing-the-vision_exsummary_final.pdf and R. Rowe & M. Calnan, 'Trust relations in health care--the new agenda', *Eur J Pub Health*, 2006, 16, 4–6.

36 The PLoS Medicine Editors (2010), 'Drug Companies Should Be Held More Accountable for Their Human Rights Responsibilities', 7(9) *PLoS Med*, e1000344. https://doi.org/10.1371/journal.pmed.1000344.

3 KEY PATENT LAW PRINCIPLES AND THE PHARMACEUTICAL SECTOR

3.1 Introduction

This chapter provides a brief descriptive analysis of patent law principles as far as relevant to allow a good understanding of the CL context. It focuses on the nature of patent rights and the rationale for patent protection (Section 3.2), the patent application procedures in Europe (Section 3.3), the most important patentability criteria and patenting strategies in the sector (Section 3.4) and relevant exceptions and limitations (Section 3.5). This descriptive analysis is vital for a good understanding of the implications of the use of CLs in the sector and the available legal 'toolbox' which exists to deal with excessive pricing in the sector, and to examine to what extent modifications are required.

Although a discussion of the rationale and justification of the patent system may seem rather academic, it is relevant to note that there are other theories than the traditional 'utilitarian' approach that can be used to justify the existence of patent systems and to assess the balance achieved within the system. The grant of patent rights focused on stimulating R&D and reward for investments is not the only justification theory that underpins the patent system. Patent rights are exclusive rights and are limited in terms of material scope, temporal scope and geographical scope. In addition, patent systems contain various 'checks and balances' (exclusions to patentability, exceptions and exemptions to infringement) to strike a balance between the rights of the inventors/applicants/owners and the rights and interests of users/licensees of the patented technology, the general public and key stakeholders, such as patients, hospitals and health insurance systems.

3.2 The Nature of Patent Rights and the Patent Rationale

Patent rights are *exclusive* rights, limited in scope and term, that enable the patent owner to prevent third parties not having the owner's consent from making, using, offering for sale, selling, or importing the patented invention during a period of maximum 20 years (cf. Art. 28, 33 TRIPS).[37] Patent owners also have the right to assign, or transfer by succession, the patent and to conclude licensing contracts. Patents provide a *negative*, exclusive right and not a positive right to sell or produce. This is especially important in the pharmaceutical sector where many other regulatory requirements need to be fulfilled before a product can actually be put on the market. It is also relevant for biologics where one product often comprises several technologies for which the patents are not necessarily owned by the same entity and thus a license from third parties would be required.

Patent rights are *territorial* rights; in order to get patent protection patent applications must be filed in each country/region in which patent protection for the invention is sought in accordance with the law of that country or region (see Section 3.3). Therefore, in countries where the inventor or applicant did not file for patent protection or where the application was rejected,[38] (s)he will not be able to prevent third parties from exploiting the patented invention. As applying for and maintaining patent protection is quite expensive, applicants – in particular SMEs and universities, but also large companies – will consider carefully in which countries it is strategically most important to get patent protection (see also Section 3.3). Therefore, before entering into an analysis of the potential use of CLs, it is vital to always first examine the patent landscape to determine what relevant granted patents or pending patent applications exist in the relevant country that cover the product of interest.

Patent attorneys carefully describe the invention in the patent claims on behalf of the patent applicant and judges will interpret those claims to identify the material scope of the invention and to assess a potential infringement. Patent claims can relate to products and processes, but also to medical

37 Agreement on Trade-Related Aspects of Intellectual Property Rights, Annex 1C World Trade Agreement, 1994, available at https://www.wto.org/english/docs_e/legal_e/27-trips.pdf.

38 Or for European 'bundle' patents: in EPC Member States where the patent was not validated, see Section 2.3.2.

uses/indications, formulations, administration and dosage regimes (see Section 3.4).

The rationale for patent protection can be distinguished between more utilitarian approaches, natural rights theories (e.g. Locke's labour theory) and theories focused on distributive justice (based on Rawles' theory of justice).[39] Generally the utilitarian approach is emphasized in the literature and in practice. According to the utilitarian approach, patent rights are essential to reward the inventive efforts and investments of the patent owners. Patent rights stimulate R&D by allowing patent owners to prevent free-riding and to recoup their investments. However, patents also operate as a kind of 'social contract'; as part of the social contract the patent owner discloses the invention and in exchange the owner gets a temporary exclusive right; a '*quid pro quo*'. The disclosure allows others to build on the invention or to invent around it. Moreover, it should allow easy replication by others upon patent expiry.

Patents are not absolute rights, they are limited in terms of material scope, temporal scope and geographical scope. Moreover, patent rules at the international, European and national level contain exceptions and limitations that operate in different phases of the pre-grant and post-grant stages of the 'life' of a patent (e.g. public order and morality exemption, research exemption, 'bolar' exemption, CLs, see below in Sections 3.4 and 3.5). These exceptions and limitations are meant to carefully balance the interests of innovators, users and the public interest. This balance is also particularly important if one views the patent system from the perspective of the theory of distributive justice. Advocates of a justification theory based on distributive justice will generally emphasize the distributive implications of the patent system and the need to include fairness considerations to achieve a proper balance within the patent system.

Patents are commonly regarded as the pillars on which the pharmaceutical industry rests. While the role and importance of the patent system as such has been challenged in some fields of technology, it is generally assumed to be essential for incentivizing investments in pharmaceutical R&D in view of the high R&D costs (see Section 2.4), but also to facilitate technology transfer and open innovation.[40] Carefully delineated patent rights supported by a stable and effective patent governance system[41] are considered essential for innovation ecosystems to flourish and to facilitate collaboration, which is key in view of the growing complexity of R&D in the pharmaceutical sector (see Section 2.4).

In this sector, the importance of striking the right balance between rewarding innovation and ensuring that medicines are available and affordable is particularly critical. Over time many proposals for alternative or complementary incentives for the sector have been made. To achieve global pharmaceutical equity in a sustainable way, push and pull mechanisms have been proposed to allow for more equitable global health outcomes. [42]

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39 See e.g. S. Sterckx (2005), 'Can drug patents be morally justified?', Sci Eng Ethics, 11(1), 81-92.

40 Main reasons indicated are the expensive, risky and lengthy clinical trials required to show safety and efficacy, the absence of government involvement in drug development, and the fact that many pharmaceutical products are relatively easy to 'copy' once they have achieved market approval – however, the latter does not seem to apply to biologics. For a comparative analysis, see for instance D. Guellec and B. van Pottelsberghe de la Potterie, The Economics of the European Patent System: IP Policy for Innovation and Competition, Oxford University Press, 2007.

41 For instance patent offices that carry out high-quality examination of the patents within a reasonable period of time, (specialized) court system with predictable case-law regarding patent validity and infringements offering legal certainty.

42 Examples are research grants, subsidies, tax credits (push models), advanced purchase commitments, patent buy-outs and prize models (pull models). A concrete example of a prize model is Health Impact Fund, which is also regaining an interest in the context of the COVID-19 pandemic. J. Love (2014), *Alternatives to the patent system that are used to support R&D efforts, including both push and pull mechanisms, with a special focus on innovation-inducement prizes and open source development models*, Geneva: WIPO,

Apart from patent protection, the protection of trade secrets (see also Art. 39(2) TRIPs) is also very important in the sector (as in other sectors). Trade secrets can cover both early stage developments (that will be patented at a later date) and developments that for different reasons (i.e. difficulty to determine infringement, quickly evolving technology) will never be patented. Companies are generally cautious in distinguishing between inventions or parts of inventions that can effectively generate exclusivity when protected by a patent (i.e. a patent that can be policed) and what information cannot be protected or would lead to protection that is difficult to enforce, such that it is best kept secret and protected as trade secrets. In principle, when patent protection is applied for, the requirement of an enabling disclosure under the European Patent Convention (EPC)[43] should prevent applicants from not disclosing essential information about the invention. However, the European patent system does not require the disclosure of the "best mode" of the invention. Accordingly, typically primarily the inventions or components of an invention that are necessary to obtain patent protection will be included in an application, whereas other inventions or aspects – such as for instance details/aspects of a manufacturing process – will in many cases be kept secret. In this respect, protection of the invention through patent protection and trade secret protection are complementary. Therefore, in case a CL would be granted, it would need to be assessed whether the licensee will actually be able to market the competing product at the same quality or will encounter challenges in getting access to relevant data and know-how protected by trade secrets. From the perspective of the above-mentioned disclosure theory, the public interest will likely benefit more from incentives and rewards offered by the patent system, because the publication of patent applications and granted patents will enable other innovators to 'build' on those inventions preventing the duplication of R&D.

3.3 Patent Application Procedures

Despite the availability of so-called "European patents" under the EPC and harmonisation efforts at the EU level, such as the Biotechnology Directive[44] and the Unitary Patent Package[45] (not yet entered into force, see below), patent law is still not fully harmonized in Europe. As a result, the interaction between EU law, the EPC and national patent law is an area fraught with complex legal and governance issues.

We briefly describe the application procedures, the specificity of European patents, and the role of the Unitary Patent Package, as this information is relevant to have a basic understanding of the procedures to appreciate the implications for CLs for 'classic' European patents and European patents with unitary effect.

In Europe, applicants can apply for patent protection at the national level in accordance with national patent law or can apply at the European level through the harmonized grant procedure of the European Patent Organization (EPOrg).[46] The EPOrg is an intergovernmental organization

CDIP/14/INF/12, September 19, 2014), available at http://www.wipo.int/meetings/en/doc_details.jsp?doc_id=287218; F. Mueller-Langer (2013), 'Neglected infectious diseases: Are push and pull incentive mechanisms suitable for promoting drug development research?' *Journal of Health Economic Policy and Law,* 185–208.

43 Convention on the Grant of European Patents (European Patent Convention), 17th Edition, November 2020, available at https://www.epo.org/law-practice/legal-texts/epc.html.

44 Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, [1998] OJ L 213, p. 13–21.

45 The Unitary Patent Package consists of the following three legal instruments: Regulation (EU) No 1257/2012 of the European Parliament and of the Council of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection, [2012] OJ L 361, p. 1–8; Council Regulation (EU) No 1260/2012 of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection with regard to the applicable translation arrangements, [2012] OJ L 361, p. 89–92 and the Agreement on a Unified Patent Court, [2013] OJ C 175, p. 1–40.

46 At the international level, the World Intellectual Property Organization (WIPO) administers the Patent Cooperation Treaty (PCT, 1970). It provides a unified procedure for filing patent applications to protect inventions in each of its

independent from the EU and not bound by legislation or policy adopted by the EU institutions. If a patent application is filed at the executive of the EPOrg, the European Patent Office (EPO), an EPO examiner will verify whether the patentability criteria are fulfilled (i.e. novelty, inventive step, industrial applicability, enabling disclosure) (see Section 3.4). Examiners have a technical background and special expertise in patent law. Their most important task is to assess the invention in the light of the available 'prior art'. The examination phase is sometimes referred to as the 'pre-grant phase'. If all criteria are fulfilled, the European patent is granted. During the 'post-grant phase' third parties can oppose a patent based on arguments which challenge the patentability of the claims until nine months from the grant of the patent.

After the patent is granted, the European patent has to be validated in all the EPO Member States where the patent owner wishes to protect the invention and will become a "bundle of national patents". Despite some harmonization, this still involves translation and representation costs in some countries and maintenance fees become due in all countries where the patent is validated. Moreover, a patent owner who would like to enforce its patent rights against an infringer will need to do so at the national level in each country where infringement is believed to take place before a national court on the basis of national patent law. In practice, this often leads to parallel litigation in various EU Member States and potentially to different judgements regarding the validity of the patent and the infringement. It is clear that such parallel procedures result in legal uncertainty. We note here that third parties who want to apply for a CL, also need to follow the national procedures of the relevant Member States and comply with the requirements for CLs in the national patent acts concerned (see Sections 5.3 and 5.4).

In view of the high validation and maintenance costs, litigation costs and legal uncertainty of the current European Patent System, the EU has attempted for many decades to create a Community patent, later referred to as an EU patent, and a centralized patent jurisdiction. In 2012 these attempts resulted in the adoption of the Unitary Patent Package, which provides a legal basis for the creation of European patents with unitary effect (hereinafter 'unitary patents') and for the establishment of a Unified Patent Court (UPC), a centralized and specialized court system. The UPC will have jurisdiction over unitary patents and "classic" European patents. For now, the Unitary Patent Package did not yet enter into force as the ratification process for the UPC Agreement has repeatedly been delayed.[47] However, in view of the ratification by Austria on 18 January 2022 of the Protocol on the Provisional application of the UPC Agreement, the last stage of the preparations for the UPC has just started (e.g. appointment of judges, testing electronic case management system). The launch of the new system is currently expected for the second half of 2022 or early 2023.[48]

The advantage of the creation of unitary patents is that patent owners of European patents may request for unitary effect at the EPO. Unitary effect means that it shall provide uniform protection and shall have equal effect in all the participating[49] Member States without need for validation or

contracting states. By filing one international patent application under the PCT, applicants can simultaneously seek protection for an invention in a large number of countries. So the PCT does not lead to the grant of an international patent but simplifies filing for patent protection in various countries. In practice, the PCT procedure is very important, but less relevant for the scope of the current report and, hence, it will not be described in more detail in the text.

47 This delay was due to the implications of the Brexit and several constitutional complaints before the German constitutional court, the Bundesverfassungsgericht.

48 For more information, see: https://www.unified-patent-court.org/.

49 It is important to note that not all EU Member States are participating in the Unitary Patent Package. For instance Spain did not agree with the package, which is why the enhanced cooperation procedure was used to adopt the package. Therefore, patent owners will still need to validate their European patents in Spain. Moreover, also for non-EU Member States, which are members of the EPOrg validation of European patents will still be required. Finally, upon entry into force of the system unitary patents may not cover all participating Member States as some of them may not yet have ratified the UPC Agreement at that moment. Outstanding ratifications are likely to take

maintenance at the national level. Infringement and validity are decided on by the Unitary Patent Court, made up of judges from different countries. Unitary patents may only be limited, transferred or revoked, or lapse, in respect of all the participating Member States. This feature of the unitary patent is key for safeguarding the uniform nature and legal certainty. However, it also means that a patent which is invalidated, will be invalid in all the participating Member States. This has been a reason for companies, including those in the pharmaceutical sector, to express some doubts as to whether they will likely request unitary effect for their most valuable patents. Once the Unitary Patent Package will finally enter into force, many larger companies will, despite the expected cost benefit, probably take a 'wait and see' approach and may test the system by requesting unitary effect for non-core patents in their patent portfolio. Small and medium-sized enterprises will likely consider different issues and interests in comparison to the big players. It remains to be seen whether the Unitary Patent Package will indeed enter into force in 2022 and will be able to fulfil the promises regarding the reduction of costs and increase of legal certainty. We will return to the implications of the creation of the unitary patent for CLs (i.e. the grant of CLs for unitary patents will remain within the powers of the Members States) and the role of the UPC in Section 5.2.2.2.

3.4 Key Patentability Criteria and Patenting Practices in the Pharmaceutical Sector

Historically many countries originally excluded pharmaceutical products from patentability to ensure access to and affordability of medicines. This type of 'discrimination' of a particular technology field is no longer possible for WTO Member States[50], as it is prohibited by Article 27 of the TRIPS Agreement. National and European patents are thus granted for *any inventions, in all fields of technology*, provided that they are new, involve an inventive step and are susceptible of industrial application (Art. 52 EPC, see also Art. 27 TRIPS).[51]

An invention shall be considered to be **new** if it does not form part of the so-called "state of the art" (Art. 54 EPC). The state of the art comprises everything made available to the public by means of a written or oral disclosure, by use, or in any other way, before the date of filing of the patent application. In addition, under the EPC, the content of patent applications, the dates of filing of which are prior to the date of filing of the patent application concerned and which were published on or after that date, shall be considered as "state of the art" for the determination of novelty only.

An invention shall be considered as **involving an inventive step** if, having regard to the state of the art, it is not obvious to a so-called "person skilled in the art" (Art. 56 EPC). The perspective of the person skilled in the art is decisive for determining what is obvious in the context of patent law. The skilled person is presumed to be a skilled practitioner in the relevant field of technology who has average knowledge and ability and is aware of what was common general knowledge in the art at the relevant date. The skilled

place successively, so there may be different generations of unitary patents with different territorial coverage. The coverage of a given generation of unitary patents will stay the same for their entire lifetime. These characteristics of the unitary patent add considerable complexity to the already rather complex European Patent System

50 With an exception for least developed countries (LDCs), which benefit from a transition period based on Article 66(1) TRIPs. In November 2015, the TRIPs Council took a decision that further extends this transition period until 1 January 2033 or when a particular country ceases to be in the least developed category if that happens before 2033. For more information, see: https://www.wto.org/english/tratop_e/trips_e/ldc_e.htm.

51 An invention shall be considered to be new if it does not form part of the state of the art (Art. 54 EPC). An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art (Art. 56 EPC). An invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry (Art. 57 EPC).

person is also presumed to have had access to everything in the "state of the art" and to have the means and capacity for routine work and experimentation which are normal for the field of technology concerned.

According to Article 57 EPC, an invention shall be considered as **susceptible of industrial application** if it can be made or used in any kind of industry, including agriculture. For the day-to-day patent practice, the novelty and inventive step requirements are the most important. In the policy making context, the application of these criteria is less disputed, apart from the need to 'raise the bar' or to 'improve patent quality'.[52]

In line with the above-mentioned disclosure theory, patent applications also need to **disclose the invention in a manner sufficiently clear and complete** for it to be carried out by a person skilled in the art (Art. 83 EPC also referred to as "enablement" or "sufficiency" criterium). This means that a detailed description of at least one way of carrying out the invention must be given. The description must disclose any feature essential for carrying out the invention in sufficient detail to render it apparent to the skilled person how to put the invention into practice. It should, nevertheless, be noted that in practice the application by the EPO examiners of the criterium under inventive step (Art. 56 EPC) that the "problem must (plausibly) be solved over the entire scope of the claim" is also aimed at limiting the scope of protection of the patent to what the applicant is entitled to, based on the disclosure of the invention.

Despite the fact that pharmaceuticals are no longer excluded from patentability, a number of exclusions are still important for the pharmaceutical sector. For instance, patents are not granted to discoveries or scientific theories "as such" as they are not regarded as inventions (Art. 52(2) EPC) or for inventions which are considered contrary to public morality (Art. 53(a) EPC) [53]. The exclusion for discoveries was important to establish a 'minimal' criterion for biotechnological inventions, which are often based on components found in the animal or human body, such as DNA and proteins. The distinction between discoveries and patentable inventions was tackled in the EU Biotechnology Directive, see Art. 3 and 5 EU Biotechnology Directive. These provisions, also integrated in the EPC Implementing Rules (Rules 27, 29), have contributed to creating legal certainty regarding patentability of biotechnological inventions in Europe. As biotech has been gaining momentum and advances new technologies, new issues have arisen with regard to the assessment of inventions that are contrary to public morality which have been tackled by the CJEU, the EPO and national patent offices (such as inventions involving the use of human embryos). In other countries, such as the US and Australia, courts have seriously restricted the eligibility for patent protection of key inventions for the pharmaceutical sector, resulting in legal uncertainty and modifications of patenting practices for those jurisdictions adopted in the sector.[54]

European patents are not granted for methods of treatment of the human or animal body by surgery or therapy and diagnostic methods practised *on* the

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52 See for instance: G. Scellato et al. (2011), *Study on the quality of the patent system in Europe*, Tender MARKT/2009/11/D, March 2011.

53 This provision has received a lot of attention in the patent literature regarding the pharmaceutical sector. In practice, patent examiners generally try to circumvent this exclusion as it requires an ethical assessment rather than a technical, scientific analysis. The exclusion was also included in the EU Biotechnology Directive (Art. 6 EU Biotechnology Directive and Rule 28 EPC Implementing Rules) and became the object of two well-known judgements of the Court of Justice of the EU (CJEU) on stem cell patents, see Case 34/10, Oliver Brüstle v Greenpeace eV., ECLI:EU:C:2011:669 and Case C-364/13, International Stem Cell Corporation v Comptroller General of Patents, Designs and Trade Marks, ECLI:EU:C:2014:2451 and a decision of the Enlarged Board of Appeal of the EPO G02/06 (Use of embryos/WARF) of 25 November 2008, ECLI:EP:BA:2008:G000206.20081125.

54 See for instance: M. Aboy et al. (2020), 'One year after Vanda, are diagnostics patents transforming into methods of treatment to overcome Mayo-based rejections?', 38 *Nature Biotechnology*, 279–283; M. Aboy, et al. (2019), 'How does emerging patent case law in the US and Europe affect precision medicine?', 37 *Nature Biotechnology*, 1118–1125; M. Aboy et al. (2019), 'Mayo's impact on patent applications related to biotechnology, diagnostics and personalized medicine', 37(5) *Nature Biotechnology* 513-518; R.C. Dreyfuss et al. (2018), 'Patenting nature—a comparative perspective', 5(3) *Journal of Law and the Biosciences*, 550–589; R. Sachs

human or animal body (Art. 53(c) EPC).[55] In order to ensure that inventions in the field of medicine could be protected by patents, the EPC does provide for the patentability of "compounds or compositions for use in such methods". Therefore, the EPO can allow claims directed to compounds or compositions for use in therapy (where the compound/composition was not previously known as a medicament) or for use in a defined method of treatment provided they meet the other patentability requirements. Additionally the exclusion of Art. 53(c) EPC does not relate to methods practiced *ex vivo* or *in vitro*.[56]

The EPC thus allows for the protection of a compound or composition for a novel therapeutic use (so-called "medical use patents") (Art. 54(4) EPC). Moreover, the provision of a compound or composition for the treatment of a disease can be patentable even if the substance or composition is already known to be used for treating a different disease (further medical use) (Art. 54(5)), provided that use is novel and involves an inventive step. In addition, a different therapeutic use of a substance or composition may be based not only on the treatment of a different disease but also on the treatment of the same disease by a different therapeutic method differing for example in the dosage, administration regime, group of subjects or route of administration.[57]

The availability of further medical use claims can be employed by the pharmaceutical industry to extend the term of protection on a product by the filing of sequential applications on incremental improvements. For instance, it is quite common that a pharmaceutical company will file a first patent application when a class of compounds with a given activity is identified, and file further applications at later time points when the compound with the strongest activity is identified, the optimal formulation for administration, the optimal dosage, etc. As a result, the final product on the market may be covered by a 'cluster' of several patents, all with different expiry dates and not necessarily owned by the same patentee (i.e. resulting in fragmentation of the patent landscape).

Box 1 – Example Cluster of Patents

As an example EP0590058 filed in 1992 and owned by Genentech, is the basic patent relating to trastuzumab, a humanized monoclonal antibody used in the treatment of breast and gastric cancer. This patent claims several sequences of humanized heregulin antibodies and was later complemented with additional protection via a Supplementary Protection Certificate (SPC). In 1996, Genentech filed a patent application on a specific freeze-dried formulation for monoclonal antibodies including trastuzumab, which can be used for subcutaneous administration after reconstitution. In 1998, Genentech filed a patent on the use of trastuzumab for treatment of malignant breast cancer characterized by overexpression of ErbB2 (HER2) in combination with a taxoid. Genentech filed an application on a protein purification method via ion exchange chromatography and the anti-HER2 antibodies with a certain amount of acidic variants obtained after this ion exchange chromatography step in 1999. In 2000 Genentech filed yet a further patent application on the use of anti-ErbB2 antibody in the treatment of cancer where tumor cells overexpress the ErbB2 protein and another application on a specific dosing schedule for the treatment of breast cancer with anti-ErbB2 antibodies.

Some of the patents granted from these applications were later revoked in opposition or in court proceedings, but in principle they extended

(2015), 'Preserving the Future of Personalized Medicine', 49 *U.C. Davis L. Rev.*, 1881-1940; T. Minssen & R. Schwartz (2016), 'Separating sheep from goats: a European view on the patent eligibility of biomedical diagnostic methods', 3(2) *Journal of Law and the Biosciences*, 365–372.

55 See for instance: Enlarged Board of Appeal of the EPO G01/07 (Treatment by surgery/MEDI-PHYSICS) of 15 February 2010, ECLI:EP:BA:2010:G000107.20100215.

56 Enlarged Board of Appeal of the EPO G 0001/04 (Diagnostic methods) of 16 December 2005, ECLI:EP:BA:2005:G000104.20051216.

57 Enlarged Board of Appal EPO G 0002/08 (Dosage regime/ABBOTT RESPIRATORY) of 19 February 2010, ECLI:EP:BA:2010:G000208.20100219.

protection on certain trastuzumab-based products for several years beyond the original patent.[58]

Articles 54(4)and (5) EPC are also important for the field of pharmaceutical research known as 'repurposing'. It may be quicker and cheaper to develop a drug for a new use if it is already known to be tolerated by the human body. However, repurposing involves some risks as well, for instance for getting the new use successfully through phase 2 and 3 clinical trials and for ultimately getting the required marketing authorizations.[59] Empirical research shows a substantial upward trend in the past 10 years (since 2010) for patents with claims to new medical indications of existing compounds. Such patents are granted to large pharmaceutical companies as well as to universities and publicly funded research institutes.[60] Some experts have criticized Articles 54(4) and (5) EPC for harming repurposing activity rather than promoting it by allowing it to be patent protected.[61] Differently, Aboy et al. show that the provisions in the EPC appear to encourage early disclosure of new medical uses in the first patents claiming novel products (to avoid third parties acquiring rights to certain uses of the product) and, thus may also support the public interest by disseminating new scientific knowledge through the disclosure function of the patent system.[62] Therefore, patent experts have mixed views on the impact of the rules on access to medicines.

The EPC also contains certain requirements which relate more to the format of the claims (the relevant wording that defines the scope of protection) rather than to the patentability of the subject matter *per se*. For instance, the claims must be **clear and supported by the application as filed** (Art. 84 EPC). The claims must also be **unitary**, i.e. relate to only one "invention" or must be based on a "common inventive concept". Whether this is the case often depends on the prior art that is identified in a search carried out by the EPO. If lack of unity is determined, the applicant will only be able to pursue one invention but does have the opportunity to pursue the other inventions in a **divisional application**. Divisionals are separate and independent from the earlier 'parent' application, but they rely on the same originally filed description, and keep the same filing and priority dates as the parent application, meaning that they expire at the same time as the parent application, irrespective of when the divisional application was actually filed. Thus, the use of divisional applications will not extend the term of protection on a given product.

A European patent application may give rise to multiple divisional applications, which, themselves, may give rise to multiple divisional applications, but all based on subject matter that was disclosed in the originally filed application. The filing of such divisional applications is not limited to subject matter that is not unitary with the claims of the parent application, but the scope of the claims of a "voluntary" divisional application must be different from that of the parent[63] (or any other patent family member).

The availability of voluntary divisional applications and the extensive use thereof by the bigger players in the pharmaceutical industry (the filing and accrued annuity fees are often prohibitive for smaller players) has led to some controversy. The examination of divisional applications continues also

58 For more information, see e.g. E. Moorkens (2020), 'An overview of patents on therapeutic monoclonal antibodies in Europe: are they a hurdle to biosimilar market entry?' MAbs, 12(1),1743517.

59 A. Breckenridge & R. Jacob (2019), 'Overcoming the legal and regulatory barriers to drug repurposing', 18(1) *Nat. Rev. Drug Discov.*, 1–2. M. Aboy et al. (2021), 'Mapping the European patent landscape for medical uses of known products', 39 *Nature Biotechnology*, p. 1336.

60 M. Aboy et al. (2021), p. 1342.

61 See e.g. G. Dutfield (2017), 'Healthcare innovation and patent law's 'pharmaceutical privilege': is there a pharmaceutical privilege? And if so, should we remove it?', 12 *Health Econ. Policy Law*, 453–470 and S.F. Halabi (2018), The Drug Repurposing Ecosystem: Intellectual Property Incentives, Market Exclusivity, and the Future of "New" Medicines', 20 *Yale J. Law Tech.*, 1–73.

62 *Ibid*, p. 1342.

63 Enlarged Board of Appal EPO G 0004/19 (Double patenting) of 22 June 2021, ECLI:EP:BA:2021:G000419.20210622.

if the parent application is withdrawn or revoked, which, under certain circumstances, can lead to considerable legal uncertainty for third parties because, even where the claims were refused in the parent application every pending application covering the product is a potential legal threat until it itself is also refused or abandoned.

The Administrative Council of the EPOrg at some point limited the possibilities and time periods during which voluntary divisional patent applications could be filed, yet this limitation was cancelled several years later. In March 2021 the European Commission has opened a formal antitrust investigation against pharmaceutical company Teva. This investigation assesses whether Teva has illegally delayed the market entry and uptake of medicines that compete with its blockbuster multiple sclerosis drug Copaxone by – amongst others – strategically filing and withdrawing divisional patent applications, repeatedly delaying entry of its generic competitor.[64] This is the Commission's first formal investigation into potential abuses relating to the misuse of patent procedures in the pharmaceutical industry.

Multiple patent applications that relate to the same product are sometimes referred to as "patent clusters" or "patent thickets".”[65] The Pharmaceutical Sector Inquiry found that individual medicines may be protected by up to nearly 100 product-specific patent families, which can lead to up to 1,300 patents and/or pending patent applications across EU Member States.[66] A company that wishes to enter the market will need to analyse and possibly confront this complex landscape of patents and pending patent applications which will lead to uncertainty and will affect their ability to enter the market. The European Commission has expressed concerns about these strategies in its sector inquiry.

Protection of a patent for a specific product that is undergoing regulatory approval can be further extended by an SPC.[67] The availability of SPCs is aimed to offset the loss of patent protection for pharmaceutical products that occurs due to the long period[68] required for testing and clinical trials prior to obtaining regulatory marketing approval. SPCs can provide supplementary protection for a maximum of five years. A six-month additional extension is

64 Antitrust: Commission opens formal investigation into possible anticompetitive conduct of Teva in relation to a blockbuster multiple sclerosis medicine, Press Release, 4 March 2021, available at https://ec.europa.eu/commission/presscorner/detail/en/ip_21_1022.

65 Robin Feldman (2019), ‘Drugs, Money, and Secret Handshakes: The Unstoppable Growth of Prescription Drug Prices, Cambridge University Press.

66 European Commission, Pharmaceutical Sector Inquiry - Final Report, available at https://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf.

67 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, [2009] OJ L 152, p. 1–10. We note that the Unitary Patent Package did not explicitly provide for a 'unitary SPC'. To ensure that companies which choose unitary patent protection can benefit from the SPC extension, the European Commission is working on the articulation of unitary patent protection and SPC legislation. In 2019 the Regulation was amended (Regulation (EU) 2019/933 of the European Parliament and of the Council of 20 May 2019 amending Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products, [2019] OJ L 153, p. 1–10) to include a ‘manufacturing waiver’, which entitles EU-based companies to manufacture a generic or biosimilar version of an SPC-protected medicine during the term of the certificate, if done either for the purpose of exporting to a non-EU market, or for stockpiling during the final 6 months of an SPC ahead of entry into the EU market. The aim of this regulation is to remove a major competitive disadvantage of EU-based manufacturers compared to manufacturers based in non-EU countries (where SPC-type protection is not available or not enforceable) and ensure a better deal for patients. See also Section 2.3.4.

68 The actual length of the period will depend on the indication. Typically, it takes several years in order to determine long-term toxicity and efficacy, but it can also be shorter if the results can be assessed quickly (e.g. the COVID-19 vaccines).

available if the SPC relates to a medicinal product for children.[69] SPCs are nationally issued, administered and managed. A recent consultation has shown that, while SPCs appear to support research on new active ingredients and to have remained fit for purpose, the fact that SPCs are nationally administered undermines the effectiveness and efficiency of the SPC system.[70] This creates legal uncertainty, red tape and extra costs for businesses who would like to use the system, especially SMEs. National examination and grant procedures also entail extra costs and administrative burden for national administrations. In addition, the overall transparency of the SPC system is suboptimal, especially in a cross-border perspective. This may be detrimental for both innovators and generics manufacturers.[71] The results of the consultation by the European Commission and several studies show the advantages and potential of a 'unitary' SPC to overcome these issues.[72] The existence of SPCs supplementary to patents is also relevant in the context of CLs. As CLs are granted at the national level and SPCs as well, the lack of unitary character does not raise major challenges at present but may do so after the entry into force of the Unitary Patent Package, unless the EU would also establish a complementary system of unitary SPCs and unitary CLs.

3.5 Exceptions to Patent Rights Relevant for the Pharmaceutical Sector

Countries may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties (Art. 30 TRIPs). The three conditions in Article 30 ('limited', no unreasonable conflict with a normal exploitation of the patent' and 'no unreasonable prejudice to the legitimate interests of the patent owner') are cumulative and need to be assessed on a case-by-case basis. It provides rather flexible guidelines and leaves a large margin of discretion for legislatures and courts when they need to assess exceptions in national patent acts.[73] Many countries, including Belgium, include exceptions in their patent legislation that are particularly relevant for the pharmaceutical sector and that are deemed legitimate within the scope of Article 30 TRIPs. Examples are:

1. **Research or experimental use exemption**

   This exemption allows the use of the invention for research and experimentation and for teaching purposes – it may be particularly appropriate to create a favourable environment for innovation and experimentation. It allows third parties to 'invent around', to improve the patented invention, to test whether the invention works and has been

69 Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, [2006] OJ L 378, p. 1–19.

70 Commission Staff Working Document, Executive Summary of the Evaluation of the Regulation (EC) No 469/2009 of the European Parliament and of the Council concerning the supplementary protection certificate for medicinal products, and Regulation (EC) No 1610/96 of the European Parliament and of the Council concerning the creation of a supplementary protection certificate for plant protection products, SWD(2020) 293 final, p. 3-4.

71 *Ibid*.

72 Commission Staff Working Document, Evaluation of the Regulation (EC) No 469/2009 of the European Parliament and of the Council concerning the supplementary protection certificate for medicinal products, and Regulation (EC) No 1610/96 of the European Parliament and of the Council concerning the creation of a supplementary protection certificate for plant protection products, SWD(2020) 292 final.

73 C.M. Correa (2020), *Trade-Related Aspects of Intellectual Property Rights: A Commentary on the TRIPS Agreement*, Second Edition, Oxford University Press, p. 296.

sufficiently disclosed or to evaluate the patented invention in order to request a license.[74] In many European and other countries, the scope of the exemption is limited to research *on* an invention (i.e. research aimed at verifying the utility of the patented invention or at improving it) as opposed to *with* an invention (i.e. use of the patented invention in the research as a tool or instrument), but also covers research for commercial purposes.[75] Interestingly, with the adoption of the EU Biotechnology Directive Belgium extended the scope of its research exemption to research *with* an invention (see Art. XI.34(b) Belgian Code Economic Law (BCEL) going beyond the scope of the exemption in other EU countries. Nonetheless, the actual interpretation and implications of this broad research exemption are unclear, as it has never been challenged in court. Yet, for researchers the broad exemption functioned as a kind of "safety net" and some claim that the broad research exemption has attracted some businesses (including in the medical field) to Belgium that benefit from the broad exemption. Upon entry into force of the Unitary Patent Package, the exemption will be aligned with research exemptions in other EU countries and the text of the UPC Agreement (on research *on*), which is narrower than the current exemption.[76]

2. Bolar exemption[77] or 'early working' exemption

The Bolar exemption makes it possible to conduct the clinical trials required to obtain regulatory approval for the generic/biosimilar during the patent/SPC protection period of the original product. The rationale for this exemption is to allow for the swift introduction of generic medicines shortly after the expiry of the patent/SPC term of the original product. In the absence of a Bolar exemption, tests for regulatory approval of generic medicines could only be conducted after the patent/SPC expiry of the original product, which would delay their market entry by months or even years. The compliance of the 'Bolar' exemption with Article 30 TRIPS was tested in a case before the WTO Dispute Settlement Body *Canada-Patent Protection for Pharmaceutical* Products (WT/DS114/R). This type of exemption has been established in numerous jurisdictions, including the EU (Art. 10(6) Directive 2001/83/EC).[78,79]

Despite the EU harmonization, the scope of application of the exemption is not the same in all the EU Member States. Some Member States apply the exemption in line with the 'minimum standard' of the Directive (*narrow scope*), while most countries have expanded the exemption to studies and trials that are useful, but not 'necessary', to obtain a marketing authorisation, and/or for studies and trials related to a marketing authorisation (MA) application in non-EU/EEA countries (see for instance France, Germany, Italy, Ireland and the UK) (*broad*

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74 *Ibid*.

75 *Ibid*.

76 Wet van 19 december 2017 houdende wijziging van diverse bepalingen betreffende de uitvindingsoctrooien in verband met de implementering van het eenheidsoctrooi van het eengemaakt octrooigerecht, *BS* 28 December 2017, 115647. Interestingly, to our knowledge there has not been an evaluation of the impact of the broad research exception on stimulating R&D in Belgium before the adoption of this modification.

77 This exception is named after the famous case *Roche Products Inc v Bolar Pharmaceutical Co*, 733 F.2d 858, Fed Cir, cert denied 469 US 856, 1984, in which the US court denied Bolar the right to start the FDA marketing approval process before the expiry of the patent. As a follow-up, the US Drug Price Competition and Patent Term Restoration Act (1984) allowed the start of procedures for marketing approval of generic products before the expiry of the patent.

78 EU legislation also foresees an SPC manufacturing waiver which allows, under certain conditions, generics to be manufactured during the SPC term for export or storing purposes.

79 J. Straus (2014), 'The Bolar exemption and the supply of patented active pharmaceutical ingredients to generic drug producers: an attempt to interpret Article 10(6) of Directive 2004/27', 9(11) *Journal of Intellectual Property Law & Practice*, pp. 895–908.

scope).[80] In Belgium, the exemption is currently included in the legislation on pharmaceuticals (Art. 6bis §1 Wet op de geneesmiddelen [Law on Medicinal Products] 25 March 1964 (BS 17 April 1964, 4206), but will be explicitly included in Article XI.34 BCEL upon the entry into force of the Unitary Patent Package. The text of the Belgian exemption is equivalent to the text in the Directive and, hence, adopts a *narrow scope*. [81]

This fragmentation in terms of the scope of application of the Bolar exemptions in national European patent acts means that clinical trials may or may not fall into the scope of the exemption depending on the country where the trials are carried out. Moreover, a lack of clarity exists whether the Bolar exemption is applicable in the context of outsourcing, for instance in case the clinical trial depends on the supply of API from third parties. It is unclear whether in such cases the supply of API would fall within the scope of the exemption, and therefore if the third-party supplier – that does not conduct the studies and trials itself – is covered.[82] According to empirical research, most (61%) stakeholder groups (law firms, associations, originator companies and generic companies) favoured a broad Bolar exemption over a narrow one.[83]

If and when the UPC Agreement enters into force, the scope of the exemption will also depend on the nature of the relevant patent (i.e. 'classical' European bundle patent or unitary patent) and whether the UPC has jurisdiction. This is because the UPC Agreement contains a *narrow* Bolar exemption (Art. 27(d) UPC Agreement) and refers to the provisions in the Directive. As a consequence, unitary patents and European patents litigated before the UPC would be subject to a narrow exemption.[84] In a study regarding the functioning of SPCs, the MPI recommended to expand the scope of the Bolar exemption.[85]

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80 Max Planck Institute for Innovation and Competition (MPI) (2018), *Study on the Lega Aspects of Supplementary Protection Certificates in the EU*, European Commission, available at https://ec.europa.eu/docsroom/documents/29524 (hereinafter MPI Study SPCs), p. 340.

81 This will likely be problematic for so-called 'comparative trials', as comparative trials are not 'necessary' for regulatory approval. If a narrow scope is applied, one may expect significant delays for the approval of generics or biosimilars. For more information, see e.g.: KCE (2021), *Evidence Gaps for Drugs and Medical Devices at Market Entry in Europe and Potential Solutions*, KCE Report 374, available at: https://kce.fgov.be/sites/default/files/atoms/files/KCE_347_Evidence_gaps_Europe_Report_V2.pdf.

82 The Supreme Court of Poland considered this issue in 2013 and decided that in such cases third-party suppliers could not rely on the Bolar exception under Polish law. In parallel proceedings in Germany the Düsseldorf District Court took the same view, but the Düsseldorf Court of Appeal referred the question to the CJEU. However, as the case was subsequently settled, the CJEU did not issue a judgement in the end Case C-661/13 *Astellas Pharma Inc v. Polpharma SA Pharmaceutical Works* ECLI:EU:C:2014:588 (withdrawn) .

83 Allensbach survey (Question 65) conducted as part of the MPI study (2018).

84 Whenever the UPC will have jurisdiction, the narrow scope will be applicable, but the UPC will not have jurisdiction in all cases e.g. when a patent owner has used the so-called "opt out option" for European patents or during a transition period as long as not all participating Member States in the UPC Agreement have actually ratified the Agreement. Moreover, some EU countries are staying out of the Patent Package for various (political) reasons (e.g. Spain, Poland) and they will, hence, be able to continue to use the interpretation they prefer.

85 MPI Study SPCs (2018), p. VII, 361-371.

3. Pharmacy exemption

This exemption allows the preparation of medicines for individual cases according to a prescription by a pharmacy. The pharmacy exemption is also included in the Belgian Code of Economic Law (Art. XI.34(c) BCEL, after modification upon entry into force of the Unitary Patent Package Art. XI.34(e) BCEL)).[86]

This exemption is also relevant for debates regarding excessive pricing for medicines which allow for pharmaceutical preparations. In fact, in the Netherlands in 2019 a patent exemption for the preparation of medicines in pharmacies was introduced (Art. 53(3), second sentence Dutch Patent Act 1995) as recommended by the Council for Public Health and Society in its report *Development of new medicines; Better, faster, cheaper*.[87] In the Netherlands, several (hospital) pharmacies are relying on this exemption for the preparation of medicines, in particular for orphan drugs to ensure their availability and affordability (see for instance preparation of chenodeoxycholic acid (CDCA) for the treatment of cerebrotendinous xanthomatosis (CTX), a rare metabolic disease – Leadiant case before the ACM (see also Section 5.2.2.5).

However, pharmacy production of lower-priced medicines is only available for certain drugs (e.g. not too complex to prepare) in specific circumstances and depends on the availability of raw materials, which may be hampered if pharmaceutical companies or suppliers of APIs would impose restrictions or unreasonable conditions. However, competition law could play a role in dealing with such restrictions. In Section 5.5 we explain that in the Netherlands the proposal for a CL for excessive pricing was envisioned as part of a larger 'toolbox' for authorities to respond to excessive pricing cases (by strengthening the position of the authorities towards the companies). The pharmacy exemption was part of this toolbox.

Even though this report is not focused on the pharmacy exemption, we believe it is important to examine the proposal regarding CLs taking into consideration the availability of other instruments, such as the pharmacy exemption. Moreover, CLs could be a tool to protect a pharmacist in case companies would start an infringement action. While patent law does not apply to individual preparations by pharmacies, other rules will govern the definition, the quality, safety and traceability of such preparations. These rules are briefly described in Appendix 5.

Together with CLs these exemptions are, thus, an important element of the 'checks and balances' within patent systems. A proposal to strengthen the CL mechanism, should hence also take into consideration the scope, interpretation and use of these exemptions in Belgium. Our analysis shows that the scope of the exemptions is debated (narrow Bolar exemption in Belgium and in the UPC Agreement, see point 2) and will likely change (scope of the research exemption will be aligned with the UPC Agreement, see point 1). This will have an impact on incentives in the sector both on the side of patent owners and users.

3.6 Interim Conclusion

The current regulatory landscape for the pharmaceutical sector consists of many areas of the law that operate at different governance levels. These tools are used by pharma companies to develop a portfolio around their products consisting of exclusive patent rights, SPCs, trade secrets, data and market exclusivity (for the latter, see especially Chapter 4). Typically, not one patent will be relevant, but rather a cluster of patents related to products and processes, medical uses, formulations, administration and dosage regimes. All of these may have different dates of expiration and may potentially be owned by different entities. In addition, the production and development process and the access to the market may be protected

86 "§ 1. De uit een octrooi voortvloeiende rechten strekken zich niet uit tot : […] c) de bereiding voor direct gebruik ten behoeve van individuele gevallen op medisch voorschrift van geneesmiddelen in apotheken noch tot handelingen betreffende de aldus bereide geneesmiddelen;"

87 Council for Public Health and Society (2017), *Development of new medicines; Better, faster, cheaper*, available at: https://www.raadrvs.nl/documenten/publications/2017/11/09/development-of-new-medicines---better-faster-cheaper.

through trade secrets (see briefly in Section 3.2) and data and market exclusivity (see Chapter 4), patent system (and more particularly the provisions on first and second medical use claims) is developed to ensure exclusivity, there appears to be a growing concern that the government should have more leverage to control problematic use of these rights, not only in the context of a health crisis but also when this affects accessibility and affordability of medication. One option would be to limit the exclusive rights afforded by patents or to extend the exceptions to patent infringement. The EPO has in recent years become more critical of broad medical use claims by more heavily relying – as part of the inventive step requirement "that the problem has plausibly been solved over the entire scope of the claim". On the other hand, there have been suggestions in various countries to extend the exceptions to patent infringement such as the Bolar exemption and to increase the use of the pharmacy exemption.

Such changes at the level of patentability or limitations on infringement however may not be the most suitable tools to address specific concerns of excessively priced medicines. They imply a change in the system irrespective of the behaviour of the patent owner, the nature of the product, or the size of the patent portfolio. It seems that this would address in a rather general manner a very specific problem. Of course every limitation on the exclusivity conferred by patent protection allows for more competition which generally will result in lower pricing of medicines and in this way could theoretically help prevent situations of excessive pricing. However, it does not appear that extending the existing exemptions will be sufficient. For instance, the pharmacy exemption will only be useful for a limited number of drugs. Also, when considering a limitation of patent rights *per se* or the extent to which certain rights can be enforced against third parties, the impact on all players in the field should be carefully considered, as this may affect small players (with often more limited patent portfolio's) more than larger ones. Moreover, a limitation of patent rights may also result in decreasing investments on the long term.

To address "excessive pricing", CLs may appear to be more tailored to tackle a very specific problem. Indeed, CLs require an analysis on a case-by-case basis taking into consideration the specific circumstances (see Sections 5.2.1 and 5.3). However, as explained in Sections 5.2.2.5 and 5.4, one of the major challenges is defining the exact criteria that will address excessive pricing situations.

The different strategies offered by the patent system imply that in order to determine which patent rights should be the subject of a CL to allow generic production by a third party, a careful analysis of the IP landscape is required. Further difficulties may arise if a product is covered by patents from different parties. Moreover, as explained briefly in Section 3.2, it needs to be determined whether with a CL, the licensee will be able to market the competing product of the same quality and if so whether this can be done at a reduced price or whether the licensee will still encounter challenges in getting access to relevant data and know-how protected by trade secrets. In addition, access to clinical trial information and the relevant market may further be blocked by acquired data and market exclusivities (see Chapter 4). Finally, the originator company may also have exclusive access to the APIs which in practice prevents third parties from developing a comparable product. The discussion on tackling excessive pricing situations should thus not only consider the actual criteria and procedure for granting a CL in cases of excessive pricing, but also needs to consider the other forms of exclusivity which will likely have an impact on the ability to bring a generic drug on the market.

Key points

- **Patent rights are negative exclusive rights containing various 'checks and balances' (exclusions to patentability, exceptions and exemptions to infringement) to strike a balance between the interests of innovators, users and the public interest.**
- **National and European patents are granted for any inventions, in all fields of technology, provided that they are new, involve an inventive step and are susceptible of industrial application (Art. 52 EPC, see also Art. 27 TRIPS).**
- **In the field of pharmaceuticals, European patents are not granted for methods of treatment of the human or animal body**

by surgery or therapy and diagnostic methods practised on the human or animal body (Art. 53(c) EPC).

- **However, the provision of a compound or composition for the treatment, prevention or diagnosis of a disease can be patentable. In addition further medical uses are patentable not only for compounds or composition for the treatment of a different disease but also for the treatment of the same disease by a different therapeutic method differing e.g. in the dosage, administration regime, group of subjects or route of administration (provided of course that they meet the other criteria of patentability, including novelty and inventive step).**
- **Exceptions to the exclusive rights conferred by patents (different from CLs) relevant for the pharmaceutical sector include the research and experimental use exemption, the Bolar exemption and the pharmacy exemption. These are defined by national law. Implementation of these exceptions (Art. 30 TRIPs) should be 'limited', should not unreasonably conflict with a normal exploitation of the patent' and should not cause 'unreasonable prejudice to the legitimate interests of the patent owner'.**

4 LEGAL AND GOVERNANCE FRAMEWORK FOR REGULATORY EXCLUSIVITIES AND TRANSPARENCY OF CLINICAL TRIALS DATA

4.1 Introduction

The access to and use of medical data, including data generated in clinical trials sponsored by the industry, pharmacovigilance data, patients' data from patient files and electronic health records, mobile apps, and real world data has become increasingly important in the innovation discourse. In many fields access to data form the basis for innovative efforts through e.g. big data analysis and real world evidence. In the pharmaceutical industry, clinical trials data (CTD) has an additional role as the key unlocking the market for pharmaceutical products, due to the regulatory requirement to demonstrate the safety and efficacy of products. The design and adoption of regimes governing the access, use and protection of CTD thus add a substantial competitive impact on the competition dynamics in the sector. Since access to such data is crucial for the generic and biosimilar industry, it has also become an important factor in the access to medicines and pricing debate. The EU regime for regulatory data and market exclusivities and their interface with national CL regimes play an important role within that narrative.

Some commentators emphasize that regulatory exclusivities may have significant detrimental effects on static and dynamic competition in the pharmaceutical industry, as well as to the access to essential medicine since they may increase costs and delay the market approval for generics, biosimilar and follow-on innovation.[88] Other commentators highlight that the provision of regulatory exclusivities is a suitable, sufficiently flexible and

[88] See e.g. E.F.M. 't Hoen et al. (2017), 'Data exclusivity exceptions and compulsory licensing to promote generic medicines in the European Union: A proposal for greater coherence in European pharmaceutical legislation', *J Pharm Policy Pract*.

necessary incentive for rewarding the costly development of complex pharmaceutical products towards MA.[89]

The following sections will first address the international and European legal and governance framework related to regulatory exclusivities and some trends and common practices, strengths and weaknesses of the regime (Section 4.2). This is followed by a brief analysis of the status of European law regarding CTD transparency requirements (Section 4.3). The chapter closes with some preliminary conclusions. The implications of these frameworks for the effectives of CLs will then be further explored in Section 5.6.

4.2 The International and European Legal and Governance Framework related to Regulatory Exclusivities

4.2.1 The International Legal Framework for Regulatory Exclusivities: TRIPs Agreement

Article 39 of the TRIPs agreement requires that Member States shall provide effective protection from "unfair competition". This requirement includes the protection of undisclosed information. Article 39(3) TRIPs refers specifically to the protection of data that is submitted to authorities for the purpose of obtaining an MA for pharmaceutical products. However, on this point the TRIPs agreement provides a regime of *de minimis* IP protection and does not explicitly mention regulatory exclusivities. Thus, the current debate on regulatory exclusivities and their interface with CLs also relates to the question of what this TRIPs mandated minimum level of protection for undisclosed information and clinical trials data against unfair competition actually entails.

Article 39(3) TRIPs stipulates that the subject of protection is data the origination of which involves a considerable effort, while the purpose of protection is to safeguard against unfair commercial use. But what do these terms "considerable effort", "unfair" and "commercial" mean and how may they be construed in a TRIPs consistent manner? Recent debates concerning the effectiveness of CLS have fueled the on-going discussion as to whether the vague obligation enshrined in Article 39(3) should encourage Member States to replace regulatory exclusivity regimes with other alternative legal remedies that could address unfair competition, such as data compensation schemes.[90]

4.2.2 The European Legal Framework for Regulatory Exclusivities

The European IP and regulatory systems (be it on the national or EU level) and the TRIPs Agreement principally recognize that it is desirable to have additional legal instruments specifically protecting investments linked to the costly commercialization and MA procedure for pharmaceuticals. Although patents were created to stimulate investments in R&D, it turned out that they are not always useful for this task. As shown in Chapter 3, many steps in the innovation process, processes, methods and products are either not patentable by their very nature or are likely invalidated in patent challenges. Therefore, the European IP and regulatory systems provide for various forms of additional protection that are either implicitly accepted or explicitly provided for under the TRIPs agreement.[91] Some are of a supplementary character and linked to the patent protection, such as SPCs (see Section 3.4). Other forms of protection, however, are independent from patents, such as the protection of CTD through regulatory data exclusivity, regulatory market exclusivities or trade secrets (for a comparison, see Table 1).

89 See e.g. B.N. Roin (2009), 'Unpatentable Drugs and the Standards of Patentability', 87 *Texas Law Review*, 503-570.

90 E.F.M. 't Hoen (2022), 'Protection of Clinical Test Data and Public Health: A Proposal to End the Stronghold of Data Exclusivity', in: C.M. Correa & R.M. Hilty (eds.), *Access to Medicines and Vaccines*, Springer, Cham.

91 Cf. for example Art. 33 TRIPs (allowing implicitly for SPCs), and Art. 39 TRIPs (providing explicitly for trade secrets and data exclusivity, albeit with ambiguous formulations that resulted in different interpretations).

Table 1 – Comparative Overview: Forms of Protection

	Patent	SPC	Regulatory Data Protection	Market exclusivity	Trade Secrets
Protects	All products (compounds) analogues, uses, formulations, processes claimed in the patent	Any product (compound) protected by a basic patent and with a valid MA	Compound (and sometimes formulation) having a MA	Drug having MA	Information (including commercial confidential information/know how/Data)
Against	Manufacture, sale use or import (if a claim to a product)	Manufacture, sale, use or import (if a claim to a product)	Grant of MA based on originator's data. Generic companies could still apply for MA based on their own clinical trial data	Grant of MA "for the same therapeutic indication, in respect of a similar medicinal product" (as for orphan drugs); Generic companies cannot apply for an MA with their own CTD	Misappropriation
Exceptions	Depends on national law, for instance: - Private and non commercial use - Research exemption - Pharmacy exemption - Bolar exemption (see Section 3.5)	- Private and non commercial use - Experimental use relating to the subject matter of the invention. - SPC manufacturing waiver (since July 2019, see: Regulation (EC) No. 2019/933): export to markets outside the EEA where protection does not exist or has expired.	None or limited, such as any use that does not require MA	None	- Freedom of expression/ information - Revealing misconduct, wrongdoing or illegal activity - Legitimate disclosure by workers to their representatives - Protection of legitimate interests
Period	20 years from application	Lesser of 5 years from expiry of basic patent and 15 years from first EU grant of MA	Variable. In the EU so far 6 -10 years from first grant of MA. "8+2+1" for products with MA granted after November 2005	May vary. 6-10 years for orphan medicinal products	Potentially indefinite, limited by secrecy
Requirements	Patentability – novelty, inventive step, industrial applicability, sufficient disclosure etc.	Basic patent valid plus local MA	MA	MA	- Secret - Commercial value since secret - Reasonable steps have been taken steps to keep it secret

Moreover, the European system recognizes specific *sui generis* forms of protection e.g. for dosage regimes useful for *paediatric* applications and marketing exclusivities providing a very strong form of protection for orphan drugs during a limited period of time. These aim particularly at fostering the development of specific inventions and applications that are useful for the treatment of children (*paediatric extensions*) or very rare and neglected diseases (*orphan drugs*).

These forms of protection are characterized by different features and purposes and some of them are limited to a certain category of drugs. Table 1 summarizes the basic differences and similarities of the various forms of protection outlined above.

In Chapter 2 we explained that pharmaceutical companies seeking to obtain an MA must carry out pre-clinical and clinical trials to generate the data that is required by drug regulatory authorities in order to assess whether a medicinal product is safe and effective. These data are at least in principle the property of the sponsor of all those trials and investigations. Accordingly the sponsor (also called the reference product sponsor (RPS), i.e. the holder of the license for the reference product) could theoretically prohibit any third party from utilizing them.[92]

However, when considering the effects of this ownership of data in practice, and in particular for biologicals[93], it is in the public interest that the test data related to the original "reference product" could be used by generic

92 Generic companies that would try to cross-refer to corresponding data of the originator's products MA and would therefore need the consent of the originator MA holder, which would most likely not be voluntarily granted.

93 S. Sorscher (2009), 'A longer Monopoly for Biologics?: Considering the Implications of Data Exclusivity as a Tool for Innovation Policy', 23 *Harvard J. L. & Tech*., at 285-87.

applicants.[94] The ability of generic industry to speed up development and regulatory approval by making use of such data is of particular relevance when there are no alternative treatments and the price set by the originator is very high. Generic companies, health care providers and patient groups often share a substantial interest that generic drug applications are allowed to cross-refer to the original test data in e.g. abridged proceedings to save costs and time when providing the necessary evidence that the generic products are "bioequivalent", i.e. as safe and effective as the "reference product", or in the case of biologics "biosimilar". In addition, the possibility to cross-refer to previously generated test data avoids the need for repetitive testing on animals or human beings, which is undesirable from an economic and sometimes also ethical point of view.[95]

At the same time, however, it was recognized that innovators and the original clinical trials sponsors should not be placed at a disadvantage by enabling other parties to rely on and use the previously generated data without any financial compensation.[96] An innovation system that does not acknowledge and reward the risks and considerable investments involved in pre-clinical and clinical trials would put the incentive to invent and the incentive to develop products based on such inventions at risk. Such a risk is particularly significant, if the underlying technology is not patentable or if the underlying patents are either too narrow and susceptible of invalidity attacks or, if they have been granted in the early stages of research, close to expiration after the grant of the MA.

In order to address this dilemma, policy considerations resulted in the introduction of provisions stipulating that any third party, such as generic or biosimilar applicants, would have to wait for the expiration of a limited post MA-period of "data exclusivity" before being allowed to cross-refer to the data included in the registration dossiers related to reference products. This concept is called "regulatory data exclusivity".[97] These additional regulatory exclusivities are granted automatically without a requirement to show their necessity.[98] The EU data exclusivity rules can thus be described as the result of a policy mandated balancing act to protect ethical values and to further improve the conditions for manufacturers of generic medicinal products to enter the market as soon as the protection period has ended by allowing cross-reference to reference products, on the one hand, and to protect the interests of the innovative industry to a long period of data exclusivity and thus the incentive to innovate and invest in clinical trials, on the other hand.[99] This specific balancing act resulting in limitations of the protection granted is also the main reason why data exclusivity has to be regarded as a separate right that must be differentiated from the related protection of confidential data and trade secrets.[100]

Put differently, regulatory *data exclusivity* protects regulatory data generated by an innovator company and prohibits authorities, such as the EMA, to

94 P.W. Grubb & P.R. Thomson (2010), *Patents for Chemicals, Pharmaceuticals, and Biotechnology*, Oxford University Press, at 268.

95 D.M. Dudzinski (2005), Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies, 60(2) *Food & Drug L.J.*, 143-260, at 194.

96 M. Hiemstra (2010), 'Obtaining a Marketing Authorisation: Abridged procedure', in: S. Shorthose (ed.), *Guide to EU Pharmaceutical Regulatory Law*, Wolters Kluwer, Ch. 5. at 219.

97 Grubb & Thomsen (2010), at 268 (reminding that "regulatory data exclusivity" is sometimes also called "regulatory data protection"; not to be confused with protection of private or personal data).

98 For a critical analysis, see e.g. Medicines Law and Policies (2019), *European Union Review of Pharmaceutical Incentives: Suggestions for Change*, available at: https://medicineslawandpolicy.org/wp-content/uploads/2019/06/MLP-European-Union-Review-of-Pharma-Incentives-Suggestions-for-Change.pdf.

99 Hiemstra (2010), at 219.

100 T. Cook et al. (2009), *Pharmaceuticals, Biotechnology and the* Law, Springer, at 530 ff. (noting that although data exclusivity stems from laws regulating confidential information and is actually addressed in the same Art. 39(2) TRIPS mandating protection of confidential information, it is a separate right which must be discussed separately).

consider generic applications relying on – or cross-referring to – the innovator's data to get a MA.[101] Although the costs involved in generating such data may result in *de facto* market exclusivity for drugs with dossiers that are protected by data exclusivity, only the *de lege* protection conferred by regulatory *market exclusivity* can actually *guarantee* market exclusivity during its period of protection.[102] In particular, a generic competitor cannot circumvent *market exclusivity* by generating its own data and submitting a new application for e.g. EMA approval. This is one of the main differences in comparison to regulatory *data exclusivity*, which does not prevent generic companies to apply for MA in parallel by conducting their own clinical trials.

Thus *market exclusivity* for e.g. orphan drugs represents an absolute bar to approval of the same or a highly similar drug for the same indication. During the protection period it confers a powerful *de lege* exclusivity effectively and completely preventing generic competition. In particular *orphan drugs* are considered to necessitate such special protection, since their small potential market requires legal certainty and the creation of strong incentives for their development.

On the other hand, if the period of market exclusivity is not accompanied by any data exclusivity, generic or biosimilar companies would principally be allowed to cross-refer to innovative test data during the market exclusivity period and could thus more time- and cost-efficiently prepare and file their applications for MA. This would make it more likely that generic products could enter the market shortly after the expiration of the marketing exclusivity period. If there would be an equally long *data exclusivity* protection available in addition to market exclusivity, however, the *de facto* market exclusivity for complex pharmaceutical products might exceed the *legal* period of regulatory data- and/or market exclusivity. In such a situation generic or biosimilar companies would first be able to cross-refer to the originator data at the end of the exclusivity period. Unless they have generated their own test data, which might not be economically reasonable or would result in more expensive drugs, this could lead to a further delayed market entry for generics and biosimilars. For this reason, the EU system introduced a staggered 8+2+1 approach.

The EU rules governing regulatory exclusivity changed in 2005. Under the old regime the period of data exclusivity depended very much on the choice of national or centralized MA procedures and lasted either 6 or 10 years from the first MA in the EU.[103] The current rules under Directive 2001/83/EC[104] and Regulation (EC) No. 726/2004[105] adopted the so called "8+2+1" year rule.[106] According to the 8+2+1 approach data exclusivity applies during the first 8 years from the grant of the innovator company's MA. Following the expiration of the first 8 year-period a generic company may start to cross-refer to the pre-clinical and clinical trial data of the originator in their regulatory applications. However, since the data exclusivity period is followed by a market exclusivity period, generic competitors still cannot market their product for another 2 years. Following the period of 10 years (8+2) from the grant of the innovator company's marketing authorization, the generic company may then also market its products, provided that the innovator product does not qualify for a further one year of exclusivity. This additional 1 year of protection could be granted in a number of

101 *Ibid*, at 529 ff.

102 As will be demonstrated below this is an important limitation. As a matter of fact, data exclusivity can under certain circumstances become a more effective tool for delaying generic entry than limited market exclusivities.

103 Member States also have the option of only providing for six years of data exclusivity, but only for medicinal products with MA applications that were filed nationally before November 2005.

104 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, [2004] *OJ* L 311, 67-128.

105 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, [2004] *OJ* L 136, 1-33.

106 See also: M.S. Sinha et al. (2022), 'Addressing Exclusivity Issues During the COVID-19 Pandemic and Beyond', in: G. Cohen et al. (eds.), *COVID-19 and the Law: Disruption, Impact and Legacy,* Cambridge University Press, available at: https://ssrn.com/abstract=3889894.

circumstances, such as 1 year additional *market exclusivity* for a new therapeutic indication for the relevant medical product which brings significant benefit in comparison with existing therapies (Art. 10(1), para. 4 Directive 2001/83/EC, cf. Art. 14(11) Regulation (EC) No. 726/2004).[107] In such a situation the generic companies can only market their product after 11 years from the grant of the innovator company's MA. Moreover, an additional 1 year *data exclusivity* may be available for a new therapeutic indication of a *well-established* substance, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication (Art. 10(5) Dir. 2001/83/EC) (=+1 WEU). An additional 1 year of *data exclusivity* may also be available for a change in classification of a medicinal product (e.g., from prescription drug to over-the-counter) on the basis of significant pre-clinical tests or clinical trials (Art. 74(a) Dir. 2001/83/EC). These additional terms of exclusivity are not cumulative, which means that the total duration of protection cannot exceed eleven years.[108]

In addition to the 8+2+1 regime, the EU law also recognizes specific *sui generis* forms of protection aiming particularly at fostering the development of specific inventions and applications for the treatment of children (*paediatric extensions*) or rare diseases (*orphan drugs*). These may encompass dosage regimes useful for *paediatric* applications under Regulation (EC) No. 1901/2006[109] (e.g. 6 months SPC extensions) and strong marketing exclusivities (10-12 years) for *orphan drugs* and *paediatric orphan drugs* under Regulation (EC) No. 141/2000[110].

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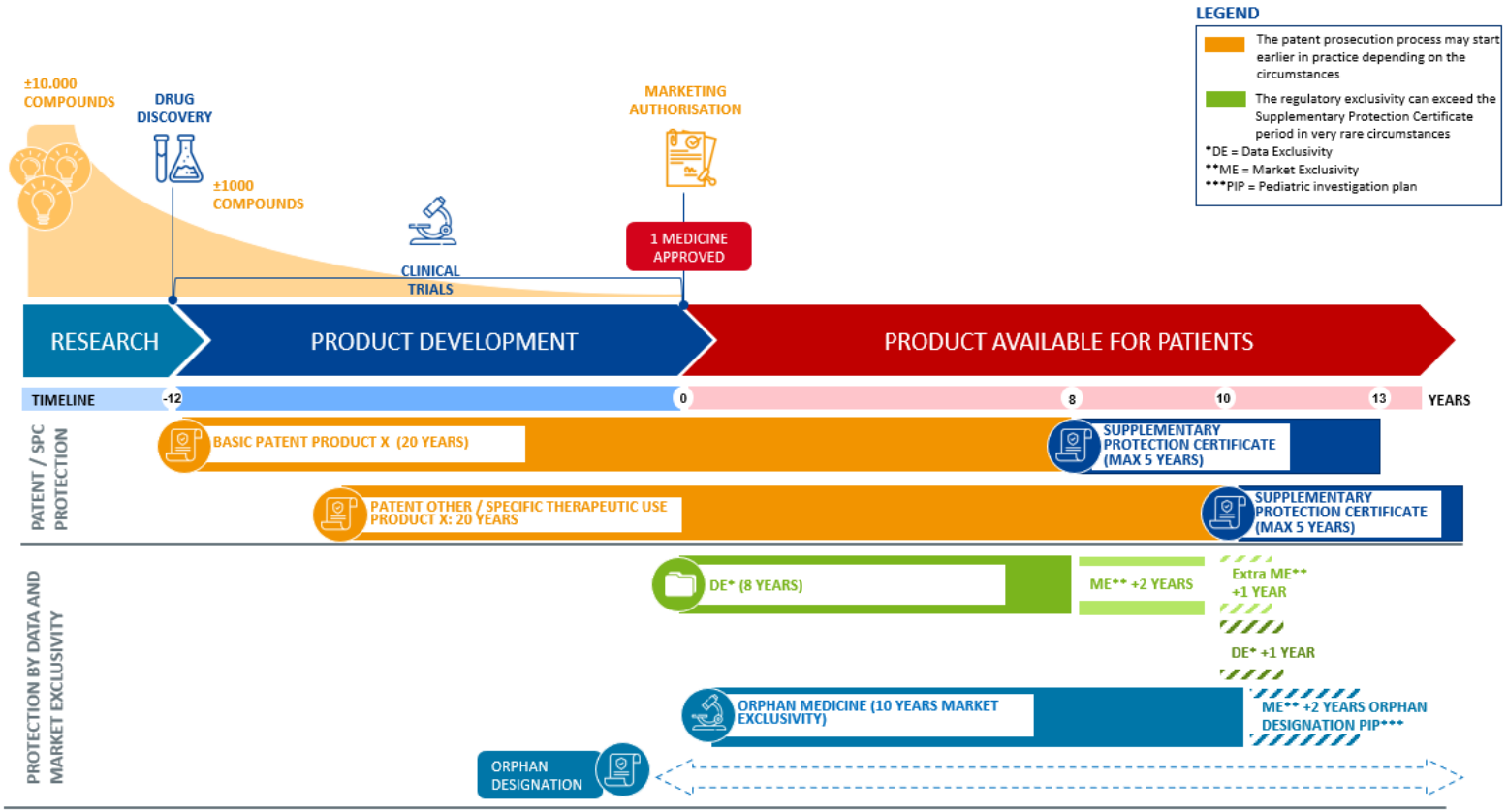
107 For initial MA applications submitted after 20 November 2005 and authorization of new indication within 8 years.

108 Cf. Sinha et al. (2022), at fn. 14.

109 Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, [2006] *OJ* L 378, 1-19.

110 Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, [2000] *OJ* L 18, 1-5.

Figure 1 – Patent Protection and Regulatory Exclusivities[111]



111 This figure is adapted from an existing figure of the European Federation of Pharmaceutical Industries and Associations: https://www.efpia.eu/about-medicines/development-of-medicines/intellectual-property/

This rather strong potential protection in combination with an increased focus of the pharmaceutical data and AI-driven technologies and clinical trial data transparency, explains why policy makers, innovative pharmaceutical companies and other stakeholders have shown a keen interest in regulatory exclusivities. Due to their broad application and the many uncertainties on how to interpret Article 39 TRIPs (see Section 4.2.1), which opens up for more flexibility in the use of regulatory exclusivities in comparison to the more static patent system, it can be expected that regulatory exclusivities will represent one of the main issues in future innovation policy debates.

4.2.3 *Trends, Business and Legal Practices regarding Regulatory Exclusivities*

As recently demonstrated in the debate concerning excessive pricing and the controversy about IP Waivers during the COVID-19 pandemic, regulatory exclusivities represent a key challenge in the present global debate on pharmaceutical IP policy-making. Moreover, it is becoming increasingly relevant as an additional IP layer of protection which affects research-based institutions and companies, as well as the generic and biosimilar industry.[112] For this reason any innovation system will have to carefully consider the interface of regulatory exclusivities with patent law and patent strategies, excessive pricing and an effective CL system.

The rising economic significance of data exclusivity is a combination of several inter-related factors, some of which had been mentioned above, such as (1) the increasingly lengthy and costly process of clinical trials; (2) the ongoing innovative productivity challenges the industry is currently facing; (3) the establishment and refinement of novel pathways for the approval of "biosimilars"; (4) increasing patent litigation; (5) a shift towards data and AI-driven precision medicine and the increasing importance of data and know-how for complex biologics; (6) technical and legal developments rendering an increasing number of compounds or processes more predictable and resulting in less broad product patents and more narrow claims to specific methods and new medical uses; and (7) the recent initiatives and legislative activities stimulating more transparency and sharing of CTD.[113] A closer look on the particular features characterizing data exclusivity and its role in the European pharmaceutical innovation system indicates why the above mentioned factors have resulted in a more prominent role of regulatory exclusivities.

Most importantly, since regulatory exclusivity can be viewed as a specific expression of trade secrets, the duration of the protection conferred by data exclusivity for a specific medicinal product is principally *independent of the term of any patent or SPC* related to that same product. Under the current EU regimes, for example, regulatory exclusivities may in some cases extend beyond the expiry of relevant patents, and, more rarely, SPCs.[114]

This feature of regulatory data or market exclusivity becomes particularly interesting for pharmaceutical companies in cases where patent or SPC protection is weak or where there is no protection available at all. This could concern situations where the technology is predictable or where the core of the invention is directed to natural phenomena or data. It could also concern cases where the patent protection would be very narrow or dependent, e.g. when relating to a new formulation, physical form, synthetic process or a

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112 See e.g. T. Minssen (2012), *Assessing the Inventiveness of Bio-Pharmaceuticals under European and US Patent Law*, Ph.D. dissertation, Lund University Faculty of Law, at 315 et seq.

113 *See* also M.P. Pugatch (2004), *Intellectual Property and Pharmaceutical Data Exclusivity in the Context of Innovation and Market Access*, ICTSD-UNCTAD Dialogue on Ensuring Policy Options for Affordable Access to Essential Medicines (Bellagio, October 2004), at 1, available at: Http://www.iprsonline.org/unctadictsd/bellagio/docs/Pugatch_Bellagio3.pdf.

114 *Ibid,* at. 1 (adding that although the extent to which the term of data exclusivity extends beyond the term of patent protection is not clear, as empirical evidence is often inconclusive, it can be assumed that, for the majority of drugs, the maximum period of data exclusivity (in the EU and the US 10 years and 5 years respectively from the day of registering the drug) is shorter than the 20-year patent term (and the possibility to extend the patent term by an additional period of up to 5 years)).

new medical use of a known compound and not to a new chemical compound or other active substance (see Section 3.4).

In summary, four main cases in which regulatory exclusivities can affect the overall period of *de facto* market exclusivity, and, hence, access and affordability of the relevant drug beyond what is available through patent protection, can thus be described as follows. The *first* is a situation in which the development period of a given drug is particularly long with patent protection only available at the early stages of product development (as is often the case in biotechnology). The *second* case involves drugs, where the patent protection is limited to very narrow claims or where key patents have been contested in court e.g. for lack of inventive step. This can be particularly relevant if the partial or complete protection is invalidated in patent litigation. The *third* related case concerns old or obvious compounds and processes with a high therapeutic potential that are already from the outset clearly unpatentable. Regulatory data and market exclusivity periods are a crucial issue for such technologies since the total absence of patents and SPCs, or "weak" patent protection (patents likely to be invalidated), has no effect on the drug producer's position with regard to data and market exclusivity. Moreover, while data exclusivity would theoretically still allow generic companies to generate their own CTD, it often has the *de facto* effect of precluding generic companies from obtaining MA due to the costs associated with generating new CTD (on costs, see also Section 2.4). Finally, the *fourth*, and most significant case in the context of this study, concerns situations where the patent has been subject to a CL and regulatory exclusivities stand in the way of rapid MAs and manufacturing of relevant drugs.

In other words: regulatory exclusivities can provide considerable incentives to develop new and innovative medicines. They often represent a type of protection that is difficult to circumvent and once this form of protection is granted it cannot be challenged by competitors or generic companies in the same way as patents. Pharmaceutical companies are thus provided with more legal certainty and can avoid costly patent enforcement. Consequently, regulatory exclusivities may under the current framework provide the most or even only effective protection that would economically justify the development of specific pharmaceutical products in certain cases.[115] It differs from patent protection *inter alia* in terms of its shorter duration, but also its later starting point, the lack of any obligation to comply with conventional requirements for patentability, such as novelty and inventive step, and the way in which (like SPCs) it protects only the particular pharmaceutical which has obtained an MA (see Table 1 and Box 1).[116]

Due to the aforementioned characteristics and legal effects that contrast post-MA exclusivity periods from other forms of exclusive rights and incentives, regulatory exclusivities are frequently debated and proposed in policy circles as an additional pull-tool for bridging market failures. Further reasons can be mentioned in support of the argument that well-designed regulatory exclusivity regimes could potentially represent a more fine-tuned and precise pull instrument for the regulation and protection of both conventional pharmaceuticals and biologics than patents or SPCs. While the patent regime can generally be regarded as a relatively static and inflexible form of protection due to the TRIPs Agreement's fixed protection period and the requirement of technological neutrality in patent law, the basic data exclusivity framework as mandated by the ambiguous language in Article 39(3) TRIPs seems to provide for much more leeway to dynamic and flexible adjustments or technology specific solutions. Among other things it appears to be possible to differentiate between various categories of pharmaceutical products to create special incentives for desirable technologies with market failures and broken innovation pipelines, such as antibiotics and antimicrobials.[117] In view of the anti-discriminatory rules in e.g. Article 27, 28

115 Cf. B.N. Roin (2009), 'Unpatentable Drugs and the Standards of Patentability', 87 *Texas Law Review*, 503-570.

116 T. Cook (2016), *Pharmaceuticals, Biotechnology and the Law*, Lexis Nexis, 3rd ed., at 534, 558 ff.

117 Cf. P.H.D. Batista et al. (2019), 'IP-Based Incentives Against Antimicrobial Crisis: A European Perspective', 50 *IIC*, 30–76.

and 33 TRIPs this appears to be very difficult in patent law.[118] Similar considerations apply for emerging areas of pharmaceutical innovation, such as big data and AI driven technologies in precision medicine, where patents do not play an equally central role, or are not available due to their limited applicability for the protection of data.[119]

Another issue that has to be considered in this context is that regulatory exclusivities are not bound by the minimum 20 years of protection requirement in Article 33 TRIPs. Regulatory exclusivities could potentially allow for both shorter and longer periods of protection depending on the relevant technology. For example, true break-through drugs involving radical innovation, high costs and extremely lengthy clinical trials could in principle be rewarded with a longer regulatory exclusivity period than more trivial innovations. In addition to these flexibilities, other benefits can be mentioned, such as (1) the narrower scope of protection for regulatory exclusivity, which is limited to the MA context[120] (see Table 1); (2) the possibility to introduce further exemptions and limitations to regulatory exclusivities due to the open language of Article 39(3) TRIPs allowing for various interpretations. This could include the possibility to introduce alternatives to regulatory exclusivities such as a data compensation schemes that would make the CTD available for a reasonable fee with the regulatory authorities acting as brokers; and (3) the later starting point of regulatory exclusivities after the MA, which implies that costs and time involved in the development process have already occurred, which increases the legal certainty of the reward[121], and renders it less likely that innovators will claim the reward without having invested in substantial innovative inputs.

Although a more elaborated discussion of these issues falls outside the scope of this study, they provide additional support for the aforementioned argument that regulatory exclusivities and other alternatives under Article 39(3) TRIPs will likely become an increasingly important factor for devising future innovation policies. This must also involve a careful consideration of their potential negative effects, such as their detrimental impact on the effectiveness of CL mechanisms. If the system is not carefully designed and applied, such exclusivities might contribute to abuses. A badly designed, overly protective data and/or market exclusivity system can thus become an important risk-factor for unjustifiable distortions of competition, overly long extensions of monopolies, excessive drug pricing and access to health care problems.[122] While data exclusivities can play an important role in taking into account and rewarding innovative inputs that are not covered by patents and SPCs some commentators therefore also stress that they might involve risks and potential costs "both by allowing innovators to charge monopoly prices

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118 See also J. Thomas (2006), *Proprietary Rights in Pharmaceutical Innovation: Issues at the Intersection of Patents and Marketing Exclusivities*, CRS REPORT FOR CONGRESS, at 19, available at: http://ipmall.info/hosted_resources/crs/RL33288_060320.pdf. It could, however, also be argued that Article 30 and 31 TRIPS provide some leeway in this respect. See e.g. T. Sommer (2007), 'The Scope of Gene Patent Protection and the TRIPS Agreement – An Exclusively Nondiscriminatory Approach?', 38 *IIC*, 30-51.

119 Cf. T. Minssen & J. Pierce (2018), 'Big Data and Intellectual Property Rights in the Health and Life Sciences', in: *Big Data, Health Law, and Bioethics*, Cambridge University Press, 311-323, at 322-323.

120 Cf. D. Bucknell (ed.) (2011), *Pharmaceutical, Biotechnology and Chemical Inventions*, Volume II, Oxford University Press, at 550 -551.

121 This does, however, not necessarily mean that investments involved in the drug development process should not affect the *determination* of the appropriate protection period to be granted. The difference is that once data exclusivity is granted the protective period is unlike patents not affected by the costs and duration of R&D that was required for the MA. If plausible and predictable principles are developed for the determination of the period of protection data exclusivity may thus provide for more legal certainty than patents.

122 Cf. Y. Heled (2012), 'Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?', 18 *Mich. Telecomm. & Tech. L. Rev.*, 419, 464-70 and E. Lietzan (2016), 'The Myths of Data Exclusivity', 20 *Lewis & Clark L. Rev.*, 91 (available at SSRN: https://ssrn.com/abstract=2653770.

to consumers and by failing to reward innovative output according to its value in improving human health".[123]

However, unlike the patent exemptions or limitations such as the CL regime for patents, there is currently no exception to the regulatory exclusivity regime available under EU pharmaceutical law. Even in cases of national health emergencies, urgent public need or excessive pricing, there are no explicit waivers or limitations codified in EU law to allow for market authorization of a generic drug or biosimilar before the aforementioned exclusivity periods expire (with the exception of the waiver in Regulation No. 816/2006 on the CL for export to countries with public health problems, see also Section 5.6).[124] This leads to a paradox since effective and result-oriented CLs of patents blocking the manufacture of generics or biosimilars is a matter of national law, whereas regulatory requirements for EU-wide MAs, including data exclusivity, are a matter of EU pharmaceutical legislation. In other words: these interacting legal frameworks are incoherent, i.e. "both with regards to the effective use of compulsory licensing by EU Member States and with respect to public interest exceptions to data exclusivity more broadly".[125]

4.3 Legal and Governance Framework related to CTD Transparency

4.3.1 Introduction

As outlined above and setting aside concern about long-term effects on the innovation system, there is a clear connection between the potential effectivity of CLs or broader health crisis-related IP waiver proposals, and the possibility to waive relevant regulatory data and market exclusivities. While the possibity to cross-refer to CTD from the originator, and to set-aside market exlusivities, could speed up the production of cheaper generic producs, the situation appears to be more complicated with regard to biologics, such as mRNA platform vaccines, antibodies etc. The production of such complex drugs does not only require access to the right equipment, technology platforms, supply chains of raw material and access to sensitive drug delivery infrastructures, it also requires access to tacit knowledge, such as typically trade secret protected know-how and skills.[126]

As discussed in Section 3.4, the disclosure and enablement requirements in patent law typically do not diclose such know-how, so the question is in how far the waiver of regulatory data exclusivity could help in the case of more complex drugs. Obviously this would in part depend on what sort of data

123 *Cf.* S. Sorscher (2009), 'A longer Monopoly for Biologics?: Considering the Implications of Data Exclusivity as a Tool for Innovation Policy', 23 *Harvard J. L. & Tech*., at 285-87, adding at 303: "As a market-driven incentive, data exclusivity will continue to encourage investment into me-too products and discourage investment into products targeted at less lucrative diseases. In addition, it will promote aggressive marketing of monopoly-priced products at the expense of more cost-effective alternatives. While the costs of data exclusivity cannot be eliminated without choosing an alternative innovation incentive mechanism, Congress should make efforts to minimize these inherent disadvantages by calculating an appropriate data exclusivity term and limiting opportunities for extension. (internal citations omitted)."

124 E.F.M. 't Hoen et al. (2017), 'Data exclusivity exceptions and compulsory licensing to promote generic medicines in the European Union: *A proposal for greater coherence in European pharmaceutical legislation*', 10 *Journal of pharmaceutical policy and practice*, 19.

125 *Ibid.*

126 N. Price et al. (2020), 'Knowledge transfer for large-scale vaccine manufacturing', 369 *Science,* 912-914 and D. Matthews & T. Minssen (2021), 'US U-Turn on COVID IP Waiver Alone Will Not Solve Vaccine Crisis – Intellectual Property Is an Important Part of the Debate, but Greater Transparency Is Required', May 2021, a shortened and edited version of this opinion was published by The Financial Times on June 17th, 2021, available at SSRN: https://ssrn.com/abstract=3881020.

could be provided by the EMA and other medical authorities if the regulatory exclusivities are waived. This insight leads to several follow-up questions, such as (1) to what extent would R&D and manufacture relevant CTD and related meta data need to be disclosed to the authority at all to comply with the MA procedure and (transparency) obligations under the Clinical Trials Regulation?; and (2) if the relevant data has been submitted and the autority is aware of it: would the full disclosure of the relevant data upon enforcing a waiver also require waivers of trade secrets protection or other legal obstacles since the full disclosure might be challenged by originators based on arguments relating to the protection of commercially valuable confidential information or privacy?; and finally (3) what sort of MA data would be relevant for reproducing/manufacturing of the drug and how – and on which basis, if any – could the disclosure of such data be required or incentivised?

In that regard, it is important to understand the requirements, conditions, procedures and level of CTD transparency. As a matter of fact, global and European efforts have long been underway from campaigners, researchers, and patient groups to increase data transparency for clinical trials.[127] Since 2010, the EMA has developed policies to release documents based on transparency regulations.[128] Its policy on the transparency of clinical data rests on the belief that it would reinforce public trust and confidence in the EMA's scientific and decision-making processes in addition to preventing duplication of clinical trials and promoting innovation in the area of new medicines.[129]

4.3.2 *European Legal Framework for Clinical Trial Data Transparency*[130]

The way clinical trials are conducted in the EU changed considerably with the full application of the Clinical Trials Regulation (Regulation (EU) No. 536/2014)[131] – which was adopted already in 2014 – on 31 January 2022.[132,] The Regulation includes wide-ranging CTD transparency requirements and harmonises the assessment and supervision processes for clinical trials throughout the EU, via a Clinical Trials Information System (CTIS). CTIS will contain the centralised EU portal and database for clinical trials foreseen by the Regulation. The EMA sets up and maintains CTIS, in collaboration with the Member States and the European Commission.

Meanwhile, earlier corresponding policy initiatives, such as the EMA policy 0070, have already considerably increased public access to CTD.[133] The new disclosure rules not only encompass the results of clinical studies, but also pertain to anonymized patient level data and other detailed information

127 Z. Kmietowicz (2014), 'Transparency campaigners welcome new rules for clinical trials in Europe', BMJ, 348, available at: http://dx.doi.org/10.1136/bmj.g2579.

128 EMA, *EMA policy on access to documents*, POLICY/0043, EMA/729522/2016, 4 October 2018, available at: https://www.ema.europa.eu/documents/other/policy/0043-european-medicines-agency-policy-access-documents_en.pdf.

129 EMA, Clinical data publication, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac05809f363e.

130 This section is partially derived from: T. Minssen et al. (2020), 'Clinical trial data transparency and GDPR compliance: Implications for data sharing and open innovation', 47(5) *Science and Public Policy*, 616-626.

131 Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, [2014] *OJ* L 158, 1-76.

132 https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation

133 EMA (2014), *EMA policy on publication of clinical data for medicinal products for human use*, POLICY/0070, EMA/240910/2013, 2 October 2014, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf, *cf.* EMA (2018) *EMA's Clinical data publication (Policy 0070) report Oct 2016- Oct 2017*, 16 July 2018, EMA/630246/2017, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2018/07/WC500252071.pdf.

from clinical trials dossiers. In simple terms, CTD transparency implies that decisions and data from clinical studies are widely shared with other researchers, clinicians, and the public.[134] These new initiatives are generally perceived as much welcomed developments for the enhancement of science, scientific collaboration, trust and open innovation.

The drug industry has, for multiple reasons, supported some of these developments and has even responded with its own transparency projects, including initiatives by GlaxoSmithKline, AstraZeneca, Sanofi, and Pfizer.[135] But, even though compliance with the new transparency requirements is increasing[136], the disclosure of clinical data by the EMA has also led to opposition from the pharmaceutical industry in granting access to specific information submitted in the dossier of an application for an MA for a medicinal product.[137] Opponents of disclosure often contend that much of the information contained in clinical trial reports is covered by a general presumption of confidentiality. This argument regarding confidentiality stems partly from concern over the transmission of valuable data to competitors and partly from the obligation to maintain confidentiality of different kinds of information. In this regard it is important to remember that in addition to commercially sensitive scientific information, know-how and business information, CTD encompasses personal data pertaining to different participants such as patients, personnel, sales, sub-contractors etc. Clinical trial sponsors are thus also controllers of data and have a responsibility to maintain the confidentiality obligations provided for by laws such as the GDPR. Therefore, companies will not only refer to the protection of information relevant from an IP perspective, but also refer to the GDPR when arguing for the non-disclosure of data sets. Although, there are definitely ways to avoid identifiability of patients based on CTD in large clinical trials, this could become particularly relevant in the context of trials regarding ultra-rare diseases with small patient groups.

4.3.3 *Trends, Business and Legal Practices regarding Clinical Trials Transparency*[138]

The EMA's transparency policy has led to several proceedings before the European Court of Justice of the European Union (CJEU).[139] So far, these proceedings have primarily concerned the issues of protecting commercially confidential information and trade secrets,[140] but it is easy to imagine how personal data protection rules, such as the GDPR, will also be invoked in future proceedings.

134 Institute of Medicine (2015), *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk*. Washington, DC, The National Academies Press.

135 N. Price & T. Minssen (2015), 'Will clinical trial data disclosure reduce incentives to develop new uses of drugs?', 33 *Nat Biotechnol.*, 685-686.

136 S.M. Lassman et al. (2017), 'Clinical trial transparency: a reassessment of industry compliance with clinical trial registration and reporting requirements in the United States', 7 *BMJ Open*, available at: http://doi: 10.1136/bmjopen-2016-015110.

137 In AbbVie v. EMA an interim relief against disclosure was sought, cf. General Court, 23 April 2013, *AbbVie v EMA*, case T-44/13R, ECLI:EU:T:2014:694. On appeal, this interim relief was set aside, cf. CJEU, 28 November 2013, *EMA v. AbbVie*, case C-389/13P, ECLI:EU:C:2013:794.

138 This section is partially derived from: T. Minssen et al. (2020), 'Clinical trial data transparency and GDPR compliance: Implications for data sharing and open innovation', 47(5) *Science and Public Policy*, 616-626.

139 See CJEU Case T-73/13, *InterMune UK a.o. v EMA* (29 June 2015); Case C-406/16 Pari Pharma v EMA, para. 36 (18 October 2016); Case T-718/15, PTC Therapeutics International v EMA (5 February 2018); Case T 729/15, MSD Animal Health Innovation and Intervet international v EMA (5 February 2018); Case T-33/17, Amicus Therapeutics UK and Amicus Therapeutics v EMA (25 September 2018); and most recently, Case C-175/18 P, PTC Therapeutics International Ltd v European Medicines Agency, European Confederation of Pharmaceutical Entrepreneurs (22 January 2020).

140 See e.g. CJEU, Case C-175/18 P, PTC Therapeutics International Ltd v European Medicines Agency, European Confederation of Pharmaceutical Entrepreneurs (22 January 2020); See also: CJEU, Case T-235/15**,** Pari Pharma v EMA, para 36 **(**5 February 2018).

The relevance of these decisions has increased since 2014, when the EMA amplified its data sharing policies through the afore-mentioned Policy 0070[141], which removed access restriction to allow researchers to download, save, and print clinical study reports for academic and non-commercial research purposes.[142] Moreover, the adoption of the Clinical Trials Regulation introduced significant changes in terms of the transparency scenario. This regulation provides that all relevant information regarding the clinical trial should be submitted through the publicly accessible EU portal. It is hoped that publicly available information contained in the EU database will contribute to protecting public health and fostering the innovation capacity of European medical research, while recognizing the legitimate economic interests of sponsors (Recital 67 Clinical Trials Regulation).

However, while offering access to the data and information contained in the public database, confidentiality is respected where it is essential to protect: (1) personal data; (2) commercially confidential information, in particular the MA status of the medicine, unless there is an overriding public interest; (3) confidential communication between Member States in the preparation of their assessment; and (4) supervision of clinical trials by Member States (Art. 81(4) Clinical Trials Regulation). This provision in the Clinical Trials Regulation also corresponds with the general EU regulation related to public access to documents.[143] Moreover, the EMA has also added two sets of requirements to the functional specifications for applying the above exceptions, including features to support making information public[144] and disclosure rules describing the practical implementation of the transparency rules[145].

A report published in July 2018, revealed that during the first year of implementation (October 2016-17) of the clinical data publication policy (Policy 0070), the EMA had published clinical reports for about 50 medicinal products under this framework.[146] The report provides a detailed picture of how the data is disclosed, including information on who had accessed the data and how it was processed following from the request for access.[147] These early disclosures did not yet include raw data or individual patient data from the clinical trials.

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141 POLICY/0070, EMA/240910/2013, supra n. 133.

142 R. Watson (2014) 'European Medicines Agency changes policy on clinical trial data publication', BMJ Clinical Research, 4073, available at: <http://dx.doi.org/10.1136/bmj.g4073> accessed 11 December 2018. See also S. Bonini et al. (2014), 'Transparency and the EMA-Sharing of Clinical Trial Data', 371 *NEJM*, 2452-2455.

143 Regulation (EC) 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents, [2001] *OJ* L 145, 43-48.

144 For more information, see: https://www.ema.europa.eu/en/documents/other/revision-section-6-functional-specifications-european-union-eu-portal-eu-database-be-audited-ema/42176/2014-setting-out-features-support-making-information-public_en.pdf.

145 For more information, see: https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf

146 EMA (2018), EMA's proactive publication of clinical data a success, News, 16 July 2018, available at: https://www.ema.europa.eu/en/news/emas-proactive-publication-clinical-data-success stating: "The report covers one year from the launch of EMA's clinical data website on 20 October 2016 and lists the 50 medicines for which clinical data were published, including orphan, paediatric, biosimilar and generic medicines, as well as the corresponding 54 regulatory dossiers. These data have attracted a total of 3,641 users, resulting in 22,164 document 'views' and 80,537 'downloads' for non-commercial research purposes. The report sheds light on the total number of documents published, the amount of commercially confidential information (CCI) redacted and the anonymisation techniques used. EMA accepted 24% of CCI redactions proposed by pharmaceutical companies, with the result that only 0.01% of 1.3 million pages published contained CCI redactions."

147 *Ibid.*

More recently the EMA has been advancing with the implementation of its Transparency Policy and aims to publish the individual patient data contained in these clinical trial reports.[148] Providing access to the individual patient data collected in clinical trials could enhance research that may advance medical science or improve patient care. In turn, this helps to ensure that the data provided by research participants are used to maximum effect in the creation of new knowledge and understanding.[149] Although there are clear benefits to providing greater access to individual patient data, a number of aspects require careful consideration. These include providing access in ways where the risks to patient privacy and confidentiality are minimized, and the commitments made to patients via informed consent processes are adhered to.[150] It also calls for greater attention to issues of GDPR mandated personal data protection[151], data transfer, the use of publicly available data, as well as commercially confidential information and trade secrets protection under the new Trade Secrets Directive.

In particular, the recent judgment of the CJEU in *PTC Therapeutics International Ltd v. EMA* [152] confirms the permissive approach that the EMA has been adopting in relation to transparency requests vis-à-vis attempts to redact information based on the protection of commercial confidential information and trade secrets. It is noteworthy, that the CJEU cases related to the previous regulatory framework did not consider the more permissive approach to the publication of clinical trial documents and data under the new Clinical Trial Regulation. However, the CJEU confirmation of the EMA approach to assessing whether information is commercially confidential in the context of clinical trial disclosures could be interpreted as a tacit approval of the EMA's understanding of the commercial confidential information exception in the context of implementing the disclosure rules under the Clinical Trial Regulation.[153] It will thus be assumed that it will be increasingly difficult for companies to successfully resist disclosure of most of the information in clinical study reports[154] or other documents lodged as part of a marketing authorization application.[155]

The CJEU also indicated that there are situations where a party may successfully argue for concealing or erasing certain commercial confidential information. Companies would need to submit detailed evidence of how disclosure of this information would endanger certain innovative strategies or the potential of IP protection in a country outside the EU. It can thus be assumed that the CJEU and the EMA will continue to take a case-by-case,

148 EMA, *Background to clinical data publication policy*, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000556.jsp&mid=WC0b01ac05809f363f.

149 S. Hughes et al. (2014) 'Preparing individual patient data from clinical trials for sharing: the GlaxoSmithKline approach', 13(3) *Pharmaceutical Statistics*, 179-183.

150 *Ibid.*

151 See also T. Minssen et al. (2020), 'Clinical trial data transparency and GDPR compliance: Implications for data sharing and open innovation', 47(5) *Science and Public Policy*, 616-626.

152 CJEU, 22 January 2020, Case C-175/18P, *PTC Therapeutics International Ltd v. European Medicines Agency, European Confederation of Pharmaceutical Entrepreneurs*, ECLI:EU:C:2020:23.

153 See also J. Bore (2020), 'CJEU rejects presumption of confidentiality of documents lodged as part of a marketing authorisation application', Allen & Overy Life Sciences Blog, 23 January 2020 available at: https://www.allenovery.com/en-gb/global/blogs/life-science/cjeu-rejects-presumption-of-confidentiality-of-documents-lodged-as-part-of-a-marketing-authorisation-application.

154 A clinical study report (CSR) is a report of an individual study of an investigational medicinal product conducted in trial subjects, in which the clinical and statistical description, presentations, and analyses are integrated. see: EMA, FAQs, Clinical Study Report Commission (March 2021, available at: https://www.ema.europa.eu/en/documents/other/faqs-clinical-study-reports-submission-ctis-training-programme-module-13_en.pdf (with further references).

155 Bore (2020).

line by line, word by word approach to the redaction of such documents before disclosure.[156]

In the context of CLs aimed at allowing faster entry of generics to impact pricing, increased clinical trials transparency therefore is a potentially enabling factor with however some clear limitations. Several considerations contribute to this assessment, such as: (1) the persisting possibility to redact commercially confidential information and trade secrets protection; (2) the actual information that is needed to manufacture a drug (or to determine whether a price is excessive) may not be included in the clinical trial report; and (3) the limited scope of disclosure required under the data transparency regime (similar to the limitations of the patent disclosure requirement). In combination, these issues might render it less useful to enable the manufacture of more complex drugs. After all, data that is necessary to demonstrate the safety and efficacy of new compounds does not necessarily require the disclosure of tacit knowledge on how to effectively manufacture more complex biologics. However, it could be argued that more information would need to be disclosed to demonstrate the safest manufacture of such products. Hence, it will not only continue to be crucial to clarify what the exemption from the commercial confidential information exemption, i.e. "overriding public interest", exactly means and if it can be effectively enforced. It will also be important to clarify what sort of disclosure could be justified under the *ratio legis* of the relevant provisions. Finally, one may also wonder to what extent information on the complexity and costs of the clinical trials could be required and, if so, through which regulatory framework.

4.4 Interim Conclusion

Regulatory exclusivities can provide a strong patent-independent incentive to undertake the costly development of both small and large molecule pharmaceuticals. As Article 39(3) TRIPs allows for considerable flexibility in designing the scope and period of protection for such exclusivities, they are also considered to be useful tools for shaping future innovation policies. However, overly strong protection of regulatory exclusivities could have significant detrimental effects on static and dynamic competition in the pharmaceutical industry. In particular, increased data and market exclusivities could have an impeding effect on the mechanisms in place to ensure access to and the affordability of medicines, such as the use of CL mechanisms to address excessive pricing. This raises numerous complex issues in relation to the interpretation of the TRIPs flexibilities and the interplay between EU legislation and national law.

Depending on what information would have to be disclosed according to the *ratio legis* underlying a particular regulatory framework, increased clinical trials transparency could in theory operate as an enabling factor with regard to both manufacturing innovative drugs and assessing "excessive" pricing practices provided that information on R&D costs would be available. Even though companies may encounter legal challenges in arguing for the redaction or erosion of some crucial data, in practice the actual available information will likely remain rather limited. Section 5.6 will elaborate on the interface of regulatory exclusivities with CL and will make some suggestions that can be used for inspiration for devising new policies.

156 *Ibid.*

Key points

- **According to the 8+2+1 approach data exclusivity applies during the first 8 years from the grant of the innovator company's MA. Following the expiration of the first 8 year-period a generic company may start to cross-refer to the pre-clinical and clinical trial data of the originator in their regulatory applications. The data exclusivity period is followed by a market exclusivity period of 2 years during which generic competitors still cannot market their product. Following the period of 10 years (8+2) from the grant of the innovator company's MA, the generic company may then also market its products, provided that the innovator product does not qualify for a further one year of exclusivity.**
- **Even in cases of national health emergencies, urgent public need or excessive pricing, there are no explicit waivers or limitations in EU law to allow for MA of a generic drug or biosimilar before the aforementioned exclusivity periods expire. This will likely hamper the opportunities for granting CLs in case of excessive pricing.**
- **The EMA policy 0070 and other policy initiatives considerably increased public access to CTD. The Clinical Trials Regulation includes further wide-ranging CTD transparency requirements and harmonises the assessment and supervision processes for clinical trials throughout the EU.**
- **Increased clinical trials transparency is a potentially enabling factor In the context of CLs aimed at allowing faster entry of generics to impact pricing. However, it has some limitations which might render it less useful to enable the manufacture of more complex drugs. After all, data that is necessary to demonstrate the safety and efficacy of new compounds does not necessarily require the disclosure of tacit knowledge on how to effectively manufacture more complex biologics.**

5 COMPULSORY LICENSING

5.1 Introduction

Whereas generally patent owners can decide whether they are willing to license their patented invention or not and if so under which conditions, under CL and government use mechanisms the government or a court can compel a patent holder to license the rights. However, it is important to note that the CL only operates as an exception to patents and does not affect relevant trade secrets and regulatory exclusivities directly.

This Section contains a description of the international and European legal and policy framework for CLs (Section 5.2), the Belgian legal framework (Section 5.3) and a comparison of CL mechanisms for public health in various other countries (Section 5.4), with a separate Section focusing on recent developments in this context in The Netherlands (Section 5.5). The separate section regarding the Netherlands has been added, because in the Netherlands a proposal regarding CLs for excessively priced medicines was made as well and a commission on CLs was set up to provide advice.

In the different Sections systematic attention will be paid to the concept, legal grounds for granting CLs, conditions and limitations for granting CLs, the procedure, and the actual use of CLs in practice. In Section 5.6 we identify the implications of the data and market exclusivities on the grant of CLs and in Section 5.7 we explore the strengths and weaknesses of CLs from a legal perspective.

5.2 The International and European Legal and Policy Framework for Compulsory Licensing

5.2.1 CLs & the International Legal Framework: Paris Convention and TRIPs Agreement

The Paris Convention for the Protection of Industrial Property[157] (hereinafter 'Paris Convention' (PC)) of 1883 already provided a legal basis for Member States to grant CLs. All EU Member States are members of the PC. Article 31 TRIPs also affirms the right of Member States to grant CLs, it implicitly confirms their autonomy to determine the legal grounds on which such licences can be granted and sets a detailed list of conditions and limitations that need to be respected by WTO Member States.

5.2.1.1 CLs & Paris Convention

Article 5A(2) PC states that each country has the right to take legislative measures providing for the grant of CLs to prevent the abuses which might result from the exercise of the exclusive rights conferred by the patent, for example, failure to work.[158] CLs are compared with the 'forfeiture of the patent', the complete "loss" or revocation of the patent which is the ultimate last resort mechanism and which cannot be provided for except in cases where the grant of CLs would not have been sufficient to prevent the said abuses. This can be regarded as a proportionality test. No proceedings for the forfeiture of a patent may be instituted before the expiration of two years from the grant of the first CLs. Moreover, a CL may not be applied for on the ground of failure to work or insufficient working before the expiration of a period of four years from the date of filing of the patent application or three years from the date of the grant of the patent, whichever period expires last (Art. 5A(4) PC).[159] This will allow patent owners a reasonable period of time to prepare the exploitation of the patent without allowing the owner to block indefinitely the exploitation by others while not exploiting it him/herself. The CL for failure to work will be refused if the patentee justifies inaction by legitimate reasons. Article 5A(4) PC also clarifies that CLs are non-exclusive and non-transferable, even in the form of the grant of a sub-license, except with that part of the enterprise or goodwill which exploits such license. Following the Paris Convention, most countries in the world already provided one form or another of CLs in their legislation at the time of the negotiations of the TRIPS Agreement.

5.2.1.2 CLs & TRIPs Agreement

Article 31 TRIPs does not refer to the widely accepted notions of 'non-voluntary' or 'compulsory' licenses but employs the notion 'Other Use Without Authorization of the Right Holder'. These "other uses" include both CLs and government use which typically involves a slightly different procedure but has similar effects to CLs. Article 31 contains a detailed set of conditions and limitations for the grant of such licenses. Conditions and limitations relate to a case-by-case assessment, reasonable efforts to negotiate a license, the non-exclusive and non-transferable nature of CLs, adequate remuneration, access to court, an export restriction and the limited duration of the CL (see also Section 5.2.1.3). In this way, industrialized countries tried to limit the discretion for the grant of CLs. The use of CLs and

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157 Paris Convention for the Protection of Industrial Property (1883) (as amended on September 28, 1979), available at: https://wipolex.wipo.int/en/treaties/textdetails/12633.

158 The interpretation of the concept of 'abuse' in the Paris Convention has been subject to debate. Moreover, some authors argue that CLs may only be granted in cases where 'abuse' can be established. Nothing in Article 31 TRIPs seems to confirm that interpretation (C.M. Correa (2020), Trade-Related Aspects of Intellectual Property Rights: A Commentary on the TRIPS Agreement, Second Edition, Oxford University Press, p. 306). For more information on the notion o 'failure to work, see Section 5.2.1.3.

159 Some authors argue that this requirement should be imposed to all CLs. However, the common interpretation nowadays seems to be that this requirement only applies to failure to work or insufficient working (C.M. Correa (2020), Trade-Related Aspects of Intellectual Property Rights: A Commentary on the TRIPS Agreement, Second Edition, Oxford University Press, p. 306).

governments use has been rather limited, except in the US.[160] National provisions regarding CLs have incorporated these conditions and limitations.

Article 31 TRIPs allows Members States to determine the grounds for granting CLs.[161] Although it refers to a number of specific grounds (i.e. national emergency, anti-competitive practices, public non-commercial use, dependent patents)[162] it does not limit the discretion of Member States to include other grounds in their national patent act.[163] Moreover, through the principle of 'incorporation by reference', the grounds included in the Paris Convention are also automatically incorporated in TRIPs (i.e. abuse, including failure to work or insufficient working). Therefore, Belgium in principle has the discretion to introduce a system allowing the use by the government without the authorization of the patent-holder to address excessive prices or to modify the existing rules for granting CLs for public health reasons with this aim, as long as the mechanism would comply with the requirements of the TRIPs Agreement.

The system of CLs has been encouraged as a mechanism to address the potential hindering effects of patents in public health care. This was formally recognized during the WTO Ministerial Conference in Doha, Qatar.[164] In the Doha Ministerial Declaration the importance of CLs for access to medicines and the fact that the TRIPs agreement created significant hurdles for effective use of CLs for the supply of medicines to countries without sufficient manufacturing capacity are recognized. Art. 31(f) TRIPs restricts CLs "predominantly for the supply of the domestic market" and thus does not allow production for export to countries that do not have their own production capacity. The Doha Declaration promised in paragraph 6 an "expeditious solution" to this problem. Two years later the WTO adopted the "2003 August 30th Decision"[165] (also known as the Paragraph 6 system) creating a permanent waiver to Article 31(f) TRIPs allowing WTO Members to issue CLs specifically for export to address needs notified by other countries under the system. Since 2003 several WTO members have implemented the waiver into their own legislation including the EU and, hence, Belgium as well.[166] On 6 December 2005 WTO Members adopted a

160 The US has used CLs as a remedy in a large number of antitrust case settlements and has relied heavily on provisions regarding government use. See: J. Reichman & C. Hasenzahl (2002), 'Non voluntary licensing of patented inventions: history, TRIPs, and Canadian and United States Practice', 6(7) *Bridges*, UNCTAD/ICTSDF. Scherer (2001), 'The patent system and innovation in pharmaceuticals', *Revue Internationale Droit Economique, Special Edition*, p. 119.

161 See also para. 5(b) of the Doha Declaration on TRIPs and Public Health (see also below for para. 6 of the Declaration): "Each member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted."

162 Interestingly, earlier drafts of the TRIPs Agreement do contain other grounds as well, including failure to work and public interest. See: D. Gervais (2008), *The TRIPs Agreement: Drafting History and Analysis*, 3rd ed., Sweet & Maxwell, pp. 384-390.

163 There is only one exception: in the case of semi-conductor technology, CLs will only be granted for public non-commercial use or to remedy a practice determined after judicial or administrative process to be anti-competitive (Art. 31(c) TRIPs).

164 WTO Doha Ministerial Declaration on the TRIPS Agreement and Public Health 2001; J. Reichman (2009), 'Compulsory Licensing of Patented Pharmaceutical Inventions: Evaluating the Options', 37 *Journal of Law, Medicine and Ethics*, 247-263, available at: https://scholarship.law.duke.edu/faculty_scholarship/2126.

165 Implementation of paragraph 6 of the Doha Declaration on the TRIPS Agreement and public health, Decision of the General Council of 30 August 2003, WT/L/540 and Corr.1, 1 September 2003, available at: https://www.wto.org/english/tratop_e/trips_e/implem_para6_e.htm#asterisk.

166 Regulation (EC) No. 816/2006 of the European Parliament and of the Council of 17 May 2006 on compulsory licensing of patents relating to the manufacture of pharmaceutical products for export to countries with public health problems, [2006] OJ L 157, 1-7.

Protocol amending the TRIPs Agreement to formally include the 2003 August 30th Decision in Article 31*bis* TRIPs. This amendment went into force in January 2017 and is the only amendment to the TRIPs Agreement since the 90s.

While the system is open to all WTO Members, many high-income countries including the EU and its Member States agreed to opt out of using the Article 31*bis* TRIPs mechanism as an importer for their own medicines supply (given that it was mainly aimed at supporting access to medicines in developing countries) (see Section 5.3.2 with respect to Belgium). Arguably it is questionable whether this waiver could actually be used for member states which would like to use the system to import medicines to bring down prices for very expensive medicines. It specifies that a member state can export generic pharmaceutical products produced under a CL "to meet the needs of importing countries". It is not clear if an excessive price would be considered to represent such a "need".[167]

Moreover, for now the waiver has had a relatively limited impact. In the almost 20 years that the waiver exists, it has been used only *once* by Rwanda to order a generic fixed-dose-combination HIV medicine from a Canadian generic pharmaceutical manufacturer Apotex.[168] This procedure took 4 years and required significant civil society involvement. Stakeholders involved have called the procedure 'unworkable'. In addition, the waiver system can only be used on a case-by-case and on a country-by-country basis making it highly inefficient. Therefore, for generic companies it is difficult to generate economies of scale and to safeguard predictability of market prospects when they are exploiting a CL in this context. However, Boulet & 't Hoen pointed to an interesting option for regional economic communities that have a majority of least developed country members, such as SADC.[169] They could use the waiver to bundle demand and place orders and supply of the entire region whether developing countries or LDCs.

Some authors have noted that a more straightforward way to facilitate the supply of medicines could have been to use Article 30 TRIPs which offers a broad basis for exceptions to rights conferred to patent owners rather than a waiver and amendment of Article 31 TRIPs. This proposal may be interesting for the development of alternative mechanisms for dealing with excessive pricing that would go beyond the grant of CLs. It is noted that the legislative proposal for amendment of the Belgian law that is currently under consideration is grounded on the CL mechanism provided by Article 31 TRIPs (see Section 5.3.3).

5.2.1.3 CLs and Article 31 TRIPs Conditions & Excessive Pricing

Article 31 TRIPs contains various conditions in order to be able to invoke a CL. The CJEU has consistently stated that generally the provisions in the TRIPs Agreement do not have direct effect.[170] This was also confirmed by the Belgian Court of Cassation.[171] These conditions are also reflected in Art. XI.37-46 BCEL (see Section 5.3.1). Before we discuss the relevant conditions below, we first elaborate more about the grounds available for the grant of CLs, as this is relevant for assessing the comparative analysis in Section 5.4 and the compatibility of the Belgian legislative proposal with the

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167 This implies that generic firms in Belgium might be reluctant to produce a generic under a CL if the product relates to a small market and they are not allowed to export (see economic study).

168 M. Rimmer (2008), 'Race Against Time: The Export of Essential Medicines to Rwanda', 1(2) *Public Health Ethics*, 89–103.

169 P. Boulet & E. 't Hoen (2014), Procurement of patented medicines by SADC Member States, available at: https://medicineslawandpolicy.org/wp-content/uploads/2017/02/SARPAM-TTATM-Report-Graphics-Apr15-ENGLISH.pdf

170 See for instance: Joined Cases C-300/98 and C-392/98 Parfums Christian Dior SA v TUK Consultancy BV and Assco Gerüste GmbH and Rob van Dijk v Wilhelm Layher GmbH & Co. KG and Layher BV, ECLI:EU:C:2000:688, para 44 and Case C-89/99 Schieving-Nijstad vof and Others v Robert Groeneveld, ECLI:EU:C:2001:438, para 53.

171 Court of Cassation, 11 May 2001, N.V. Art Research & Contact, Pas. 2001, I, 839, *R.W.* 2002-2003, 658.

TRIPs Agreement (Section 5.3.3). As indicated above the Paris Convention and the TRIPs Agreement provide various legal grounds for granting CLs, but also leave discretion to the Member States.

(1) Available grounds for CLs

National Emergency or Extreme Urgency

Para 5(c) of The Doha Declaration on TRIPs and Public Health clarifies that "[e]ach member has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency". So specific measures can be taken to deal with an emergency and maintained as long as the underlying situation persists without time constraints.[172] Moreover, no formalities seem to be described for deciding what constitutes a national emergency or other circumstances of extreme urgency. No formal declaration or justification of the existence of a national emergency or situation of extreme urgency is prescribed.[173] Therefore, it appears that if an IP owner would impose extremely high prices for a life-saving drug, it could be argued that this may also amount to a national emergency or situation of extreme urgency, though this has not been tested in court.

Public Non-commercial Use (Government Use)

This is an act of the government to authorize a government department or contractor to use a patented invention without the consent of the patent owner and with a non-commercial purpose to the benefit of the general public. This is in many cases the most simple manner to address an urgent public need, because it can be decided by the government *ex officio* without the need for a third party's request and without a need to first enter into negotiations with the patent owner.[174] It is important to note that 'non-commercial' does not mean that the government could not appoint a commercial contractor, which is actually a common practice in the United States.[175] Moreover, in accordance with Article 44(2) TRIPs national laws can limit the remedies available against government use to payments of remunerations in line with Article 31(h) TRIPs, which means that no injunctions would be available for patent owners; only damages and/or a CL fee. In several jurisdictions broad exemptions for government use exist.[176] This alternative ground for granting CLs could be important in the context of the Belgian legislative proposal. Whereas the proposal has been included in the Belgian provision on the CL for public health, the proposal also indicates that the initiative for granting the CL would be taken by the government rather than by a potential licensee (see Section 5.3.3). We will return to this issue in Section 5.3.3.

Anti-competitive Practices

In various countries, including in the EU, CLs have been granted as a remedy against anti-competitive practices; in particular the United States has a long tradition in this practice. CLs have been granted in some countries by judges and competition authorities in case of "refusals to

172 C.M. Correa (2020), *Trade-Related Aspects of Intellectual Property Rights: A Commentary on the TRIPS Agreement*, Second Edition, Oxford University Press, p. 307.

173 *Ibid*.

174 *Ibid*.

175 J. Reichman & C. Hasenzahl (2002), 'Non voluntary licensing of patented inventions: history, TRIPs, and Canadian and United States Practice', 6(7) *Bridges*, UNCTAD/ICTSDF.

176 See for instance: United States: 28 U.S.C. 1498 and Federal Acquisitions Regulations Pt 27; United Kingdom: ss. 55(1) and 56(2) Patent Act; India: s. 102 Patent Act; Korea: s. 107(1)(iii) Patent Act.

license" and on the basis of the so-called "essential facilities doctrine".[177] In the United States CLs for anti-competitive practices are generally granted against a "reasonable royalty" determined on the basis of the "willing buyer, willing seller" standard or even royalty-free and patent owners can be required to make the results of their research available or transfer know-how to other industry members.[178]

Dependency of Patents

This ground is contained in Article 31(l) TRIPs and stipulates a number of conditions for its grant, which will not be elaborated in more detail as they go beyond the scope of the report. This ground is quite important to promote access to patented inventions that "involve an important technical advance of considerable economic significance in relation to the invention claimed in the first patent". What is considered an "important technical advance of considerable economic significance" is relative and will depend on what is established by national law. However, it shows that CLs can be granted for reasons that relate to more economic considerations and where patents hinder the marketing of improvements of existing technology.

Public Interest/Public Health

Even though public interest and public health are not explicitly mentioned in Article 31 TRIPs, it is clear that "each provision of the TRIPS Agreement shall be read in the light of the object and purpose of the Agreement as expressed, in particular, in its objectives and principles (para. 5(a) Doha Declaration TRIPs & Public Health). This means that Members States can adopt "measures necessary to protect public health and nutrition, and to promote the public interest in sectors of vital importance to their socio-economic and technological development". In many countries, CL mechanisms exist for reasons of public interest or public health. The importance of CLs for reasons of public health has also been confirmed explicitly in the Doha Declaration on TRIPs & Public Health. Belgium created a new CL mechanism for public health in 2005 with the implementation of the EU Biotechnology Directive. The recent legislative proposal for CLs for excessive pricing (see Section 5.3.3) involves a modification of the CL for public health in Art. XI.38 BCEL.

Abuse

Article 8(2) TRIPs (in line with the Paris Convention) also states that measures "may be needed to prevent the abuse of intellectual property rights by right holders or the resort to practices which unreasonably restrain trade or adversely affect the international transfer of technology". This provision has also been linked to the interpretation of Article 31 TRIPs and is used as a justification to employ 'abuse' as a ground to grant CLs. However, no clear definition is available as to what the concept "abuse" means and whether this is limited to a concept following principles of competition law, or whether this concept should be interpreted more broadly. This ground could be relevant for CL addressing excessive pricing as well, as excessive prices could be considered an "abuse" both in terms of competition law or more broadly as an abuse of the patent system. Whereas the Belgian legislative proposal discussed in Section 5.3.3 concerns a modification of the CL for public health, it may actually be relevant to assess whether it would not be more appropriate to consider granting a CL in case of excessive prices under the ground of "abuse".

177 Various national competition authorities (the Netherlands and Italy) have imposed fines in excessive pricing cases for reasons of abuse of a dominant position (see Section 5.2.2.5)

178 M. Finnegan (1977), *The Folly of Compulsory Licensing*, Reston, Licensing Executive Society, p. 139,140 and S. Goldstein (1977), *A Study of Compulsory Licensing*, Reston, Licensing Executives Society, p. 124.

Failure to Work

This ground was already included in the Paris Convention (Art. 5A(4) of the PC). Historically, the obligation to work – together with disclosure requirements already discussed in section 2 – has been one of the foundations of the patent system. Failure to work is presented in the PC as an example of "abuse" and means that the patent owner is not or insufficiently exploiting the patented invention. The Paris Convention imposes a period of four years from the date of filing or three years from the date of the grant of the patent, whichever periods expires last. It also provides that a CL for failure to work or insufficient working must be refused if the patent owner justifies the inaction by legitimate reasons.

Obligations to work are generally imposed by countries to attract production to their territory; sometimes for protectionist reasons. Countries adopt divergent perspectives as to whether importation may satisfy working requirements and this has triggered quite some academic debate.[179] However, this obligation seems to have been tempered and tends to be interpreted in a more flexible manner by industrialized countries in order to enable transnational trade and globalization of markets. Demand can, thus, be met by either local production or imports.[180] Nonetheless, for developing countries the obligation to work and the opportunity to grant CLs in case of failure to work may act as an important counterbalance and incentive for technology transfer. Developed countries such as the United States have, however, countered CLs for failure to work in a rather aggressive manner in the past. This ground may, hence, not be the easiest tool to mobilize within the context of excessive prices.

No consensus seems to exit as to the 'correct' interpretation of "no or insufficient working" in more specific cases. One may for instance wonder whether failure to work covers situations where the company does not file a request for reimbursement in a particular country. 'Working' seems to cover the activities mentioned in Article 28 TRIPs and hence making or importing the products may in theory be sufficient to fulfil the 'working requirement'. Moreover, if the patent owner has legitimate reasons for not requesting the reimbursement, this ground would not be applicable anyway. If no legitimate reasons would exist, 'abuse' going beyond the failure to work could perhaps be invoked in particular circumstances, as "exorbitant prices" were generally believed as an example of an 'abuse'.[181]

Please note

With regard to the implementation of paragraph 6 of the Doha Declaration on TRIPs and Public Health the General Council Chairperson has stated that it is generally accepted that CLs should be used in good faith and are not regarded as an instrument to pursue industrial or commercial policy objectives.[182] However, to overcome the problem of limited manufacturing facilities in some countries there may be a desirability to use CLs to allow

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179 See e.g. T. Cottier et al. (2012), *Use It or Lose It? Assessing the Compatibility of the Working Requirements in the Paris Convention & TRIPS, NCCR Trade Regulation*, Working Paper No 2012/11, June 2012, available at: https://www.wti.org/media/filer_public/fa/65/fa65ab77-c496-45d1-9753-b226b61dba8d/2012_06_13_use_it_or_lose_it.pdf).

180 D. Gervais (2008), *The TRIPs Agreement: Drafting History and Analysis*, 3rd ed., Weet & Maxwell, pp. 391.

181 See e.g. Cottier et al. (2012), at p. 10 and references cited there.

182 Cf. for instance General Council Chairperson's statement, WT/GC/M/82, 13 November 2003, para. 29: […] Before adopting this Decision, I would like to place on the record this Statement which represents several key shared understandings of Members regarding the Decision to be taken and the way in which it will be interpreted and implemented. I would like to emphasize that this Statement is limited in its implications to paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health. "First, Members recognize that the system that will be established by the Decision should be used in good faith to protect public health and, without prejudice to paragraph 6 of the Decision, not be an instrument to pursue industrial or commercial policy objectives."

technology transfer, capacity building in the pharmaceutical sector and to facilitate local production.[183] Whereas this may be considered justifiable for developing countries, high-income countries may need to be more careful in presenting CLs as an industrial policy instrument. In particular because of potentially far-reaching economic consequences. As also mentioned in the economic study, the pharmaceutical industry has developed a carefully balanced system of differential pricing for LDCs, low- or middle income countries (LMICs) and high-income countries. The consequences of an increased use of CLs in high-income countries/a particular high-income country, even one with a relatively small market like Belgium, will likely be very different from the impact in least developed countries (LDCs) and LMICs and may generate more debate and potentially even trade retaliations. This seems important to consider when CLs for excessive pricing would be presented as part of industrial policy.

(2) Case-by-case Determination

CLs can only be granted on the basis of one of the available grounds taking into consideration the 'individual merits' of the proposed use. Therefore, CLs cannot relate to patents defined by subject-matter, or patent owner. However, it has been argued that it should be possible to grant CLs for patents that are needed to address a specific need, such patents relating to different aspects of a particular disease or for instance a cluster of patents (see Section 3.4) relating to a particular product or process. Correa indicates that it may not even be necessary to determine the relevant patents precisely,[184] but there does not seem to be a specific basis for suggesting that this is possible within the current legal framework. Moreover, in many cases, it may be rather difficult to identify all relevant patents required to be able to market the medicine of interest, as the patent landscape of pharmaceuticals is becoming increasingly complex and fragmented. It cannot be denied that in order to be effective, it would be important to have a CL regarding all patents that are infringed by the production, commercialization, import (if applicable) and use of the drug.

(3) Article 31(b) – Reasonable Efforts to Negotiate

Prior to the grant of a CL the proposed licensee should have "made efforts to obtain authorization from the right holder on reasonable commercial terms and conditions" provided that those efforts "have not been successful within a reasonable period of time". The licensee is thus obliged to enter into negotiations with the patent owner. The interpretation of what are "reasonable commercial terms and conditions" and "a reasonable period of time" is left to national law. It will likely depend on the nature of the technology and (global) licensing practices.[185] However the TRIPs Agreement foresees exceptions to this requirement for prior negotiations (1) in the case of a national emergency or other circumstances of extreme urgency; (2) in cases of public non-commercial use; or (3) in case of licenses granted to remedy anti-competitive practices. The patent owner must nevertheless be informed as soon as reasonably possible. The question is whether one of these exceptions for prior negotiations would apply in situations of excessive pricing. The Belgian proposal discussed in more detail in Section 5.3.3 is based on the CL for public health, and the Doha Declaration on TRIPs & Public Health seems to give quite some discretion to Member States in identifying a public health emergency or circumstances of extreme urgency. No case-law exists, however, as to when this requirement would be fulfilled and to what extent the evaluation of the

183 *Ibid*, para. 7.

184 C.M. Correa (2020), Trade-Related Aspects of Intellectual Property Rights: A Commentary on the TRIPS Agreement, Second Edition, Oxford University Press, p. 310.

185 D. Gervais (2008), *The TRIPs Agreement: Drafting History and Analysis*, 3rd ed., Sweet & Maxwell, p. 391. For instance, regarding the "reasonable period of time", the Indian Patents Act requires it not ordinarily exceed a period of six months under Section 84. However, in BDR v. Bristol Myers Squibb, Patent Comptroller (2013), the patentee applied delaying tactics to avoid granting the voluntary licence to the potential licensee (for more information, see L. Van Anh (2021), Compulsory patent licensing and access to medicines: A Silver bullet approach to public health, Palgrave, p. 101-103.

emergence of a situation of extreme urgency needs to be objectified. Moreover, the CL could also be based on public non-commercial use (government use) or anti-competitive practices rather than public health and thus the exception for prior negotiations would be applicable. This also appears to be in line with the reasoning in the Belgian proposal.

(4) Article 31(c) – Limited Scope and Duration

The scope and duration of the CL needs to be limited to the purpose for which it was authorized (e.g. end of a national emergency, price decrease). This may imply that it is actually important to list carefully the patents/patent applications and maybe even the claims in the relevant patents. Yet, potential licensees can apply for a license with broad coverage and extending until its expiry, which according to Correa has been a generally accepted practice under the Paris Convention.[186] This may actually be vital to incentivize the licensee to make the necessary investments in getting a MA and to set-up manufacturing facilities. However, it is rather unlikely that systems where CLs would automatically run until the end of the patent term would be compatible with this requirement.[187]

(5) Article 31(d) and (e) – Non-exclusive, Non-assignable Licences

All CLs must be non-exclusive and non-assignable, in the latter case except with the part of the enterprise or goodwill in respect of which the license was granted. The provision does not expressly extend to sub-licensing (cf. Art. 5A(4) *in fine* PC).

(6) Article 31(f) – Predominant Supply to the Domestic Market

This obligation does not apply to licenses granted to remedy anti-competitive practices. It implies that CLs can be given exclusively or predominantly for export. We note, however, that the issuing of CLs predominantly for the supply of the domestic market does not mean 'only' for the supply of the domestic market. A limited amount of export in addition to a predominant supply of the domestic market is possible. The vague wording of Article 31 TRIPs does not provide any specific guidance on this and, thus, national law may adopt different standards in this respect based on sales value or volume.

As described in Section 5.2.1.2 this requirement is waived by art. 31*bis* TRIPs in case Member States are approached by countries having insufficient manufacturing capacity and under very specific circumstances and strict requirements. The waiver has only been used once since the mechanism was put in place in 2003 and the procedure is considered rather burdensome. For more information on the implications of the opt-out for Belgium, see Section 5.3.2.

(7) Article 31(g) – Termination

CLs will be terminated if and when the circumstances which led to it cease to exist and are unlikely to recur. The competent authorities will have the authority to review, upon motivated request, the continued existence of these circumstances. However, a termination will also be subject to adequate protection of the legitimate interests of the licensee. The latter is vital, as this would otherwise dilute the potential of any CL mechanism, as it would disincentivize potential licensees to start making the necessary preparations for the use of the invention.

(8) Article 31(h) – Adequate Remuneration

The patent owner will receive adequate remuneration in accordance with "the circumstances of each case, taking into account the economic value of the authorization". An exception is provided for cases where the use is permitted to remedy a practice determined to be anti-competitive (Art. 31(k) TRIPs). The interpretation of what is "adequate" and the procedure to determine what is deemed adequate are left to national law. The term

186 C.M. Correa (2020), Trade-Related Aspects of Intellectual Property Rights: A Commentary on the TRIPS Agreement, Second Edition, Oxford University Press, p. 310.

187 D. Gervais (2008), The TRIPs Agreement: Drafting History and Analysis, 3rd ed., Sweet & Maxwell, p. 392.

"adequate" was a US proposal preferred over "fair and equitable" supported by other countries. This section was one of the most controversial and ambiguous sections in the TRIPs Agreement.[188]

In terms of "the circumstances of the case", it seems self-evident to take into consideration the objective of the CL, the circumstances of the licensee, the (economic) circumstances in the country, the needs of patients and the type of product. The "economic value" will likely depend on the degree of inventiveness (e.g. pioneer or add-on patent), the scope of the patent, the size of the market, the maturity of the technology, its relevance, the degree of competition by substitute technologies, the revenues that may be generated by the licensee, etc.[189] If the technology is not (yet) available in the particular Member States practices in other countries or worldwide markets will need to be assessed to determine the value.[190]

It would be desirable for national authorities to have some clear guidance as to how "adequate remuneration" needs to be determined. A wide spectrum of what is considered "adequate" is available: ranging from a level of remuneration comparable to what the patent owner would have been able to obtain through voluntary transactions to a level that also takes into account public funding that the patent owner received to develop the invention (including funding for academic or public research institutes), the degree to which R&D costs have been amortized and R&D commitments of the patent owner.[191] The WHO has also issued 'Remuneration guidelines for non-voluntary use of a patent on medical technologies'[192] which gives an overview of methods of calculation that may be reasonably applied to determine an "adequate" level of remuneration, see e.g.:

(i) Japan Patent Office Guidelines (1998) – applied to government-owned patents – allowing for normal royalties of 2% to 4% of the price of the generic product, which can be increased by as much as 2% for a range of 0-6%

(ii) UNDP Human Development Report (2001) – proposes a base royalty rate of 4% of the price of the generic product, which can be increased or decreased by 2% depending on the innovative nature of the medicine or the role of government funding;

(iii) Canada Government Royalty Guidelines (2005) – guidelines adopted for CLs for export to countries that lack manufacturing facilities in accordance with the current Article 31bis TRIPs. These guidelines establish a gliding scale of 0.02-4% of the price of the generic product based upon the country rank in the UN Human Development Indicator;

(iv) Tiered Royalty Method (differs from (i)-(iii) because the royalty rate is not based on the price of the generic product, but on the price of the patented product in the high-income country. The base royalty is 4% of the high-income country price, which is adjusted for relative income per capita or for countries facing a particularly high burden of disease relative income per person with the disease.

188 Ibid, pp. 393-394 and M. McGrath (1996), 'The Patent Provisions in TRIPs/Protecting Reasonable Renumeration for Services Rendered – or the Latest Development in Western Colonialism?, 7 EIPR, pp. 401 et seq.

189 See e.g. C.M. Correa (2020), Trade-Related Aspects of Intellectual Property Rights: A Commentary on the TRIPS Agreement, Second Edition, Oxford University Press, p. 312 and D. Gervais (2008), The TRIPs Agreement: Drafting History and Analysis, 3rd ed., Sweet & Maxwell, p. 393.

190 D. Gervais (2008), The TRIPs Agreement: Drafting History and Analysis, 3rd ed., Sweet & Maxwell, p. 394.

191 C.M. Correa (2020), Trade-Related Aspects of Intellectual Property Rights: A Commentary on the TRIPS Agreement, Second Edition, Oxford University Press, p. 312.

192 WHO/TCM/2005.1, available at https://apps.who.int/iris/bitstream/handle/10665/69199/WHO_TCM_2005.1_eng.pdf?sequence=1&isAllowed=y.

These calculation methods may, however, not necessarily be appropriate for the situation of CLs granted to address excessive pricing for medicines in Belgium. Belgium is itself a high-income country and many of the most prominent cases alleging "excessive pricing" that have triggered the attention of the public and policymakers relate to relatively rare diseases, for which the market is limited. It seems of interest to consider the few cases in high-income countries where CLs have been granted in the past.

For instance, in the *Merck v. Shionogi* case[193] in Germany, the Federal Patent Court held that a royalty is based on the specific circumstances of the case, including the deterring effect of the patent, the contribution ratio of the patent to developing the substance at issue and the extent to which further development is necessary. The amount of the license fee was then determined by way of an estimate taking into account the principles developed for assessing the license amount and the indications presented by the parties. It is unclear which "principles" the court is considering here. A royalty rate of 4% of the net sales price of the product was determined. However, in this case the ground for granting a CL was based on the public interest (not excessive pricing) and the patent owner was not exploiting the patent in Germany, which is arguably different from the situation where a CL would be considered to address the excessive price of a medicine developed by the patent owner.

(9) Article 31(i) and (g) – Judicial Review

The legal validity of any decision to grant a CL and the associated remuneration shall be subject to judicial review or other independent review by a distinct higher authority in that Member, i.e. with the power to overturn the decision of the granting authority. However, this does not mean that a CL could not immediately be granted subject to later review. This is especially important in cases related to the national emergency or concrete urgency, public interest/public health or in case of anti-competitive practices.

5.2.2 CLs & the European Legal and Policy Framework: The EU Biotechnology Directive and the Unitary Patent Package, the EC Action Plan and Competition Law

CLs are relevant in the post-grant phase of the patent. No detailed European harmonization exists regarding CLs; not within the context of the classical European 'bundle' patents, nor for unitary patents. The rules on CLs are primarily determined in the national patent legislation of Member States. However, several legal instruments touch upon this issue (see Section 5.2.2.1 EU Biotechnology Directive and Section 5.2.2.2 Unitary Patent Package), the EC Action Plan and the Pharmaceutical Strategy identified several implications of CLs (Sections 5.2.2.3 and 5.2.2.4). Moreover, in the application of EU and national competition law courts and competition authorities have elaborated on the potential anti-competitive effects of excessive pricing in the pharmaceutical sector (Section 5.2.2.5).

5.2.2.1 CLs & the EU Biotechnology Directive

The EU Biotechnology Directive does not contain any detailed provisions on CLs. However, it does create a basis for granting CLs in case there is a dependence between a patent granted for a biotechnological invention and a plant variety. So, in the field of exploitation of new plant characteristics resulting from genetic engineering, guaranteed access must, on payment of a fee, be granted in the form of a CL where, in relation to the genus or species concerned, the plant variety represents significant technical progress of considerable economic interest compared to the invention claimed in the patent. The same is foreseen where the invention represents significant technical progress of considerable economic interest (Art. 12 EU Biotechnology Directive). More importantly, the Belgian implementation legislation of the EU Biotechnology Directive introduced a new CLs provision for public health reasons going beyond what was required by the directive.[194] This CL is described in more detail in Section 5.3.1 and it is the basis of the

193 Federal Patent Court, Case No. 3 Li 1/16, Judgement 21 November 2017, ECLI:DE:BPatG:2017:211117U3LI1.16EP.0 (2018) 120 GRUR, 803.

194 G. Van Overwalle (2006), 'The Implementation of the Biotechnology Directive in Belgium and its Aftereffects: The Introduction of a New Research

recent legislative proposal for excessive pricing in Belgium (see Section 5.3.3).

5.2.2.2 CLs & the Unitary Patent Package

The entry into force of the Unitary Patent Package (2012) has been delayed numerous times due to various political and legal developments (i.e. Brexit, constitutional complaints before the German Constitutional Court against the ratification of the UPC Agreement). At present it is expected that the package will enter into force in 2022, but this is still uncertain. In Section 5.3.2 of this report the Unitary Patent Package is introduced and its relevance is explained. It goes beyond the scope of this report to describe the detailed features of the unitary patent and the UPC. In this section we will consider the envisaged approach towards CLs.

Despite the objective to unify patent infringement and validity procedures for the UPC, Recital 10 of Regulation 1257/2012 regarding the unitary patent states that "[c]ompulsory licences for European patents with unitary effect should be governed by the laws of the participating Member States as regards their respective territories."[195] While the Paris Convention and the TRIPs Agreement have had a certain harmonizing influence on the grant of CLs (see Section 5.2.1), each Member State has considerable discretion to define the grounds justifying the grant of a CL, the material criteria and the procedure. The entity responsible for granting CLs differs from state to state. In some cases courts grant CLs (e.g. dependent patents), whereas licenses in the public interest/public health are often granted by the government or a particular Ministry (see Section 5.3.1 for Belgium), or by competition authorities in case of anti-competitive practices. In order to obtain CLs for more than one of the participating Member States, applications to each of the competent national authorities are required, implying significant effort and cost as well as legal uncertainty.[196] This may be a reason for potential licensees not to apply for CLs in particular countries even when these would be justified.[197] A "one-stop shop" for the grant of CLs would increase legal certainty for all stakeholders.[198] Moreover, it would reduce the costs and enable more efficient procedures. It is noted in this regard that the CJEU stated in *Pharmon v. Hoechst* that the exhaustion rule[199] does not apply to products sold under a national CL. [200] A 'unitary' CL would allow free movement of these goods.

Exemption and a Compulsory License for Public Health', 37 *International Review of Intellectual Property and Competition Law* (IIC), pp. 889-920.

195 DUNLOP, H., 'Compulsory Licensing under a Unitary Patent', EIPR;2017;39:393.

196 Katharina Kaesling (2013), 'The European Patent with Unitary Effect – a Unitary Patent Protection for a Unitary Market?', DOI: 10.14324/111.2052-1871.004, *UCL Journal of Law and Jurisprudence*, 87-111.

197 Here we note that the Belgian proposal provides a basis for the Minister to initiate the CL mechanism without the need to reply to a concrete application by an potential licensee.

198 Katharina Kaesling (2013), 'The European Patent with Unitary Effect – a Unitary Patent *Protection for a Unitary Market?', DOI: 10.14324/111.2052-1871.004, UCL* Journal of Law and Jurisprudence, p. 109; Jaeger and others (n 20) 821; Jaeger, 'The EU Patent', (n 23) 71f.

199 The principle of patent exhaustion means that once a product covered by a patent is legitimately put on a market by the patent owner (or with the owner's consent), such a product can circulate freely within that market without the need for any authorization from the patent owner. Thus, the exclusive right of the patent owner to sell that product in that market is considered to be "exhausted". It is therefore a crucial issue for patent owners, as well as for anyone dealing with the import/export of patented products. Although the basic concept of patent exhaustion is recognized in most jurisdictions, its application differs considerably between jurisdictions. Notably, there are national, regional, and international forms of patent exhaustion. The EU has adopted a regional form of exhaustion.

200 In *Pharmon v. Hoechst* (CJEU, 9 July 1985, Pharmon BV v Hoechst AG, Case 19/84, ECLI:EU:C:1985:304) a CL was granted for one Member State and the licensee sold patented products, in breach of an export prohibition, to a third party in another Member State where the proprietor also held a patent.

It would have been desirable for the Regulation on the unitary patent to have foreseen a single procedure for applying for a CL. However, as it is possible that the conditions for granting a CL may not be met in every state, such a procedure would in any case have to allow for a certain level of differentiation. As it is quite unlikely that the implementation of a single procedure will happen anytime soon, it would be advisable for participating Member States, to explore opportunities for coordination of CLs regarding unitary patents once the Unitary Patent Package has entered into force. This also seems to be in line with plans expressed by the European Commission in its most recent Action Plan (see Section 5.2.2.3). Irrespective thereof, it appears that any envisaged change of the legislation on CLs in Belgium should of course be considered in a European context.

5.2.2.3 CLs in the EC Action Plan

In the Action Plan the Commission emphasizes "the need to ensure that effective systems for issuing compulsory licenses are in place, to be used as a means of last resort and a safety net, when all other efforts to make IP available have failed".[201] As CLs are mainly governed by national law, the Commission calls on Member States (1) to ensure that the tools they have are as effective as possible (e.g. fast-track procedures for CLs in emergency situations) and (2) to establish stronger co-ordination of the use of the last resort measure of CLs to avoid distortive effects on innovation and trade and to engage in more information sharing between Member States (e.g. duration of and royalties CLs). This proposal received some push-back from the pharmaceutical industry.[202] Nonetheless, the European Parliament confirmed recently that it is "convinced that to fight global health emergencies, address the accessibility of certain medical products, and allow life-saving interventions in the public interest voluntary pooling of patents, compulsory licensing and flexibilities provided for in the WTO TRIPS Agreement are important"; and that it "*calls on the Commission, therefore, to analyse and explore possible options for ensuring effectiveness and better coordination of compulsory licensing in the EU*, *taking into account cases in which it has been used in the Union, the reasons for its use, the conditions under which it was granted, its economic consequences and whether it achieved the desired effect*".[203]

At the moment of finalization of this report (April 2022), the Commission was running a consultation of the public and stakeholders for evidence for an impact assessment on the Commission's future legislative work aimed at dealing with the fragmentation and the lack of optimal and coordinated EU CL rules.[204] The Commission is considering various options, such as: a) no policy change (baseline scenario); b) non-legislative measures (e.g. guidelines and recommendations for granting CLs in times of crisis at national level, improving coordination of how national CLs are issued); c) legislative changes: i) creating an EU coordination mechanism for CLs in times of crisis with or without harmonising national CL laws; ii) establishing an "EU-level CL" for use in a crisis; and iii) streamlining CLs for export purposes. The Commission could also plan a combination of non-legislative and legislative measures. The insights gained from this consultation process

The CJEU held that the conditions for exhaustion were not fulfilled, because patent owners cannot be deemed to have given consent in the case of a CL.

201 European Commission, Communication 'Making the most of the EU's innovative potential An intellectual property action plan to support the EU's recovery and resilience', COM/2020/760 final.

202 J. Byrne (2020), 'Compulsory Licensing is not an effective policy tool, warns EU biopharma group as it reacts to European IP Action Plan, available at: https://www.biopharma-reporter.com/Article/2020/11/26/Compulsory-licensing-is-not-an-effective-policy-tool-warns-EU-biopharma-group-as-it-reacts-to-European-IP-action-plan.

203 An intellectual property action plan to support the EU's recovery and Resilience, European Parliament resolution of 11 November 2021 on an intellectual property action plan to support the EU's recovery and resilience (2021/2007(INI)), P9_TA(2021)0453, available at: https://www.europarl.europa.eu/doceo/document/TA-9-2021-0453_EN.pdf.

204 For more information on the status of the consultation and the evidence received, see: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13357-Intellectual-property-revised-framework-for-compulsory-licensing-of-patents_en.

will of course also need to feed into the debate at the Belgian level regarding CLs for very expensive medicines.

Furthermore, the Action Plan includes proposals to "fine-tune the existing toolbox" in order to incentivize the transfer of IP protected technologies in times of crisis, such as patent (or IP) pooling (see Section 6.2). The relevance of patent pools (see Section 6.2) is also acknowledged by the European Parliament in the citation mentioned above.

5.2.2.4 CLs and the Pharmaceutical Strategy for Europe

As indicated throughout this report, it is vital to examine CLs in the light of broader regulatory developments in the pharmaceutical sector. Adopted on 25 November 2020, the Pharmaceutical Strategy for Europe[205] aims at creating a future proof regulatory framework and at supporting industry in promoting research and technologies that actually reach patients. It also takes into account the weaknesses exposed by the COVID-19 pandemic and suggests appropriate actions to strengthen the system. It is based on four pillars, which include legislative and non-legislative action: (1) ensuring access to affordable medicines for patients, and addressing unmet medical needs (in the areas of antimicrobial resistance and rare diseases, for example); (2) supporting competitiveness, innovation and sustainability of the EU's pharmaceutical industry and the development of high quality, safe, effective and greener medicines; (3) enhancing crisis preparedness and response mechanisms, diversified and secure supply chains, address medicines shortages, and (4) ensuring a strong EU voice in the world, by promoting a high level of quality, efficacy and safety standards. In particular the first pillar is important within the scope of this report. The Communication on a Pharmaceutical Strategy for Europe includes a set of envisaged actions. The implementation of the strategy will span the mandate of this Commission and a proposal for revision of pharmaceutical legislation is expected in 2022. On 30 March 2021, the Commission published its Roadmap on the revision of the general pharmaceutical legislation.[206] In this Roadmap, the Commission states various policy options, including an option to "[i]mprove the provisions relevant to competition considerations especially as regards aspects that impact the generic/biosimilar competition, faster market entry of competitor products and eventually affordability. Options shall include provisions on conducting clinical trials on patented products to support generic and biosimilar marketing authorisation applications, the so-called 'Bolar' exemption" (Roadmap, elements to be covered by policy options (g)).[207]

5.2.2.5 EU/National Competition Authorities & Excessive Pricing in the Pharmaceutical Sector

Despite the general consensus on the importance of patent protection and regulatory exclusivities for the pharmaceutical sector, some of the IP strategies mentioned in Sections 2.4 and 3.4 have been the subject of the Pharmaceutical Sector Inquiry by the EU Commission,[208] investigations by national competition authorities and several cases before the General Court and CJEU.[209] In other jurisdictions, such as the US, the pharmaceutical

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205 Pharmaceutical Strategy for Europe, November 2020, available at: https://ec.europa.eu/health/sites/default/files/human-use/docs/pharma-strategy_report_en.pdf.

206 European Commission (2021), *Combined Evaluation Roadmap/Inception impact assessment for the revision of the general pharmaceutical legislation*, Ref. Ares(2021)2390324 - 07/04/2021, available at: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en.

207 *Ibid*, p. 3-4.

208 European Commission, *Pharmaceutical Sector Inquiry - Final Report*, available at https://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf.

209 Well-known examples are the AstraZeneca case related to abuse of procedures (Case C-457/10 P, CJEU 6 November 2012, ECLI:EU:C:2012:770) and the Lundbeck case related to patent settlement agreements (Case C-591/16 P, CJEU 25 March 2021, ECLI:EU:C:2021:243).

sector is also under intense antitrust scrutiny.[210] Recently, the European Commission has adopted a 'commitment decision' in the Aspen Pharma excessive pricing case[211] and the Italian, UK and Dutch competition authorities imposed record fines in excessive pricing cases.[212] Yet, excessive pricing for pharmaceuticals is one of the most contentious issues in competition law and political discourse. However, it is important to note that to date decisions of competition authorities and court cases regarding excessive pricing of pharmaceutical products have typically dealt with off-patent drugs for which patent rights were not an obstacle and CLs would not have been applicable. Moreover, it is debated to what extent competition authorities should intervene in the case of excessive pricing of patented drugs because of the risk of over-enforcement, which would reduce incentives to innovate in the pharmaceutical sector. A related challenge is how to prohibit excessive pricing without turning the competition authority into a price regulator.[213] Nonetheless, significant pressure from civil society, some governments, parliamentarians and academia on competition authorities persists to use their enforcement tools also in cases where patent owners charge allegedly excessive prices.

Irrespective of the desirability to apply competition law to pricing practices adopted for patented medicines, it can be questioned whether the criteria of "excessive pricing" are the same for newly developed drugs and off-patent drugs. Nevertheless, it is of interest to consider how competition authorities have actually assessed "excessive" pricing in these cases. As we will see in the case-law discussed below and in Appendix 1 competition authorities and courts have explored and used different methods and criteria to assess the excessive nature of the prices. Whereas not one consistent generally accepted test has been identified, the experience of competition authorities and a careful study of case-law can be used as a source of inspiration for identifying or developing methods to assess the excessive nature of prices also within the context of a CL procedure. Therefore, in this section we provide a short introduction to position the case-law within the relevant

210 See for instance: M.A. Carrier & F. Aaray (2021), 'Pharmaceutical antitrust enforcement in the United States and Chile', 8(1) *Journal of Law and the Biosciences*, https://doi.org/10.1093/jlb/lsab013.

211 The European Commission accepted commitments by Aspen to reduce prices for six off-patent cancer medicines by 73% addressing excessive pricing concerns, see: CASE AT.40394 – Aspen, available at https://ec.europa.eu/competition/antitrust/cases/dec_docs/40394/40394_5350_5.pdf.

212 Italian Competition Authority, A480 – Price Increase of Apen's Drugs, Measure No. 26185 29 September 2016, available at: https://en.agcm.it/dotcmsDOC/pressrelease/A480_eng.pdf; CMA, Auden Mckenzie and Actavis UK (now known as Accord-UK), 15 July 2021, available at: https://www.gov.uk/government/news/cma-finds-drug-companies-overcharged-nhs; CMA, Advance, 29 July 2021, available at: https://www.gov.uk/government/news/cma-fines-pharma-firm-over-pricing-of-crucial-thyroid-drug and ACM, Leadiant, 19 July 2021, available at: https://www.acm.nl/en/publications/decision-fine-leadiant-excessive-price-cdca-drug (competition cases against Leadiant are also pending in Belgium, Italy and Spain).

213 See for an overview of different perspectives: Organization for Economic Co-operation and Development (OECD) (2018a), Excessive Prices in Pharmaceutical Markets – Background Note by Secretariat, DAF/COMP/WD(2018)12, p. 27-28. For opponents, see for instance: C. Calcagno et al. (2019), 'Economics of Excessive Pricing: An Application of the Pharmaceutical Industry', 10(3) J. Eur. Comp. Law & Practice, 166-171. For proponents, see: I. Akker & W. Sauter (2021), 'Excessive Pricing of pharmaceuticals in EU law: balancing competition, innovation and regulation', December 2021, available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3991903; C. Fonteijn et al. (2018), 'Reconciling competition and IP Law : the case of patented pharmaceuticals and dominance abuse', ACM Working Paper, in: G. Muscolo & M. Tavassi (ed.), The interplay between competition Law and Intellectual Property – An International Perspective', Kluwer Law International, available at https://www.acm.nl/sites/default/files/documents/2018-03/acm-working-paper-reconciling-competition-and-ip-law-2018-03-07.pdf and F. Abbott (2016), 'Excessive pharmaceutical prices and competition law: doctrinal development to protect public health', 6 *UC Irvine Law Rev.*, 281, available at: https://scholarship.law.uci.edu/ucilr/vol6/iss3/3/.

competition law and policy framework and we add a short systematic overview of key insights derived from recent cases before the European Commission and several national authorities in Appendix 1. We note that this introduction and overview in the appendix are non-exhaustive as a detailed description goes beyond the scope of this report.[214]

1. Introduction: EU Competition Law & Excessive Pricing

The legal basis for competition authorities and courts to deal with "excessive" prices set by companies with a dominant position in the relevant market is found in Article 102(a) of the Treaty of the Functioning of the EU (TFEU) and relates to abuse that consist in "directly or indirectly imposing unfair purchase or selling prices or other unfair trading conditions".[215] The Treaty thus refers to "unfair" prices rather than excessive prices, but the case-law and legal doctrine are commonly referring to these practices as "excessive" pricing practices. In the analysis below it will be clarified how excessiveness and unfairness are interrelated according to the CJEU.

Before delving into the assessment of the abuse, competition authorities identify the "relevant market" and assess whether a particular company has a dominant position in the market concerned. In this respect, the competition authority considers alternative patented and generic medicines to the drug under investigation. The narrower the relevant market is defined, the more likely it is that a dominant position will be established. In recent years, the European Commission and other national competition authorities have generally defined pharmaceutical markets rather narrowly.[216]

The *United Brands case* of 1978 and several subsequent judgements have established a framework for assessing whether the price charged by a dominant firm may be considered excessive. According to the CJEU[217] it is advisable to determine whether the dominant company has used the opportunities arising out of its dominant position in such a way as to reap benefits which would not have been possible if there had been normal and sufficiently effective competition. A price is excessive if "it has no reasonable relation to the economic value of the product supplied".[218] This excess can for instance be determined objectively "by making a comparison between the selling price of the product in question and its cost of production, which would disclose the amount of the profit margin".[219]

The CJEU then offered a two-limbed test, which is rather flexible and still is the seminal test applied by competition authorities and courts.[220] This test can be summarized as follows: (1) whether the differences between the costs actually incurred and the price charged is excessive (cost-price analysis) (the so-called 'excessiveness limb'), and if the answer to this question is in the affirmative (2) whether a price has been imposed which is either unfair in itself or when compared with competing products (the so-called 'unfair limb').[221] We note that in the debate on CLs, no systematic and

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214 Competition decisions are often very long and contain detailed economic analyses. For more details regarding methods and criteria we point to the original sources and the references to the decisions and cases in the footnotes.

215 In terms of the role of competition law in the context of the affordability of medicines, it could also be interesting to investigate the impact of decisions of competition authorities regarding refusals to license and the essential facilities doctrine. However, that would go beyond the scope of the current report, which focuses specifically on (very) expensive medicines.

216 C. Calcagno et al. (2019), 'Economics of Excessive Pricing: An Application of the Pharmaceutical Industry', 10(3) *J. Eur. Comp. Law & Practice*, 166-171, p. 168.

217 CJEU, 14 February 1978, United Brands Company and United Brands Continental BV v. Commission of the European Communities, Case 27/76, ECLI:EU:C:1978:22, paras. 249.

218 *Ibid*, para. 250.

219 *Ibid*, para. 251.

220 T. van Helfteren (forthcoming), 'Excessive Pricing in Pharmaceutical Markets: A Review of the Legal Test for Competition Authorities', 42 *Eur. Comp. Law Rev.*, available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3872672.

221 CJEU United Brands, para. 252.

conceptual distinction is made between excessive and unfair prices; in the literature these terms are often used interchangeably. It may be relevant to consider explicitly not only whether a price is excessive, but also whether it is unfair in the given circumstances. Nonetheless, considerations about the fairness of the price may self-evidently come up in a CL procedure when the patent applicant has an opportunity to justify the high price and provide input on the merits of the CL application.

In the *United Brands* case the CJEU clarified that various methods can be used to assess the price.[222] The Court recognized that it will often be complex to determine the production costs "which may sometimes include a discretionary apportionment of indirect costs and general expenditure and which may vary significantly according to the size of the undertaking, its object, the complex nature of its set up, its territorial area of operations, whether it manufactures one or several products, the number of its subsidiaries, their relationship with each other, [etc.]".[223]

Competition authorities, including the European Commission, typically tend to adopt a rather cautious and conservative enforcement approach towards excessive prices in industries involving substantial risks in product development.[224] The general consensus seems to be that this cautious approach is also warranted, as competition authorities are ill-suited to become price regulators and continuously monitor and intervene, because they do not have the resources nor the expertise to do so. In addition, investigations by competition authorities are generally long and time-consuming. The identification of excessive prices is sometimes regarded as a "daunting, if not, impossible task", because of the lack of data and problems with the data analysis, the difficulties of identifying appropriate assessment standards and of designing and implementing suitable remedies.[225] Price regulation is generally thought of as a more effective way to deal *ex ante* rather than *ex post* with excessive pricing.[226] This recommendation to leave excessive pricing issues primarily to health authorities with the required expertise and resources, should also be taken into consideration when examining a proposal for introducing CLs for excessive pricing. For a reliable and appropriate assessment of the prices an advisory body would need to have the required economic expertise, sufficient resources, access to relevant data about costs and prices and clear guidelines on the standards and methods that may be used for assessing the excessive nature of the prices.

Only when certain stringent conditions are met will competition enforcement against exploitative excessive pricing be justified. According to a report published by the Organization for Economic Co-operation and Development (OECD) based on a comparative analysis of the competition law policies in various countries, competition enforcement against excessive prices seems to make most sense in markets with a deep-rooted dominant position where entry or expansion of competitors is unlikely to ensure effective competition in the foreseeable future.[227] The OECD also identified a number of "screens"

222 *Ibid*, para. 253 ("other ways may be devised — and economic theorists have not failed to think up several — of selecting the rules for determining whether the price of a product is unfair").

223 *Ibid*, para. 254.

224 See e.g. OECD (2018a); OECD (2018b), Excessive Pricing in Pharmaceutical Markets – Note by the European Union, DAF/COMP/WD(2018)112 and OECD (2011), 'Working Party No. 2 on Competition and Regulation, Excessive prices, European Union, DAF/COMP7WP2/WD/(2011) 54.

225 D. Evans and J. Padilla (2005), 'Excessive Prices: Using Economics to Define Administrable Legal Rules', 1(1) *J. Comp. Law & Econ.*, at 97.

226 M. Motta & A. Streel (2007), 'Excessive Pricing in Competition Law: Never Say Never?', in: *The Pros and Cons of High* Prices, Swedish Competition Authority, 14-46, at 19-20, available at: https://researchportal.unamur.be/en/publications/excessive-pricing-in-competition-law-never-say-never; OECD (2018a), p. 9, OEC (2011), p. 13 and Opinion AG, 14 September 2017, Case C-177/16, Autortiesību un komunicēšanās konsultāciju aģentūra / Latvijas Autoru apvienība v Konkurences padome (AKKA/LAA), ECLI:EU:C:2017:286, para. 105.

227 OECD (2011), para 61.

for competition intervention requiring: (1) the company to have a significant market power, close to a pure monopoly position; (2) high and durable barriers to entry (less likely that the market will self-correct within a relatively short timeframe); (3) no competition enforcement when it may adversely impact research and innovation, and (4) alternative regulatory intervention is either impossible, extremely unlikely, inappropriate or absent.[228] Typically in regulated markets public authorities exert some form of control over the forces of supply and, consequently, the scope for free and open competition tends to be reduced.[229] As the pharmaceutical market is heavily regulated and many companies have entrenched dominant positions, it is one of those markets where competition authorities at the national and European level have (cautiously) initiated enforcement activities against pricing strategies in line with these enforcement screens identified by the OECD.

The competition authority bears the burden of proof to show that all conditions of Article 102 TFEU are fulfilled. Yet, in line with the case-law of the CJEU regarding Article 102 TFEU once an authority has recorded an excess between the actual price and the benchmark price,[230] it is for the dominant company in question to provide the authority with possible justifications for the higher price. In fact, the investigating competition authority often lacks information which may be necessary to assess whether a price that appears to be above the competitive price does not, in reality, merely reflect the higher value of the underlying transaction. Such information may concern for instance the dominant undertaking's cost structure, its pricing policies and the structure of demand in the relevant market.[231] Information that is shared by pharmaceutical companies in such procedures, could be very valuable to create more transparency and insights into the cost structures for medicine production and would also be vital for CL procedures in excessive pricing cases.

2. Case-law Analysis: Standards and Methods for Assessing Excessive Pricing

As mentioned above, already in *United Brands* the Court acknowledged that various methods can be used to assess the excessive and unfair nature of the pricing practices of a dominant firm. In *United Brands* the Commission used several comparisons. The most important comparison was between UBC's prices in different Member States. In particular, the Commission found that the price in Ireland was half the price in Belgium, Luxembourg, Denmark and Germany. As internal documents of the company indicated that UBC made profits in Ireland, the Commission concluded that the prices in the other mentioned Member States, which were twice higher, were excessive. However, the CJEU critically examined the method used by the Commission and did not agree with its analysis. The Court expressed concern that the Commission had not analyzed UBC's production costs, although it could have done so. It was doubtful as to whether the price in Ireland could be used as a relevant benchmark, especially in view of the fact that UBC presented documents indicating that prices in Ireland had produced losses. In addition, the Court noted that the price difference with UBC's competitors was only 7% which could not be automatically regarded as excessive and consequently unfair. The *United Brands* case thus confirms that competition authorities should carefully consider the method that they will use and analyze cost data if available. In addition, the Court critically reviews selected benchmarks and price differences. Therefore, the body responsible for assessing the excessive nature of the price within the context of a CL procedure, should also consider various methods that can be employed and carefully assess available cost data.

The fact that a variety of methods may be used was once more confirmed by the CJEU in a recent case regarding licensing fees adopted by the

228 OECD (2018a), p. 12.

229 Opinion AG, AKKA/LAA, ECLI:EU:C:2017 :286.

230 Appendix 1 shows that various methods are used to determine the benchmark price.

231 Opinion AG, AKKA/LAA, ECLI:EU:C:2017:286, paras. 135-136.

Latvian copyright collecting society.[232] The Latvian collecting society, similar to other collecting societies, has a legal monopoly to grant copyright licenses for the public performance of musical works. The Latvian competition authority analyzed the excessiveness of the fees by comparing with similar fees imposed by other collecting societies in neighboring countries as well as taking into account the 'purchasing power parity (PPP)' index in the comparable Member States. A comparison cannot be considered to be insufficiently representative merely because it takes a limited number of Member States into account. On the contrary, such a comparison may prove relevant, on condition, that the reference Member States are selected in accordance with *objective, appropriate and verifiable criteria*. Therefore, there can be no minimum number of markets to compare and the choice of appropriate analogue markets depends on the circumstances specific to each case.[233] A comparison between the prices applied in the Member State concerned and those applied in other Member States must be made on a consistent basis.[234] It falls to the competition authority concerned to make the comparison and to define its framework. The authority has a certain margin of appreciation for defining this framework and there is no single adequate method.[235]

Such a comparison between prices charged in different Member States may also be a useful method to assess the level of the price for pharmaceutical products, provided that the Member States are selected on the basis of objective, appropriate and verifiable criteria, that the differences in pricing and reimbursement governance mechanisms in each of those Member States are taken into consideration and that the comparison is done on a consistent basis. AG Wahl and the Court confirmed that the method used by the Latvian competition authority was comprehensive and in line with the EU case-law emanating from *United Brands*.[236]

The AG and Court clarify that there is no minimum threshold above which a rate must be regarded as 'appreciably higher' and thus indicative of abuse, given that the circumstances specific to each case are decisive in that regard. A difference between rates may be qualified as 'appreciable' if it would be *significantly and persistently* (difference must persist for a certain length of time and must not be temporary or episodic) above the benchmark price.[237]

AG Wahl also refers to a number of elements, [238] related both to production and marketing and customers' demand for the products, that can be taken into consideration in assessing the "economic value" of the products: direct and indirect production costs, the cost of capital, overheads (including advertisement, R&D), quality/features of the products regarded as particularly valuable by customers or certain groups of customers (in spite of the fact that they are not reflected on the cost side). He argues that although certain types of costs may not be immediately evident or easily imputable to the supply of a given product or service (for example, unsuccessful R&D), they may nonetheless not be discounted. Otherwise investment and innovation may be discouraged.[239] This argument of the AG will resonate well with the arguments of the pharmaceutical industry that the costs of unsuccessful R&D projects should be accounted for in the prices for medicines. In addition, AG Wahl's opinion that additional benefits or advantages provided to customers/patients may justify a higher mark-up

232 CJEU, AKKA/LAA, ECLI:EU:C:2017:689.

233 CJEU, AKKA/LAA, ECLI:EU:C:2017:689, paras. 40-41 and Opinion AG, AKKA/LAA, ECLI:EU:C:2017:286, para. 61.

234 CJEU, AKKA/LAA, ECLI:EU:C:2017:689, para. 44.

235 *Ibid*, para. 49.

236 CJEU, AKKA/LAA, ECLI:EU:C:2017:689, paras. 38, 51 and Opinion AG, AKKA/LAA, ECLI:EU:C:2017:286, paras. 81, 95.

237 CJEU, AKKA/LAA, ECLI:EU:C:2017:689, paras. 55-56 and Opinion AG, AKKA/LAA, ECLI:EU:C:2017:286, paras. 106-107.

238 These factors are listed for comparing with the prices for competing products. Even though for very expensive medicines often there may be no competing products, the list of factors may still be an interesting point of reference as various costs are mentioned and also reference is made to the consumer value.

239 Opinion AG, AKKA/LAA, ECLI:EU:C:2017:286, para. 127.

over costs (even when they are not reflected on the cost side)[240] would also favor a higher economic value attributed to certain medicines, for instance with respect to follow-on innovations, such as improved dosage regimes and formulations. However, this argument has also been contested by AG Pitruzzella[241] and some competition authorities (see Appendix 1).

For now the CJEU has not issued a judgement regarding excessive pricing in the pharmaceutical sector. However, the last five years DG Competition of the European Commission (hereinafter 'the Commission') and various competition authorities have started investigations and have decided on the matter. Again it needs to be emphasized that for now all these cases relate to off-patent, generic products. They also often involve price increases that occurred after the drug was purchased from a previous owner and at a stage where the price increase could not be justified by significant R&D and investment. Moreover, these cases often address various anti-competitive practices, covering for instance agreements with potential competitors to prevent them from entering the market as well. As a result, the company concerned is often the only supplier on the market (*de facto* monopoly rather than legal monopoly based on various exclusive rights) and patients do not have access to alternative treatments despite the fact that the relevant patents have expired and, hence, the grant of a CL would not have been an option.

Whereas in 2014 the Commission had still declined to open an investigation regarding pricing practices of Gilead – despite calls for action by the European Parliament – in 2017 it did so in the Aspen case. In 2014 the Commission was mostly relying on Member States' discretion to regulate and influence prices.[242] It noted that price-setting by pharmaceutical manufacturers and healthcare systems in general takes place on a national level, allowing Member States to exercise their bargaining power. As France and other Member States had concluded or were in the process of concluding agreements with Gilead limiting the prices, the Commission decided not to interfere, but indicated that it would continue to monitor the market of hepatitis C drugs. Nonetheless, in May 2017 DG Competition did open a formal investigation into the pricing practices of Aspen. As described in more detail in Appendix 1, the Commission applied the two-limb *United Brands* test. For the first excessiveness limb, the Commission relied on a profitability analysis; although the Commission noted explicitly that various ways exist to assess the excessiveness of the profits. To assess the "unfairness" of the prices, the Commission focused on whether the prices were unfair "in itself" rather than comparing with "competing products". The Commission concluded that Aspen had not offered material improvements of the products through R&D and designed and implemented a strategy to exploit health systems and patients. The price increases were disproportionate to the limited increases in its costs of production and no legitimate reasons existed for Aspen's high prices.

In February 2021, the Commission issued a so-called Commitment Decision fixing the price that Aspen is allowed to charge for several cancer drugs. Although this decision of the Commission was not tested in court and although it relates to off-patent drugs, it provides helpful guidelines and take-aways for an application of the *United Brands* two-limb test in the pharmaceutical sector and different methods that can be used to examine the excessive and unfair nature of the prices. At various instances several national competition authorities issued decisions in excessive pricing cases and imposed significant fines, most notably the Italian, UK, Danish and Dutch competition authorities. These cases are described in Appendix 1 and show substantial similarities in terms of applying the *United Brands* two-limb test, the specific fact patterns and are quite consistent in terms of the

240 *Ibid*, para. 128.

241 Opinion AG, SABAM v Weareone World, C-372/19, EU:C:2020:598, para. 25: "[…]it is not always the case that there is a maximum price that the consumer is willing to pay for a product, with a result that, in those situations, there are no obstacles to the introduction of excessive prices. In the case of a life-saving medicine, for example, the only spending limit is the financial capacity of the purchaser (whether the patient or the national health service)."

242 European Commission (2014), Response to Parliamentary Question, P-008636/2014, 22 December 2014, available at: https://www.europarl.europa.eu/doceo/document/P-8-2014-008636-ASW_EN.html.

standards and methods used and the challenges that are encountered while carrying out these analyses.

3. Reflections EU Competition Cases Excessive Pricing relevant for CLs

The excessive pricing cases described in more detail in Appendix 1 have a number of similarities.[243] First, they relate to medicines that have long been off-patent, so there are no R&D and investment recoupment justifications applicable for the excessive prices charged, nor concerns about interfering with innovation. Only the *Leadiant* case is slightly different, as in this case regulatory exclusivities were still applicable, but yet due to the particular circumstances of the case no significant costs could be shown. Second, the claims of excessive pricing occurred suddenly and showed significant price increases for products which had been on the market for a long period of time. Third, the medicines in question are essential to patients and demand for the products is extremely price-inelastic. Fourth, no prospect of timely market entry of alternative products existed either because of supply constraints, the regulatory framework or the limited size of the market. Fifth, regulatory intervention was perceived to be unable to provide an appropriate, timely response to the price increase.[244]

Consensus exists among competition authorities that, in general, excessive prices in pharmaceutical markets where competition prevails, i.e. as regards originator medicines which are still in the phase of patent protection and/or regulatory exclusivities that preclude market competition, should not be addressed by competition enforcement against excessive pricing.[245] However, recently some authors have started to argue that one should not completely exclude the possibility of bringing excessive pricing cases with regard to patent protected pharmaceutical products.[246] The *Leadiant* case is presented as a first move in this direction, even though in that case the relevant patents had already expired and only regulatory exclusivities were in force. To minimize the impact of such actions on innovation and investment, these proponents of competition enforcement in such cases argue that one can take into account the *ex ante* probabilities of product success in the assessment of the pricing practices: the probability of success of a new pharmaceutical product should be integrated in the analysis of the costs and profit margins of the investigated company. The calculation of the costs of developing such new products would hence include a risk. In this respect, the OECD also refers to alternative methodologies apart from price/cost methodologies such as those used by regulators, such as value-based pricing. Fonteijn et al. (2018) refer to the use of a threshold value for the acceptable cost per quality of life adjusted year (QALY) to assess alleged excessive pricing practices, arguing that the use of such a threshold could improve investment decisions (focusing on welfare enhancing products) rather than harm them.[247] The OECD acknowledges, however, that such methods are extremely data-intensive and lead to significant burdens for competition authorities.[248]

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243 This analysis of the similarities between the different cases is based on OECD (2018a), p. 19, but the review of cases has been updated since the adopted of the OECD report.

244 OECD (2018a), p. 19.

245 OECD (2018a), p. 27.

246 F. Abbott (2016), 'Excessive pharmaceutical prices and competition law: doctrinal development to protect public health', 6 *UC Irvine Law Rev.*, 281, available at: https://scholarship.law.uci.edu/ucilr/vol6/iss3/3/ and C. Fonteijn et al. (2018), 'Reconciling competition and IP law: the case of patented pharmaceuticals and dominance abuse', *ACM Working Paper*, ACM, available at: https://www.acm.nl/sites/default/files/documents/2018-03/acm-working-paper-reconciling-competition-and-ip-law-2018-03-07.pdf.

247 C. Fonteijn et al. (2018), p. 13 – an idea further developed in: M. Canoy & J. Tichem (2018), ACM Working Paper 'Lower drug prices can improve innovation', available at: https://www.acm.nl/sites/default/files/documents/2018-05/lagere-medicijnprijzen-hoeven-innovatie-niet-in-de-weg-te-staan.pdf.

248 OECD (2018a), p. 28.

Key points

- Until now no national or EU competition authorities have issued decisions related to excessive pricing for patented medicines, thus all available information is from cases relating to off-patent drugs;
- Various methods have been used by competition authorities for assessing the excessive nature of prices of off-patented drugs. In addition, the impact of using other methods is verified in order to check whether it would lead to other conclusions;
- Access to relevant commercially confidential information regarding costs and pricing is essential for an appropriate analysis of the excessive nature of the price;
- No consensus exists as to the most appropriate method for calculating the costs, but the cost plus method (cost plus reasonable rate of return) is a common method used. Calculated costs cover both direct and indirect costs attributable to the products;
- No minimum threshold has been used above which a rate must be regarded as 'appreciably higher' and thus indicative of abuse, as this depends on the specific circumstances of each case. A difference between rates may be qualified as 'appreciable' if it would be "significantly and persistently" (difference must persist for a certain length of time and must not be temporary or episodic) above the benchmark price;
- For assessing the unfair nature of the prices, a price can be unfair "in itself" or "in comparison" to competing products;
- Factors that are taken into consideration by competition authorities are amongst others: (1) the way the relevant market operates - actual and potential competition (e.g. price elasticity, entry barriers, agreements to prevent entry); (2) the disproportion between the applied price and the benchmark price; (3) the disparity between the price and the "economic value" (e.g. age product, therapeutic value); (4) whether R&D investments were made and commercial risks were borne; (5) the awareness amongst the companies of the adverse effects of the pricing practices on the health system and patients; (6) whether similar pricing practices were introduced in other countries;
- A comparison can be made with competing products in other geographical markets. Reference Member States should be selected in accordance with "objective, appropriate and verifiable criteria" and should take into account the specific circumstances of the case, such as for instance different systems of pricing and reimbursement. Such a comparison should be done on "a consistent basis";
- The burden of proof regarding the abusive nature of the excessive pricing lies with the competition authorities. Companies can invoke justifications to redeem the excessive and unfair nature of the prices, for instance by showing innovation and investment costs or increases in production costs;
- Recently calls have been made to consider competition enforcement regarding excessive pricing practices related to patented medicines. In this respect, authors also provided suggestions as to the additional factors which would need to be taken into consideration in such cases in comparison to off-patent drugs (i.e. probability of success, value-based pricing).

5.3 The Belgian Legal Framework for CLs

5.3.1 Current Belgian Legal Framework for CLs

The Belgian legislation already contains several legal bases for granting a CL in specific circumstances. Firstly, the Minister of Economic Affairs can grant a CL in case the patent owner is not or insufficiently exploiting the patented invention (i.e. failure to work or insufficient working, Art. XI.37§1(1°) BCEL). In such a case the Minister can grant a CL to every interested person who can show (1) that the invention is not or insufficiently exploited by the patent owner by manufacturing or by importing the patented products (here also the term of 3 years from the grant date or 4 years of the filing date as prescribed by the PC applies); (2) that no justification exists for the failure to work/insufficient working by the patent owner; (3) that the necessary capacity is available for a significant and continuous exploitation of the patented invention; (4) that negotiations for a voluntary license have failed; (5) that the CL is granted predominantly for the supply of the domestic market; (6) that the CL is non-exclusive and non-assignable[249]; and (7) that the CL is limited in scope and duration in line with the objective of the grant of the CLs (Art. XI.37§1(1°) and §2, XI.40 and XI.46 BCEL).

This ground will only be of limited use to address instances of excessive pricing by patent holders, as excessive pricing by the patent owner by definition implies that there is working[250] of the patented invention (see also Section 5.2.1.3). Arguably this could be used as a negotiation tool to obtain a reasonable license fee from a non-practicing entity, thereby serving as a potential tool to avoid excessive pricing. The condition that the "negotiations for a voluntary license have failed" implies that there may have been negotiations but the price demanded by the patent holder is excessively high (resulting in a price increase for the medication). However there is no case law or evidence supporting that this measure can be used in practice in such circumstances. A question which arises in this context is what is the definition of a non-practicing entity and "sufficient" exploitation of the patent. A patent claim may cover a range of products for different applications of which the patent owner exploits only one. It is unclear to what extent a third party developing a product falling within the scope of the patent in a different field would still be able to apply for a CL based on the argument that the product is not being developed by the patentee for this field.

Second, a CL can be granted in case of dependence between patents (Art. XI.37§1(2°) BCEL). This occurs when an innovative company has developed a product for which it has been granted a patent but this product involves the use of a patented technology or product such that the company can only exploit the patented invention if it is authorized by the owner of that patent. In case the patent owner of the patent covering the necessary technology or product would not be willing to grant the authorization (i.e. a voluntary license), the Minister of Economic Affairs can grant a CL, provided the applicant shows that the dependent patent has a considerable technical interest and the use of the dominant patent is necessary for the exploitation of his invention. As indicated above, similar provisions also exist in case of an overlap between a patent for a biotechnological invention and a plant variety right[251] (Art. XI.3761(3°)(4°) BCEL) (see also Art. 12 EU Biotechnology Directive, Section 3.2.2.1), but this is less relevant in the present context. The conditions mentioned above under 4-7 for CLs granted for failure to work also apply to these CLs (Art. Art. XI.37§2 BCEL). This seems to be compatible with the requirements and conditions imposed by Art. 31 TRIPs.

This provision in the Belgian law makes it possible to obtain CLs also from practicing patent owners, but only for products which are themselves

249 Non-assignable means that a licensee cannot sell the CL to other companies.

250 If a company is producing in Belgium or importing and offering for sale but against very high prices than in principle the company does comply to "working" the patent despite the problems in terms of accessibility and affordability.

251 Plant variety rights are rights granted to the breeder of a new variety of plant that give the breeder exclusivity over the propagating material (including seed, cuttings, divisions, tissue culture) and harvested material of a new variety for several years.

innovative (i.e. covered by a separate patent). This requirement is in fact an incentive for innovative companies working on improvements of existing products or technologies to file patents on their innovation, even if the patent is likely to be limited in scope. This paragraph could in practice be relevant in the context of excessive pricing. Indeed, it seems more likely that a patent owner having a product on the market or in development will be reticent to grant a license on a potentially competing product and that, particularly where the products of the patent holder and the licensee would be in direct competition with each other, the absence of the competitor on the market will affect the price of the patent holder's product. Nevertheless it should be realized that these provisions are mainly aimed at avoiding that products which address an unmet need or present an important improvement are not blocked by patents and that effects on avoiding or reducing excessive pricing are likely to be limited.

The **procedure for requesting a CL by a potential licensee** is described in detail here. A potential licensee can apply for a CL with the Minister of Economic Affairs. The Minister will only decide on the application after the advice of the Commission CLs. This Commission CLs plays a rather important role in the grant of CLs (for detailed information on the Commission, see Art. XI.43 BCEL). It consists of ten members, including two experts from the Council Intellectual Property and eight members from organizations representing the industry, agriculture, commerce, small and medium-sized enterprises and consumers. The mandate of the members lasts for six years and is renewable. The Minister will assign one or more qualified officials from the Ministry to support the work of the Commission. These officials have rather extensive investigatory powers ranging from searches making copies of documents, seizure of documents, taking samples and hearing of experts (Art. XI.43§2 BCEL).

The Commission CLs will hear the parties and try to conciliate their interests. If this is not successful, the Commission will provide a motivated advice to the Minister and the Minister will decide (Art. Art. XI.41 BCEL). Within four months after the notification of the decision of the Minister, the parties will agree on their respective rights and obligations, including the "adequate remuneration" (taking into account the economic value of the license – but no guidelines are provided as to how this should be estimated). If the parties cannot agree on these rights and obligations, this will be decided by the district court (Art. XI.42 BCEL). In case of new circumstances the grant of the CLs, the respective rights and obligations and the licensing conditions can be reviewed (Art. XI.44 BCEL). For this review the same procedure will be applicable as for the grant of the CL. If the licensee engages in illegitimate conduct vis-à-vis the patent owner or does not fulfil its obligations in line with the CL, the CL can be revoked (Art. XI.45 BCEL). The Commission CLs will again be involved in the procedure for revocation and will provide advice.

In 2005, a new legal basis was created for granting a CL for "reasons of public health".[252] This legal basis was created at the occasion of the implementation of the EU Biotechnology Directive. Article XI.38 BCEL specifies that a CL can be granted for (a) medicines, a medical device or diagnostic product or a derived or combinable therapeutic product; (b) a method or product relevant for the production of one or more of the products mentioned under (a), and (c) a diagnostic method practices outside the human or animal body. The applicant for the CL (also the potential licensee) must prove that, if the CLs would be granted, (s)he has the means or the *bona fide* intention to obtain the means necessary for the substantial and continuous manufacture and/or application in Belgium of the patented invention. The CL needs to be non-exclusive and its scope and duration can be limited. Interestingly, the procedure for granting this third type of CL differs from the other types of CLs in the BCEL. This third category CL is granted by the "King" rather than the Minister. In case of a public health problem, the CL will be granted after getting the advice of the Advisory Committee on Bioethics and not from the Commission CLs. No information is available as to the support staff and their investigatory powers for the Advisory Committee (cf. above the Commission CLs). No explicit condition

252 E. van Zimmeren & G. Van Overwalle (2011), 'A Paper Tiger? Compulsory License Regimes for Public Health in Europe', 42 IIC, pp. 4-40.

is imposed that negotiations to get a license on a voluntary basis have failed.[253]

In terms of the procedure for applying for a CL for public health reasons, Art. XI. 38§2 and §6 BCEL determine that the applicant for a CL submits a request to the Minister with copy to the Advisory Committee on Bioethics. The minister forwards the application to the Advisory Committee on Bioethics within ten days. Within the same period, the Minister informs the owner of the patent(s) that is/are the subject of a request for a CL of the application and invites him/her to give an opinion on the possible grant of a CL and comments on a *reasonable*[254] remuneration in the event that a CL would be granted, to be notified to the Advisory Committee on Bioethics, within one month. The Advisory Committee on Bioethics provides the Minister with a reasoned and *non-binding* opinion on the merits of the application. Within a period of three months after receipt of the advice of the Advisory Committee on Bioethics, the Minister submits a reasoned proposal for a decision on the merits of the request for consultation to the Council of Ministers. The Minister also submits a proposal regarding the remuneration for the patent owner. If the King decides to grant the CL, he shall determine the duration, scope and other conditions of use of the CL. This will be done by decree adopted after consultation in the Council of Ministers. The exploitation scheme also includes arrangements for the remuneration for the use of the patented invention made during the grant procedure. In the event of a public health crisis and on the proposal of the Minister responsible for public health, the King may take measures by decree, adopted after consultation in the Council of Ministers, to accelerate the procedure referred to in this paragraph. He may, where appropriate, decide not to seek the advice of the Advisory Committee on Bioethics, in order to allow rapid decision-making.

Irrespective of the fact that it has not yet been tested in practice, the provision on CLs for public health reasons appear to raise a number of concerns. First, it is unclear what falls within the scope of the mechanism as no detailed guidance is given on the "public health reasons". On the one hand, this may provide the necessary flexibility to invoke grounds such as, for instance, the price of the product limiting accessibility. On the other hand, a potentially broad interpretation of this ground also creates legal uncertainty for innovative companies. It seems that it is thus important for all parties to provide some clear guidance on the interpretation of "public health reasons". Second, despite this possibility to speed up the process in the event of a public health crisis, the application procedure for CLs for public health reasons appears to be more burdensome than the procedure for the other types of CLs in terms of the various stages in the process and long decision-making processes. Third, the expertise of the Advisory Committee on Bioethics is arguably one-sided if compared to the Commission CLs prescribed for the other types of CLs. One may wonder whether more economic and commercial expertise[255] would be desirable as well to assess the "public health reasons" and to give advice on the "reasonable remuneration". Fourth, the procedure depends on the interest of a potential licensee to initiate the process. As is the case in other jurisdictions (see Section 5.4), it may appear desirable to provide opportunities for the Minister of Public Health to start the process to – in a second phase – then attract potential licensees.

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253 Moreover, it is unclear whether the Advisory Committee would hear the parties and would try to conciliate their interests (see below for the procedure). Only the opinion of the patent owner will be notified to the Advisory Committee, but what happens with that opinion in the advice is unclear

254 Interesting in view of the analysis in Section 5.2.1.3 regarding the requirement in Art. 31 TRIPs for "adequate" remuneration.

255 Persons with expertise in patent law for assessing the relevant patents and for determining whether patents are actually the key issue or whether there are other/additional problems (trade secrets, data/market exclusivity). So some commercial understanding of the sector would be desirable. Moreover, for examining what is a reasonable remuneration some knowledge of the sector seems essential (see WHO Guidelines, e.g. common licensing strategies, royalties (but depends on the method you use for determining what is reasonable).

The introduction of this new CL for public health reasons attracted quite some attention at the national and international level. It should in particular be positioned in the global debate regarding the restrictive licensing practices adopted by *Myriad Genetics* on patents covering a method for the determination of a genetic predisposition for breast cancer.[256] This debate also resulted in the introduction of an *ex officio* licensing regime for public health reasons in France.[257] Nonetheless, these regimes specifically designed to ensure access to medicines, therapies and diagnostic methods have not yet been successfully invoked in practice.[258] Although patent practitioners confirm that the existence of such mechanisms are used in practice in licensing negotiations with an unwilling licensee, only anecdotal evidence of such type of "informal" use in negotiations is available.

Finally, the Belgian legislation also provides that a CL can be granted in line with the procedure set out in Art. 31*bis* TRIPS and EU Regulation No. 816/2006 (see Section 5.2.1.2) for the manufacture and sale of pharmaceutical products, if those products are intended for export to importing countries that need access to those products to deal with public health problems. Decisions to grant, review, refuse and revoke these CLs are to be taken after consultation in the Belgian Council of Ministers (Art. XI.39 BCEL). Article 4 of EU Regulation No. 816/2006, however, provides that the eligible importing countries are those which have notified that they will make use of this provision. A number of high-income countries declared not to use this provision for import into their own country (in light of the fact that it was designed for providing access to medicines in low income countries with insufficient or no manufacturing capacity faced by public health problems). So, although no formal limitation exists on the countries that can invoke it, those high-income countries made that declaration. This is discussed more in detail below.

5.3.2 CLs and Import to Belgium

As mentioned in Section 5.2.1 the TRIPs Agreement was amended and introduced a waiver of the export restriction on medicines manufactured under CL in Article 31*bis*, which has been implemented into Belgian law in Article X1.39. The EU and its Member States, including Belgium declared, similar to other high-income countries, not to use this legislation for import, and are hence in view of this declaration ineligible to import medicines manufactured under a CL in another country. Assuming that that the condition for import "to deal with public health problems" would include issues of excessive pricing, which is not a given, the opt-out may have an impact on access to affordable generic medicines in these countries. As a corollary, this could then also be considered as potentially resulting in a higher price for the generics provided for other WTO Member States.

The opt-out has also attracted quite some attention in the context of the COVID-19 pandemic. On 7 April 2020, over 30 interest groups and 36 experts asked WTO members concerned "to notify the WTO that they have changed their policy and now consider [themselves] an eligible importing country, and in addition, to also use whatever legal means are available to revoke the opt-out as importing members, for goods manufactured under a compulsory licence".[259] The European Parliament also raised some

256 E. van Zimmeren et al. (2014), 'The BRCA patent controversies: an international review of patent disputes', in: S. Gibbon et al. (eds.), Breast cancer gene research and medical practices: transnational perspectives in the time of BRCA, London, Routledge, pp. 151-174.

257 For more information, see: E. van Zimmeren & Requena, 'Ex-offico Licensing in the Medical Sector: the French Approach', in: G. Van Overwalle (ed.), *Gene Patents and Public Health*, Brussels, Bruylant, pp. 123-147.

258 See for a rare occasion where a CL provision was successfully invoked in a public health case, the earlier mentioned German case *Shionogi v. Merck*, November 2017 and Section 5.4.7. However, the legal basis for that decision was grounded in a general public interest CL provision.

259 J. Love (2020), Open letter asking 37 WTO Members to declare themselves eligible to import medicines manufactured under compulsory license in another country, under 31bis of TRIPS Agreement, 7 April 2020, Knowledge Ecology International, available at: https://www.keionline.org/32707.

questions regarding this initiative.[260] For now, EU Member States did not really respond to this request.

In the doctrine, different views exist as to the possibility to opt-back in. Hu notes that in principle the ministerial Decision does not seem to prohibit members that opted out from opting back in, especially if the eligibility requirements as an importing country are fulfilled.[261] According to Hu WTO Members generally have the option under the Decision to modify their status as users of the system at any time.[262] Moreover, the establishment of "insufficient or no manufacturing capacity" must be product(s)-specific, which suggests manufacturing capacity circumstances may change, and thereby justifications to opt-in may arise over time. On the other hand, Abbott argues that Member States whose opt-outs are incorporated in the text of the Decision (including for the EU and its member states) would not be able to modify their status, in contrast to those that merely state their intention of opting out to the General Council.[263] Thus, it is unclear whether changing the opt-out would be a possibility. Given that making use in Belgium of a CL issued in another developed country may have significant economic[264] and political implications, it appears that an investigation into the applicability of this clause to situations of excessive pricing and the desirability of considering this change of policy should be weighed carefully.

5.3.3 *Legislative Proposal CLs*

In December 2018, a legislative proposal was submitted by parliamentary members stating that: "In order to protect public health and the financial capacity of social security and health insurance, it is proposed to expand the existing system of compulsory licensing. From now on, the Minister of Health will be able to impose compulsory licenses for a medicine, amongst others if there are serious indications that the sales prices used are disproportionate relative to the costs of production".[265] The legislative proposal is also aimed at speeding up the procedure and clarifying the process in case of a public health crisis. It maintains the role of the Advisory Committee on Bioethics in order to safeguard wide societal support. However, it proposes to enable the Minister to award the CL to a particular licensee by relying on an open competition organizing a public offer for the medicine concerned in order to ensure that the "best price" will be safeguarded. The procedure is, hence, different from the procedure described above both for the CL for public health reasons and for the other CLs, which all rely on the initiative by the licensee (see Section 5.3.1).

Below we provide a translation of the proposal in English (own translation):

260 European Parliament, Question for written answer E-000463/2021 to the Commission, 26 January 2021.

261 W. Hu (2020), Compulsory licensing and access to future Covid-19 vaccines, CEPS Research Report No. 2020/20, July 2020, p. 7.

262 See also: C.M. Correa (2020), Trade-Related Aspects of Intellectual Property Rights: A Commentary on the TRIPS Agreement, Second Edition, Oxford University Press, p. 318 and C. Garrison (2020), 'Never say never – Why the High Income Countries that opted-out from the Art. 31bis WTO TRIPS system must urgently reconsider their decision in the face of the Covid-19 pandemic', *Medicines Law & Policy*, available at https://medicineslawandpolicy.org/2020/04/never-say-never-why-the-high-income-countries-that-opted-out-from-the-art-31bis-wto-trips-system-must-urgently-reconsider-their-decision-in-the-face-of-the-covid-19-pandemic/.

263 F.M. Abbott (2005), 'The WTO Medicines Decision: World Pharmaceutical Trade and the Protection of Public Health', 99 *The American Journal of International Law*, p.336.

264 For more information regarding the economic implications of CLs, see hereinafter the report regarding the "economic consequences" by Van Dyck et al.

265 Belgium Parliament, Chamber of Representatives, Legislative Proposal to modify the Code of Economic Law regarding the application of compulsory licenses on medicines, 11 January 2019, DOC 54 3456/001. This proposal was reintroduced by Mr. Raoul Hedebouw, Marco Van Hees and Sophie Merckx in Belgium Parliament, Chamber of Representatives, Legislative Proposal to modify the Code of Economic Law regarding the application of compulsory licenses on medicines, 20 September 2019, DOC 55 0407/001.

In Article XI.38 of the Belgian Code Economic Law, inserted by the law of 19 April 2014, the following changes are introduced: 1° paragraph 12 is replaced as follows:

> *"§ 12. Notwithstanding the previous paragraphs, the Minister responsible for Public Health, without prior request, on his/her own initiative or at the request of the Minister responsible for Social Affairs, for reasons of public health and in view of the need to control social security spending, especially when there are serious indications that the selling price of a patented medicine on the Belgian market is 33% more than the total production costs of this product, can grant by Ministerial decree a license to exploit and apply an invention which is protected by a patent for the means, products, processes and methods mentioned in § 1, a), b) and c).*
>
> *Before deciding on the grant of the compulsory license referred to in the previous paragraph, the Minister consults the Minister responsible for Social Affairs and informs the Advisory Committee on Bioethics of his intention to grant a compulsory license. He also informs the owner of the patent that is the subject of the compulsory license about this intention and invites him to express his point of view to the Advisory Committee on Bioethics in this regard with copy to himself, within a time period of one month.*
>
> *The Advisory Committee on Bioethics provides the Minister with a reasoned and non-binding advice on the intention to grant a compulsory license within a period of two months counting from the date on which the Committee was notified of this intention.*
>
> *After the expiry of the period referred to in the previous paragraph, the Minister decides on the grant of the compulsory licence. If the Minister decides to grant this licence, he determines the duration, the scope and the other terms of use of that license.*
>
> *The minister grants the compulsory license on behalf of the State to a licensee through a competition in accordance with the Law of 17 June 2016 on public procurement.*
>
> *Sections 4 and 5 of this article apply to the compulsory licenses referred to in this section.*
>
> *The decisions resulting from the procedures described in this section are published in the Belgian Official Gazette and mentioned in the Collection. The grant of compulsory licenses, as well as the decisions related thereto, are published in the register.*
>
> *The compulsory license enters into force from the date of exploitation, unless the Minister gives effect to it from the date on which it was awarded.*
>
> *If new elements would arise, the Minister may, on his own initiative, on request of the Minister responsible for Social Affairs, or at the request of the holder of the patent or compulsory license, and in accordance with the procedure described in the second to fourth sections of this paragraph, by ministerial decree, proceed with a review of the exploitation conditions of the compulsory licence.*
>
> *If the holder of the compulsory license does not proceed to exploit the patented invention within a reasonable period of time after the license has been awarded, the Minister may, by ministerial decree, revoke the compulsory license";*
>
> *2° the article is supplemented by a paragraph 13, stating:*
>
> *"§ 13. Articles XI.37 and XI.40 to XI.46 are not applicable to the compulsory licenses contemplated in this article. The provisions of this article do not apply to the compulsory licenses contemplated by the Articles XI.37, XI.40 to XI.46."*

After careful analysis of this proposal, we would like to highlight **a number of observations based on the initial legislative proposal.**

First, the legislative proposal modifies the CL for **public health reasons**. Our research shows, however, that other grounds such as public non-commercial use (government use), abuse or anti-competitive practices may be alternative grounds to consider. These grounds may have certain advantages over the ground regarding public health reasons, as they do not require prior negotiations before the grant of the CL. This is an important

issue, as the proposal does not seem to require prior negotiations, which may not be compatible with the relevant provision of the TRIPs Agreement, which does require such prior negotiations in case a CL is granted for public health reasons.[266] Moreover, the concept of "abuse" may provide a link to the analysis by competition authorities of anti-competitive practices, such as excessive pricing practices (see Section 5.2.2.5). Finally, public non-commercial use (government use) is used by other WTO Member States, where the government authorizes a government department or a commercial contractor to use a patented invention without the consent of the patent owner and with a non-commercial purpose to the benefit of the general public. This is in many cases the most simple manner to address an urgent public need, because it can be decided by the government *ex officio* without the need for a third party's request and without a need to first enter into negotiations with the patent owner. Government use frameworks tend to employ public procurement competitions in a similar way as proposed here in the proposal. Therefore, arguably the proposal should be distinguished from a more 'classical' CL where a potential licensee would first start negotiations with the IP owner and after reasonable efforts to negotiate a license would apply for a CL. Based on the above, it seems relevant to reconsider whether public health is the most appropriate ground for a CL for excessive pricing or whether public non-commercial use (government use) or anti-competitive practices/abuse would be more suitable.

Second, it is unclear why the assessment of excessive pricing should be based on "serious indications that the selling price of a patented medicine on the Belgian market **is 33% more than the total production costs of this product**". It is noted that no details are provided as to how the total production costs of the product are analyzed and on the basis of what kind of data. According to an amendment of the legislative proposal of 9 February 2021 (DOC 55 0407/003) this threshold would no longer be maintained and the criterion would be broadened again to public health reasons. The notion of "public health reasons" would be understood as covering excessive prices as well.

Third, the proposal indicates that the Advisory Committee on Bioethics needs to provide the Minister with a reasoned advice on the intention to grant a CL. The members of this committee have extensive **expertise** in bioethics, but no evidence exists as to their skills of assessing the total production costs and the selling price of a pharmaceutical. It may be worthwhile to reconsider the role of the Advisory Committee on Bioethics for excessive pricing cases or to complement their expertise with experts in pricing and reimbursement, health (economic) experts and patent and competition experts.

Fourth, if the Minister decides to grant the CL, (s)he determines the duration, the scope and the other terms of use of that license. The terms of use probably also cover the remuneration that needs to be paid to the patent owner. Interestingly, whereas TRIPs refers to "adequate remuneration", Article XI.38 BCEL refers to "**reasonable**" remuneration. It would be desirable to get some more guidance as to how this "reasonable" remuneration needs to be calculated, on the basis of which method and by whom. Moreover, it is not clear whether the Minister will be required to seek any advice on these aspects and if so, from whom? The Advisory Committee on Bioethics does not seem particularly suited to assess and propose these conditions that are crucial for both the patent owner and the licensee.

Fifth, the **criteria** that will be employed in the **public procurement** competition foreseen in the proposal are not specified. It appears however that the competition would – at least – include a price/quality assessment with the guarantee that it will be sold at a price below 1.33 times the production cost, which is the criterion included in the initial proposal. In addition, these types of competitions can take a lot of time; so the CL may drive down the costs ultimately, but it may still take rather long before access

266 In an amendment of the legislative proposal of 9 February 2021 (DOC 55 0407/003) this issue has been overcome by adding a requirement of prior negotiations.

to affordable medicines for the patients is effectively safeguarded. So indicating a timeframe in the legislation for running the competition seems desirable.

Sixth, if **new elements** would arise, the Minister may proceed with a review of the exploitation conditions of the CL. Nonetheless, it is unclear what would qualify as a new element. Assume, for instance, that the patent owner decides to lower the price. If in the meantime the licensee has invested significantly to ensure production, it seems objectionable to suddenly change the conditions of the license at that moment. Alternatively, would it also be possible to cancel the CL in case of new elements?

Finally, if the holder of the CL does not proceed to exploit the patented invention within a reasonable period of time after the license has been awarded, the **Minister may revoke the CL.** What would happen in case the licensee would not sufficiently exploit the invention? Can such a situation also lead to revoking the CL? The sanction may have significant disadvantages and it seems more desirable for the government to be able to transfer the CL to another licensee so the whole procedure does not have to start over. Article 31 TRIPs excludes this option, however, as CLs need to be non-transferable.

5.3.4 Recommendations regarding the CL Mechanism for Public Health in Belgium and the Legislative Proposal for Excessive Pricing

In view of the deficiencies identified in the previous sections above for the CL for public health reasons and the legislative proposal on excessive pricing, several modifications and/or clarifications both regarding the CL for public health reasons in general and specifically for the excessive pricing proposal are suggested, relating to the material rules, the procedure and the relevant governance mechanisms.

5.3.4.1 General Recommendations for CL Mechanism Public Health

The Belgian legislation does not contain a definition or some examples as to what can be considered **"public health reasons**". This is quite remarkable as the introduction of the CL for public health reasons was inspired by the French legislation, which does refer to specific situations where the license could be issued (see Section 5.4). In the parliamentary documents reference is made to some examples, such as in case of insufficient stocks, if the quality of the drug is insufficient or in case of abnormally high prices. It could be useful for the Advisory Committee to provide more legal certainty and to provide guidelines with a (non-exhaustive) list of cases where this CL mechanism would be considered applicable.

It seems necessary to include some guidelines as to how the **reasonable/adequate remuneration** is calculated, on the basis of which method and data and by whom. The key question is of course what is "reasonable" or "adequate"; a selection could for instance be made in the above mentioned WHO Guidelines where various methods are specified. However, to determine what is reasonable, access to data regarding the direct and indirect costs and reasonable rates of return is required, which will be difficult. Moreover, the licensee needs to get access to the know-how and needs to make significant investments. One may wonder whether that leaves sufficient ground for a reasonable remuneration of the patent owner while safeguarding the cost-effectiveness of the drugs production. It is unclear whether the Minister gets any advice on what is "reasonable" and if so, by whom.

It should be considered whether the **Advisory Committee on Bioethics,** which in the proposal gives (non-binding) advice to the Minister regarding the "merits" of the CL for public health reasons, is indeed the most appropriate actor for giving advice as to whether the grant of a CL for "public health reasons" is justified, what should be the "reasonable remuneration" and the scope, duration and terms of use of the license. It would be desirable to have a committee with a mixed expertise.

A request for the grant of a CL for public health reasons may arise in urgent circumstances or an emergency situation. The current procedure does not foresee a clear procedure in case of an **emergency or situation of extreme urgency** to speed up the process. Clarification of an emergency procedure

(e.g. need for or timing of the advice from the Advisory Committee on Bioethics) seems desirable.[267]

In Section 3.4 we described common patenting practices, showing that increasingly medicines will be covered by a **portfolio or cluster of granted patents and patent applications** rather than one patent. Therefore, it appears desirable to clarify in the BECL that CLs can relate both to one patent/patent application, but, where clusters of patents/patent applications are relevant, will apply to every relevant patent of a given patent owner. As such this does not seem to be excluded by the text of the TRIPs Agreement, as the decision to grant a CL would still be made on case-by-case basis.

No arrangements seem to exist for **coordination or exchange of information with other regulatory actors or stakeholders** in deciding on the grant of a CL (e.g. health authorities, competition authorities, patent office). If the CL for public health reasons would be used more in the future, it would be vital to ensure such coordination to ensure that actors can benefit from the available expertise and that complementary mechanisms are applied in an effective manner.

No arrangements exist to **safeguard access to relevant know-how** in addition to information disclosed in the granted patents/patent applications. As was explained in Sections 3 and 4 trade secret protection is an important complement and organizations carefully define what they claim and disclose in their patent applications. It is quite unlikely that the licensee will be able to manufacture the medicines based on the information disclosed in the patents, publicly available information or CTD. Robust arrangements to safeguard access to CTD to enable the licensee to apply for an MA, are lacking as well even though transparency has been increasing recently with the adoption of the Clinical Trials Regulation, the rules adopted by EMA and the case-law of the CJEU (see Section 4.3.2). Perhaps this growing transparency in the pharmaceutical sector could be pursued further through coordination with EMA. Moreover, in order to speed up the process for licensees with a CL applying for an MA, EMA and national authorities could be invited to prioritize such applications for their accelerated assessment procedures.[268]

No regulatory arrangements exist to ensure that a licensee can actually get a MA in view of the lingering **regulatory exclusivities**. However, this is a problem which cannot be solved by the Belgian legislator and would need to be negotiated at the EU level (see Section 5.6 regarding the waiver of data and market exclusivity).

5.3.4.2 Specific Recommendations Proposal CL Excessive Pricing

One of the key challenges is to determine the **threshold for what is an excessive price**. The original proposal refers to “serious indications that the selling price of a patented medicine on the Belgian market is 33% more than the total production costs of this product”. It is unclear how this criterion has been set and it would be desirable to review it in the light of the case-law of competition authorities regarding excessive pricing practices. This case-law also provides extensive insights as to how the costs can be calculated, although not one uniform method has been adopted in practice.

The decisions of competition authorities clearly show the importance of having **access to data regarding the costs**. Those authorities have extensive investigation powers to collect commercial confidential information regarding costs and prices. Yet, they still note the challenges in identifying, collecting and analysing such data. The CL procedure for public health reasons does not contain any requirements to provide appropriate

267 In an amendment of the legislative proposal of 9 February 2021 (DOC 55 0407/003) this issue has been overcome by adding an additional section on the applicable procedure in case of a health crisis.

268 See for instance also EMA’s PRIME scheme established to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier. For more information, see: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines.

information to assess the pricing practices. Without such requirements or staff with special investigatory powers (cf. Commission CLs) it will basically be impossible to make such an assessment. Alternatively, the burden of proof may be imposed on the pharmaceutical company to show that the price is not excessive but reasonable in view of the circumstances of the case comparing the costs and prices to specific benchmarks (i.e. competing products, products sold in other countries (see Section 5.2.2.5 and Appendix 1 for more inspiration).

The CL procedure is **initiated by the government** and prescribes the use of the public procurement competition procedure. In the initial legislative proposal, no requirement for prior negotiations was included. [269] This process seems to be based more on the French ex officio regime or government use provisions in other countries than on a traditional CL mechanism. It would be desirable to clarify whether the proposal constitutes a government use provision or a CL mechanism as the current set-up seems to be more in line with what is common for government use.

Given that the proposal appears to rely heavily on the **procedure of the public procurement competition procedure**, it is essential to verify to what extent this procedure is aligned with the needs and characteristics for granting a CL (e.g. timeframe, criteria for award, non-exclusivity,[270] etc.).

In Section 5.3.3 several questions are raised regarding the **review of the CL by the Minister in case "new elements"** would arise and the implications of such a review. For reasons of legal certainty a clarification of what may constitute such a new element, the process of the review and its potential consequences is necessary.

5.4 CLs for Public Health & Excessively Priced Medicines in Other Countries

Most countries around the world have several legal bases for applying for CLs. Over time different public and private organizations have made review studies of the available CL regimes around the world (see **Box 2**). Therefore, this project has closely studied those reports, but does not provide an exhaustive overview of all available, potentially relevant CL regimes.

Box 2 – Overview Studies of CLs

WIPO

Database on Flexibilities in the Intellectual Property System https://www.wipo.int/ip-development/en/agenda/flexibilities/search.jsp?field_id=2343&type_id=2349&territory_id=

Survey https://www.wipo.int/edocs/mdocs/mdocs/en/cdip_4/cdip_4_4_rev_study_inf_5.pdf

EPO

European Patent Office, Compulsory licensing in Europe: A country-by-country overview, Munich, 2018: http://documents.epo.org/projects/babylon/eponot.nsf/0/8509F913B768D063C1258382004FC677/$File/compulsory_licensing_in_europe_en.pdf

CMS

The Compulsory Licensing eGuide, 2021: CMS Compulsory Licensing Global E-Guide Feb 2021 (1).pdf

269 We note, however, that in an amendment of the legislative proposal of 9 February 2021 (DOC 55 0407/003), a requirement of prior negotiations has been added.

270 In an amendment of the legislative proposal of 4 February 2020 (DOC 55 0407/002) this issue has been overcome by clarifying that the applicable procedure will be described in separate regulations.

The overview studies show a wide diversity of grounds that could in theory be used if a case arises where access is denied or excessively high prices are charged. Different grounds that can be identified are the following:

- failure to work or insufficient working
- public non-commercial use
- public interest/public health
- excessive pricing
- national emergency and extreme urgency
- anti-competitive practices

In Section 5.4.1 we provide a comparative analysis of CL mechanisms in various countries as far as relevant for the question related to the availability and affordability of medicines. The selection of countries is made on the basis of the different studies mentioned in Box 2. Particular attention was paid to countries where a dedicated CL mechanism exist for public health reasons or in particular high/excessive prices. In addition, key EU countries are included, several emerging economies and the UK and US. This comparative analysis is complemented by a qualitative analysis of several cases in Appendix 3.

5.4.1 Key CL Mechanisms

Table 2 included as Appendix 2 shows that basically all selected countries have established CLs for failure to work and public interest. In many cases, the legislation explicitly allows for imports to fulfil the working requirements. Some countries refer more generally to public interest, whereas others have specific CLs for public health.

Only a few countries have specific provisions on public non-commercial use/government use. However, some countries, such as for instance Ireland and the UK (so-called crown use) have rather detailed rules in their patent act related to government use and the criteria and conditions for such government use. Different from most other countries the US has no legal basis for granting CLs based on requests from interested parties but has a kind of *sui generis* regime based on government use (28 U.S.C § 1498(a)). This government use provision has been used extensively in the past, which may seem contradictory to the fierce opposition of the US to the use of CL mechanisms by other countries. In addition, 35 U.S.C. § 203 (Bayh- Dole Act of 1980) allows the US government to exercise so-called 'march-in rights' for any invention conceived or first reduced to practice in the performance of work under a federal funding agreement. Although this provision can only be invoked in specific circumstances, both US scholars[271] and politicians[272] have argued in favour of applying this provision (next to government use)[273] to ensure access to and affordability of medicines. Nonetheless, to date, government agencies have not exercised their march-in rights.

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271 See for instance: J. Penman & F. Quigley (2017), 'Better Late than Never: How the U.S. Government Can and Should Use Bayh-Dole March-In Rights to Respond to the Medicines Access Crisis', 53 *Willamette Law Review*, available at: https://ssrn.com/abstract=2928019. Differently: R.J. Ryan (2020), 'Marching Towards Disaster: Examining the Commerce Department's Administration of the Bayh-Dole Act and Whether March-In Rights Should Be Used to Reduce Drug Costs', available at: https://ssrn.com/abstract=3752916

272 See for instance a recent report by Secretary Xavier Becerra, U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, *Report To The White House Competition Council, Comprehensive Plan for Addressing High Drug Prices. A Report in Response to the Executive Order on Competition in the American Economy*, 9 September 2021, available at: https://aspe.hhs.gov/sites/default/files/2021-09/Competition%20EO%2045-Day%20Drug%20Pricing%20Report%209-8-2021.pdf.

273 See for instance: H. Brennan et al. (2016), 'A Prescription for Excessive Drug Pricing: Leveraging Government Patent Use for Health', 18 *Yale J. L. & Tech.* 275, available at: https://ssrn.com/abstract=2832948.

As the mechanisms are different and there tend to be fewer restrictions around government use than for CLs applied for by interested parties (e.g. timing and steps that must be taken prior to allowing such use), such provisions can be more easily applicable to emergency situations than the classical CLs. Therefore, within the context of the COVID-19 pandemic these provisions have also been considered as potential mechanisms to safeguard availability of certain patented products[274] and may also be relevant within the context of excessive pricing. Moreover, UK experts point to the fact that as Section 56(2)(b) clarifies that "'the services of the Crown" include "the production or supply of specified drugs and medicines", even if a product is protected by multiple patents, this would enable the government to provide authorisation without requiring specific knowledge of each potentially infringed patent.[275] This would provide more flexibility than would be possible with a CL system based on the request by an interested party which is limited to a specific patent.

Our comparative analysis of CL and government use mechanisms in other countries revealed only five examples of CL provisions that explicitly mention excessive pricing as a ground or example of a reason to grant a CL for public health reasons (France, cf. Belgian proposal). These provisions are reproduced in the box below. Interestingly, the exact terminology in each of the provisions is different. Moreover, in none of the countries a definition or threshold is provided to assess the excessive nature of the prices similar to the 33% threshold provided in the original Belgian proposal. Moreover, the procedure for granting such a CL is generally not described at all in the patent legislation or not in great detail and no reference is made to a step involving an Advisory Committee or a public procurement procedure as specified in the Belgian proposal.

Box 3 – CL Mechanisms for Excessive Pricing in Other Countries

Article L613-16 Intellectual Property Code France

Si l'intérêt de la santé publique l'exige et - défaut d'accord amiable avec le titulaire du brevet, le ministre chargé de la propriété industrielle peut, sur la demande du ministre chargé de la santé publique, soumettre par arrêté au régime de la licence d'office, dans les conditions prévues - l'article L. 613-17, tout brevet délivré pour :

- Un médicament, un dispositif médical, un dispositif médical de diagnostic in vitro, un produit thérapeutique annexe ;
- Leur procédé d'obtention, un produit nécessaire - leur obtention ou un procédé de fabrication d'un tel produit ;
- Une méthode de diagnostic ex vivo.

Les brevets de ces produits, procédés ou méthodes de diagnostic ne peuvent être soumis au régime de la licence d'office dans l'intérêt de la santé publique que lorsque ces produits, ou des produits issus de ces procédés, ou ces méthodes sont mis à la disposition du public en quantité ou qualité insuffisantes ou à ***des prix anormalement élevés***, ou lorsque le brevet est exploité dans des conditions contraires à l'intérêt de la santé publique ou constitutives de pratiques déclarées anticoncurrentielles - la suite d'une décision administrative ou juridictionnelle devenue définitive. Lorsque la licence a pour but de remédier à une pratique déclarée

274 Nonetheless, it turned out that CLs and government use are not a very efficient tool to use in emergency situations. See e.g. Matthews, Duncan (forthcoming), 'The Covid-19 Pandemic: Lessons for the European Patent System', Queen Mary Law Research Paper No. 377/2022, available at: https://ssrn.com/abstract=4022509.

275 'Crown Use during the coronavirus (COVID-19) pandemic', 9 April 2020, available at: https://www.mewburn.com/news-insights/crown-use-during-the-coronavirus-covid-19-pandemic. Moreover, in this post the authors also refer to a recent case in which the defendants successfully invoked a crown use defence before the High Court of Justice in a case related to SIM cards enabling privileged access to a mobile network in the event of a major incident being declared, IP Com v. Vodafone, 28 January 2020, available at: https://www.bailii.org/ew/cases/EWHC/Patents/2020/132.html.

anticoncurrentielle ou en cas d'urgence, le ministre chargé de la propriété industrielle n'est pas tenu de rechercher un accord amiable.

Section 84 Patent Act India

1. At any time after the expiration of three years from the date of the grant of a patent, any person interested may make an application to the Controller for grant on compulsory license on patent on any of the following grounds, namely:-
   a. that the reasonable requirements of the public with respect to the patented invention have not been satisfied, or
   b. that the patented invention is not available to the public ***at a reasonable price,*** or
   c. that the patented invention is not worked in the territory of India.[…]

Article 68 Patent Act Poland

2. The patent holder or the licensee **may not abuse his rights,** in particular by preventing the invention from being exploited by a third party, if such exploitation is necessary for the purpose of meeting home market demands and is particularly dictated by public interest considerations, and consumers are supplied with the product in insufficient quantity or of inadequate quality, or at ***excessively high prices.***
3. Preventing third parties from exploiting the invention within a period of three years from the date of the grant of the patent shall not be considered the abuse of rights, referred to in paragraph (1).
4. The Patent Office shall have the right to request a patent holder or a licensee to submit any explanations as to the scope of the exploitation of the invention for the purpose of establishing whether or not the patent is abused.
5. The provisions of paragraphs (1) and (2) shall not prejudice the provisions on counteracting monopolistic practices.

Article 56 Patent Act South-Africa

Compulsory licence in case of abuse of patent rights.

1. Any interested person who can show that the **rights in a patent are being abused** may apply to the commissioner in the prescribed manner for a compulsory licence under the patent.
2. The rights in a patent shall be deemed to be abused if-
   a. the patented invention is not being worked in the Republic on a commercial scale or to an adequate extent, after the expiry of a period of four years subsequent to the date of the application for the patent or three years subsequent to the date on which that patent was sealed, whichever period last expires, and there is in the opinion of the commissioner no satisfactory reason for such non-working;
   b. [Para. (b) deleted by s. 45 (b) of Act No. 38 of 1997.]
   c. the demand for the patented article in the Republic is not being met to an adequate extent and on reasonable terms;
   d. by reason of the refusal of the patentee to grant a licence or licences upon reasonable terms, the trade or industry or agriculture of the Republic or the trade of any person or class of persons trading in the Republic, or the establishment of any new trade or industry in the Republic, is being prejudiced, and it is in the public interest that a licence or licences should be granted; or
   e. the demand in the Republic for the patented article is being met by importation and the price charged by the patentee, his licens***ee or agent for the patented article is excessive in relation to the price charged therefor in countries where the patented article is manufactured by or under licence from the patentee or his predecessor or successor in title***.[…]

Section 46 Patent Act Thailand

At any time after the expiration of three years from the grant of a patent or four years from the date of application, whichever is later, any person may apply to the Director-General for a license if it appears, at the time when such application is filed, that the patentee unjustifiably fails to exercise his legitimate rights as follows:

1. that the patented product has not been produced or the patented process has not been applied in the country, without any legitimate reason; or
2. that no product produced under the patent is sold in any domestic market, or that such a product is sold but ***at unreasonably high prices*** **or** does not meet the public demand, without any legitimate reason.

Whether it is an application under (1) or (2), the applicant for a license must show that he has made an effort to obtain a license from the patentee having proposed conditions and remuneration reasonably sufficient under the circumstances but unable to reach an agreement within a reasonable period. The application for a license shall comply with the rules and procedures prescribed in the Ministerial Regulations.

It is interesting to note that the original Belgian provision regarding CLs for public health does not explicitly mention "abnormally high prices" even though it was inspired by the French mechanism in Article L.613-16 French Intellectual Property Code. The French procedure for applying for a so-called 'ex officio license' shows similarities to the recent Belgian proposal regarding excessive pricing. It consists of a two-step administrative procedure (Art. L.613-18 French Intellectual Property Code).[276] First, the Minister of Health makes the request to the Minister of Economy and Finance, who can then submit the patents in question to the ex officio license regime by way of an order. Then, a call for candidates must ensure that the license is granted to any qualified third party. In the absence of an amicable agreement on the price, the amount of royalties is set by the court. Similar to the observations on the limitations of CL that are being made in the present report, experts have criticized the French ex officio regime for various reasons, including (1) the need to create more flexibility in the conditions, and allow explicitly its use in case of national (health) emergencies or extreme urgency, (2) the need to add patent applications in the relevant provisions and not only granted patents; (3) the need to foresee regulatory arrangements to overcome data and market exclusivity allowing the licensee to, apply for a temporary use authorization; (4) the need for the licensee to have access to all the documents and data necessary to file an application and obtain MA; and (5) the need for access to know-how in addition to the knowledge disclosed in the patent (application). In December 2020, some changes have been made through the introduction of Art. L.3131-15 French Public Health Code, but additional modifications to Art. L613-16 French Intellectual Property Code would be required to improve the functioning of the ex officio licensing mechanism.[277]

Overall the number of granted CLs is relatively low, in particular in high-income countries, even though the legal bases for CLs are quite common. In many countries, potential licensees have applied for CLs, in particular for failure to work, but often they did not succeed. Some notable exceptions are CLs in Brazil related to efavirenz, an anti-retroviral drug. Here parties invoked public interest/public non-commercial use, as the medicines were being sold at a much lower price in other countries. The royalty was set at 1,05% of the price of the delivered product. In Denmark three cases have

276 For more information, see: E. van Zimmeren & Requena, 'Ex-offico Licensing in the Medical Sector: the French Approach', in: G. Van Overwalle (ed.), Gene Patents and Public Health, Brussels, Bruylant, pp. 123-147.

277 See for instance: M. Dehenne (2021), French bill proposal authorizing the granting of an ex officio license in the interest of public health in the event of an extreme health emergency, Kluwer Patent Blog, 28 April 2021, available at: http://patentblog.kluweriplaw.com/2021/04/28/french-bill-proposal-authorizing-the-granting-of-an-ex-officio-license-in-the-interest-of-public-health-in-the-event-of-an-extreme-health-emergency/.

been reported, two of which in the pharmaceutical sector. One dates back to World War II and is not considered to be of general application.[278] The other one is described briefly in Appendix 3. For Germany, two key CL cases related to drugs are reported and discussed in Appendix 3. In the Netherlands, an old case from 1970s provides some interesting insights regarding the notion of public interest linked to abuse, in particular in case of high prices.

Despite the existence of dedicated CL provisions related to 'abnormally high prices', 'unreasonable', 'unreasonably high', 'excessive' or 'excessively high' prices in certain countries, not many CLs have effectively been granted on the basis of these provisions either. In France, some CLs have been granted in the past but for failure to work and not in the pharmaceutical sector. In India, the ground related to unreasonable pricing has been invoked in various CL procedures but has only been granted once (see Appendix 3).[279] No Polish CL cases have been reported. In South-Africa, several CL cases have taken place, some related to excessive prices charged,[280] some related to failure to work the patent.[281] Between 2006 and 2008, the government of Thailand granted a series of CLs to allow the import of generics equivalents of seven drugs that were patent protected and used in the treatment of HIV/AIDS (efavirenz (marketed as Sustiva by Merck) and lopinavir/ritonavir (marketed as Kaletra by AbbVie, then Abbott Laboratories).[282]

Procedures for granting CLs also vary to a great extent: in some countries CLs are granted by the patent office (e.g. Austria, Thailand, South-Africa, India, UK), in other countries by a Minister (e.g. Belgium, France) or by a court (e.g. The Netherlands). In most patent acts the procedure is not described in great detail. Apart from the basic requirements listed in the TRIPs Agreement limited information is available about the procedure or the actual criteria used for granting a CL. The Irish, Indian, French and Spanish legislation provide, however, more detailed rules. The Spanish procedure even involves a detailed procedure for mediation by the registry of industrial property and provisions that promote the application for CLs (Art. 107 Spanish Patent Act).[283] In practice, this does not seem to have resulted in a substantial number of CL grants in Spain.

278 U.1943.752/2H, reported in EPO (2019), *Compulsory licensing in Europe: A country-by-country overview*, available at: https://www.neo.law/wp-content/uploads/2019/02/compulsory_licensing_in_europe_en.pdf.

279 *Natco Pharma Ltd. v. Bayer Corporation*, Order No. 45/2013 (Intellectual Property Appellate Board, Chennai), 4 March 2013.

280 *Cipla v. GlaxoSmithKline South Africa* (PTY) LTD, Government Notice 562 in Government Gazette 22128 dated 9 March 2001, ground: excessive pricing (art. 7 and 8 Competition Act); license granted, but not executed - voluntary license by the proprietor; *Afritra (Pty) Ltd and Another v. Carlton Paper of SA* (Pty) Ltd. 1992 BP 331 (CC) – CL not granted, as an excessive price cannot be established only on the basis of an argument that the applicant can sell the same product at a lower price. Other factors have to be taken into consideration, such as the cost of production and marketing of the article, and terms and conditions of the negotiations.

281 Syntheta (Pty) Ltd v. Janssen Pharmaceutica NV & Another 1998 BIP 264; Sanachem (Pty) Ltd. v. British Technology Group Plc 1992 BP 279 (CC).

282 Grounds: public non-commercial use, excessive pricing, License granted.

283 For more information, see: https://wipolex.wipo.int/fr/text/469266

5.5 CLs for Public Health & Excessively Priced Medicines in the Netherlands

In addition to the comparative overview regarding CL and government use mechanisms in the previous section, we would like to highlight specifically the developments in the Netherlands, where there has also been a very vivid debate on the affordability of medicines and various advisory reports regarding mechanisms that can be used to safeguard fair drug prices, including CLs.

This debate has resulted in the identification of a "multilevel toolbox"[284] of various measures, including a proposal regarding CLs. In Table 1 this toolbox is briefly described. It goes beyond the scope of the current report to describe each of these measures in depth. However, it is interesting to compare the Belgian proposal regarding CLs with the Dutch proposal regarding CLs, which provided a more encompassing multilevel toolbox. Moreover, already intense collaboration and coordination with the Netherlands exist (e.g. BeNeLuxA) and both Belgium and the Netherlands are rather small high-income markets.

Table 2 – Multilevel Toolbox Minister Medical Care of the Netherlands (2018)[285]

In the proposal of the Dutch Minister for Medical Care the following mechanisms are listed:

National measures:

1. Modification legislation drugs prices
2. Financial arrangement drugs
3. Modernization drug reimbursement system
4. **Price transparency (e.g. Fair Medicine Initiative)**
5. **Compulsory licensing**

Decentralized measures:

6. Transfer of expensive drugs from the extramural care to intramural care
7. Strengthening preference policy insurers, the procurement platform for expensive medicines and policy for procurement of medical devices
8. Further development of the system of barcoding of drugs and medical devices
9. **Facilitating pharmacy compounding**

International measures:

10. Study and monitor the impact of SPCs, data exclusivity and market exclusivity
11. Coordination of health technology assessments (HTAs) and price negotiations (e.g. BeNeLuxA and Horizon Scanning Initiative) – sharing technical expertise, exchanging best practices and price and market information; exploring common policy solutions and joint position statements

The proposal by the Dutch Minister for Medical Care contains a section regarding CLs as one of the different national measures envisaged. This section starts of by clarifying that the Dutch Council for Public Health and Society ('Raad voor Volksgezondheid en Samenleving') has issued an advice in favour of the use of CLs as one out of a number of measures when

284 The notion "multilevel toolbox" is actually not used in the Dutch proposal but proposed by the authors of this report for the purpose of the current report through it was inspired by the proposal by the Dutch Minister.

285 Brief van de Minister voor Medische Zorg, June 15th, 2018, Vergaderjaar 2017-2018, TK 29 477, 32 805, Nr. 489, pp. 3-15.

a patent holder maintains the intention to sell a patented drug at an excessively high price (July 2017)[286].

The letter from the Minister points out that CLs can only be used in exceptional situations if required by the public interest and that in practice in the Netherlands a CL has never been granted. Moreover, the Minister mentions that when a CL is granted, the licensee is still obliged to get MA and that data exclusivity and market exclusivity may be a barrier for getting a product on the market even if a CL is granted (as detailed in Chapter 4.2 and Section 5.6). While the Dutch Minister points out that these regulatory provisions are harmonized at the EU level, he wishes to explore the possibilities to create a waiver of data and market exclusivity at the EU level in cases where a CL is granted.[287] This is in line with our analysis in Section 5.6.

In view of the uncertainties regarding CLs, the Dutch Minister established an expert commission to examine the mechanism in a broader context, including a legal and an economic perspective.[288] Unfortunately, the expert commission did not manage to develop one joint opinion regarding these issues and encountered some procedural problems. Nonetheless, the chair of the commission, A. De Jong, shared his personal reflections on the topics discussed.[289] Even though these reflections cannot be attributed to the expert commission, and these relate in part to the efficacy of CLs as such, which is part of the economic study linked to this legal study, we provide some important points raised in these reflections below.

One of the important observations is that insufficient evidence is available regarding the impact of the use of CLs, either at a micro (case-by-case) basis or at a macro (investment and innovation climate and the long-term availability of drugs) level. De Jong also emphasizes the need for information about the use and pricing of drugs in general and the impact thereof on the quality of and the budget for healthcare. Moreover, he emphasizes the alternative route to address excessive pricing through competition law based on an alleged abuse of a dominant position by the pharmaceutical company concerned and he stresses the importance of collaborating with the competition authorities (i.e. waiting for outcome competition investigation, asking formal/informal advice from the competition authority, interim measures competition authority). Furthermore, De Jong refers to the above-mentioned multilevel toolbox approach when examining CLs and emphasizes (1) the potential of BeNeLuxA and expanding towards joint price negotiations and a broader EU 'coalition of the willing'; (2) the importance of transparency; (3) the need for expert advice on the factors determinant in the price negotiations (i.e. bandwidth socially responsible pricing); (4) the need for coordination between health and competition authorities. Finally, De Jong proposes an assessment framework (see Table 4 below) to determine whether the grant of a CL would be appropriate in a given case.

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286 Raad voor Volksgezondheid en Samenleving, *Development of New Medicines: Better, Faster Chea*per, July 2017, available at https://www.raadrvs.nl/documenten/publicaties/2017/11/09/ontwikkeling-nieuwe-geneesmiddelen.

287 See also: E.F.M. 't Hoen et al. (2017), 'Data exclusivity exceptions and compulsory licensing to promote generic medicines in the European Union: A proposal for greater coherence in European pharmaceutical legislation, 10 *Journal of Pharmaceutical Policy and* Practice, 19.

288 Brief van de Minister voor Medische Zorg, June 15th, 2018, Vergaderjaar 2017-2018, TK 29 477, 32 805, Nr. 489, p. 9. Questions for the expert commission related to the legal framework for CLs, the criteria for granting CLs, the consequences of invoking CLs for the pharmaceutical market and other domains, the proportionality of CLs and the availability of alternative legal instruments to stimulate the availability of expensive drugs and the success of such instruments. These questions are very similar to the questions covered in this report.

289 A. de Jong (2020), 'Persoonlike beschouwing over de inzet van de dwanglicenties bij hoge prijzen van medicijnen', ABDTOPConsult, June 2020, available at https://www.eerstekamer.nl/overig/20200702/persoonlijke_beschouwing_over_de/meta

Table 3 – Assessment Framework[290]

Questions
Proportionality: can the use of a CL be justified from the perspective of the relative size of the patient group, the impact of the patented drug on the health situation of the patient group in question and the budgetary impact?
Existence patent: is there a relevant patent preventing entry to the market and difficult to 'invent around'?
Manufacturing facilities/import: can the drugs be manufactured at a reasonable price and within a reasonable period of time by the potential holder of the CL? If not, can they be imported?
Other legal impediments: are there any legal provisions that will prevent the licensee from obtaining a MA e.g. trade secrets, data and market exclusivity?
Adequate remuneration: what are the costs associated with the grant of the CL?
Other risks: are there other risks involved in granting a CL? e.g. risk of late entry of medicines to Dutch market

This framework provides relevant criteria and considerations which are also reflected in the recommendations of the present report.

5.6 Implications Data & Market Exclusivities for Compulsory Licensing

At the moment, EU pharmaceutical legislation generally does not allow for exceptions to regulatory data and market exclusivities under the 8+2+1 regime. Most importantly, the EU framework, does not provide for any explicit waivers linked to CL regimes that apply within the EU territory. In contrast to provisions of CL aimed at addressing public health issues (including for export to address public health issues in countries outside the EU[291]), no exception to regulatory exclusivities exists that would apply to urgent situations, such as national health emergencies. However, Article 18 Regulation No. 816/2006 provides that applicants for CL to manufacture medicines in an EU Member State for export outside the EU may benefit from the scientific opinion procedure of the EMA or any similar national procedures intended exclusively for markets outside the EU. These scientific opinions provide a benefit/risk analysis of a medicine, designed to facilitate registration in importing countries. This procedure also allows for waivers to data exclusivity rules necessary to obtain such opinions from the EMA or national authorities. [292]

As was indicated above, the general lack of exceptions to regulatory data and market exclusivities may lead to tensions between the regulatory system on the EU level, which provides the basis for regulatory market- and data exclusivities, and the effective use of CLs with regard to patents blocking the production and use of generics and biosimilars, which still falls under the competences of the national legal systems.

A case that illustrates this dilemma very well, is the consideration of the Romanian government in 2016 to issue a CL for sofosbuvir to treat deadly

290 *Ibid*, at p. 33. Please note that the text in table 4 is not a literal citation from the report. The text has been slightly reorganized.

291 Regulation (EC) No. 816/2006 of the European Parliament and of the Council of 17 May 2006 on compulsory licensing of patents relating to the manufacture of pharmaceutical products for export to countries with public health problems [2006] OJ L157/1.

292 See E. 't Hoen (2022), 'Protection of Clinical Test Data and Public Health: A Proposal to End the Stronghold of Data Exclusivity', in: C.M. Correa & R.M. Hilty (eds.), *Access to Medicines and Vaccines,* Springer, Cham, available at: https://doi.org/10.1007/978-3-030-83114-1_7 (with further references and explanations).

infections with the hepatitis C virus (HCV). Sofosbuvir belongs to a new class of biologics which can eliminate the virus, and hence the cause of the disease, after a 12 week course of treatment. Previously only the symptoms of HCV infection could be treated. The Romanian considerations followed a 2016 WHO announcement proposing to eliminate HCV as a public health threat by 2030, targeting an 80% reduction in new chronic infections and a 65% reduction in mortality from 2015 levels.[293] The problem was that sofosbuvir could at that time only be purchased from the originator company at a price of around 50.000 euro for the 12 week antiviral treatment.[294] However, the regulatory data exclusivity for sofosbuvir expired only in 2022 and the regulatory market exclusivity would apply until 2024. Even with a CL, the registration and marketing of a sofosbuvir biosimilar would therefore not have been possible before 2022 and 2024 respectively. Since an independent development of a biologic with an equivalent effect and the generation of independent and new test data would have been prohibitively expensive, this implied that the Romanian state could not give any meaningful effect to a CL due to the protection granted by the 8+2+1 system for regulatory exclusivities.

Interestingly, other non- EU countries, such as Malaysia, did not encounter the same obstacles. In the case of Malaysia, this can be explained by having a closer look at Section 5 of the Malaysian 2011 Directive of Data Exclusivity[295] with the title "Non-Application" of Data Exclusivity. While acknowledging the availability of regulatory exclusivities, this provision stipulates that nothing in the Data Exclusivity shall:

1. (i) apply to situations where compulsory licenses have been issued or the implementation of any other measures consistent with the need to protect public health and ensure access for all; or
2. (ii) prevent the Government from taking any necessary action to protect public health, national security, non-commercial public use, national emergency, public health crisis or other extremely urgent circumstances declared by the Government."

Due to this legally codified waiver of data exclusivity, Malaysia was not prevented from registering the generic product when it granted a CL for sofosbuvir in 2017.[296] Similar legislation exists in Chili, and Columbia.[297]

The use of data exclusivity waivers in voluntary licensing set-ups and platforms, such as the Medicine Patent Pool (MPP)[298], is further indicative of the crucial role that regulatory data- and market exclusivities play for an effective promotion of access to medicine. The Medicines Patent Pool (MPP) is a United Nations-backed public health organization working to promote access to, and facilitate the development of, life-saving medicines for low- and middle-income countries.[299] To achieve these goals, the MPP collaborates with civil society, governments, international organizations, industry, patient groups, and other stakeholders to prioritize and license

293 A. Pedrana et al. (2016), 'The phases of hepatitis C elimination: achieving WHO elimination targets', 6(1) The Lancet Gastroenterology & Hepatology, 6-8 (citing WHO Global health sector strategy on viral hepatitis 2016–2021. https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/.

294 C. Paun (2016), 'Skyhigh drug prices made Romania mull unusual path', Politico, available at: https://www.politico.eu/article/high-drug-prices-romania-changes-patents-hepatitis/.

295 See: https://npra.gov.my/images/reg-info/DataEx/Directive_on_DE.pdf .

296 Y.B. Datuk Seri & S. Subramaniam, Press Statement of the Malaysian Minister of Health, 20 September 2017, – Implementation of the Rights of Government for Sofosbuvir Tablet to Increase Access for Hepatitis C Treatment in Malaysia, available at: https://kpkesihatan.com/2017/09/20/press-statement-minister-of-health-20th-september-2017-implementation-of-the-rights-of-government-for-sofosbuvir-tablet-to-increase-access-for-hepatitis-c-treatment-in-malaysia/.

297 For further examples and references with regard to Chile and Colombia, see: 't Hoen (2022), at p. 191 (with further references and explanations). See also previously: 't Hoen et al. (2017), at p. 19.

298 Medicines Patent Pool. http://www.medicinespatentpool.org/.

299 *Ibid.*

medicines and pool IP to facilitate the generic manufacture and the development of new formulations.[300] As of to date, the MPP has signed agreements with 13 patent holders for 13 HIV antiretrovirals, one HIV technology platform, three hepatitis C direct-acting antivirals, a tuberculosis treatment, two long-acting technologies, two experimental oral antiviral treatments for COVID-19 and a COVID-19 serological antibody diagnostic test.[301] Some licenses under the MPP also include waivers of regulatory exclusivities.[302] Moreover, Gilead has included the following waiver of data exclusivity in its license agreements for low income countries for the aforementioned *sofosbuvir*:

> *"Gilead agrees to provide Licensee with NCE Exclusivity, or other regulatory exclusivity, waivers as may be required by the applicable regulatory authorities in order to manufacture or sell Product in the Territory, provided such manufacture and sale by Licensee is compliant with the terms and conditions of this Agreement. Licensee agrees not to pursue or obtain regulatory exclusivity on any Product in any country within the Territory."*[303]

Similarly, several Free Trade Agreement (FTAs) that have been concluded by the US[304] and Europe[305] with third countries also allow for explicit public health exceptions to data/market exclusivity and corresponding waivers in the event of a CL. For example, Article 231(4) of the EU-Peru Agreement stipulates:

> *'[t]he Parties may regulate exceptions for reasons of public interest, situations of national emergency or extreme urgency, when it is necessary to allow access to those data to third parties".*[306]

Considering the above, it is not surprising that influential authors recommend the introduction of explicit provisions on data and market exclusivity waivers into national CL regimes.[307] These authors also highlight that it has become more important than ever for the EU and its member states to consider such an option. In fact several EU countries have indicated that they lack the negotiating power to obtain good results in price negotiations with pharmaceutical companies and several countries are exploring to amend CL provisions to strengthen this position.[308] 't Hoen et al.[309] therefore propose to codify an amendment to the EU medicines regulation that would follow the example of the Regulation No. 816/2006 on the CL for export to countries with public health problems and introduce the following waiver to regulatory exclusivities:

> *"The protection periods set out in article 14 (11) of Regulation 726/2004 shall not apply in cases where it is necessary to allow access to and the use of pharmaceutical test data to register a generic*

300 *Ibid*.

301 *Ibid.*

302 See 't Hoen (2022), at p. 195 (with further examples).

303 License agreement. Gilead. 2014, available at: https://www.gilead.com/~/media/files/pdfs/other/2014_original_hcv_licensing_agreement.pdf?la=en.

304 The United States-Peru trade promotion agreement implementation act: Statement of administrative action. Office of the U.S. Trade Representative. 2007, available at: https://ustr.gov/archive/assets/Trade_Agreements/Bilateral/Peru_TPA/PTPA_Implementing_Legislation_Supporting_Documentation/asset_upload_file194_15341.pdf.

305 European Union, Trade Agreement between the European Union and its Member States, of the one part, and Colombia and Peru, of the other part, [2012] OJ 354:3-2607, Article 231(4): '[t]he Parties may regulate exceptions for reasons of public interest, situations of national emergency or extreme urgency, when it is necessary to allow access to those data to third parties.'

306 *Ibid.*

307 See 't Hoen (2022), at p. 191 (with further references and explanations).

308 E. Rumney, 'Drug manufacturers have too much power in price negotiations, says OECD', https://www.publicfinancefocus.org/news/2017/01/drug-manufacturers-have-too-much-power-price-negotiations-says-oecd (accessed 31 January 2022).

309 See 't Hoen (2022), at p. 191 (with further references and explanations).

of a reference medicinal product, which is or has been authorised under article 6 of Directive 2001/83/EC, for reasons of public interest including public health, in case of compulsory licensing of patents, including for public non-commercial use, and in situations of national emergency or extreme urgency."

These authors also propose to opt for a data compensation regime in other cases, i.e. in addition to those involving CL and public non-commercial use of patents, where adequate compensation for the innovator and/or data generator is required. This would include the adequate remuneration for the use of test data to the holder of the marketing authorization of the reference medicinal product.[310] In other words, they encourage countries to consider replacing data exclusivity regimes with data protection regimes that recognized and reward the investment made to generate data but that do not allow the investor to exclude others from using the data.[311]

5.7 Interim Conclusion

On the basis of the literature review and the analysis above we have identified various strengths and weaknesses of CLs from a legal perspective. Below a systematic overview is provided. We include points which are specifically relevant to the pharma business and more particularly for excessive pricing focusing in particular on legal arguments.

Table 4 – Strengths and Weaknesses CLs in Europe

Strengths	Weakness
1. Tailored case-by-case analysis	1. In practice CLs rarely granted; generally especially used as negotiation tool
2. "Adequate" remuneration - at least IP owners get some remuneration in order to balance the impact of the CL on incentives to innovate	2. CL procedures and development by generic producers take time and hence CLs will generally not solve the problem quickly
3. May bring pharmaceutical companies to the negotiating table	3. Governance CLs – effectiveness of the procedure (i.e. who decides, expertise, which criteria)
	4. Need to objectify assessment "excessive" nature – guidelines? Link competition law?
	5. CL does not guarantee access to know-how, copyright protected documents and clinical trial data
	6. Limited effect without regulatory arrangements at European level for data and market exclusivity.
	7. Cost of grant and execution of the CL in comparison to the effectiveness of the CL mechanism

310 E.F.M. 't Hoen et al. (2017), 'Data exclusivity exceptions and compulsory licensing to promote generic medicines in the European Union: A proposal for greater coherence in European pharmaceutical legislation', 10 *J of Pharm Policy and Pract.,* 19 (adding: "The adequacy of the remuneration could be determined based on an audited disclosure of direct drug development expenditure by the originator […]. Alternatively, the royalty guidelines for non-voluntary use of a patent on medical technologies published by the UNDP and WHO could provide guidance for setting a remuneration rate" (internal citations omitted)).

311 See 't Hoen (2022), at p. 197.

Despite the fact that CLs are granted on a case by case basis, this ex post mechanism does not allow to impose measures that are sufficiently tailored to the circumstances of the case. Indeed, it is difficult to codify a mechanism which anticipates all possible situations where the ability to issue a CL would be desirable and ensures that when measures are taken, these will be effective. Moreover the lengthy procedure of CLs makes for limited flexibility which may limit its usefulness. A CL is typically only considered when access to a particular medicine becomes problematic while, even with a very swift CL procedure, the issuance of a license to develop a pharmaceutical will not make it available immediately.

6 COMPLEMENTARY MECHANISMS WITHIN AND BEYOND THE PATENT LAW CONTEXT

Given the general consensus that CL mechanisms should only be used in exceptional situations (which is confirmed by the economic study linked to this legal study), it is important to consider available complementary mechanisms which could also have an impact on pricing. The present report also highlights the limited effectiveness of CLs without complementary measures such as data transparency, coordination of national CLs at the EU level, coordination and collaboration between various authorities and the pharmacy exemption. These complementary mechanisms are listed following the order of the “value chain”. The further development of some of these complementary mechanisms may also contribute to create a more trusted, sustainable pharmaceutical industry. Nonetheless, these mechanisms should also be evaluated and tailored carefully to ensure that there would not be any negative impacts on the long term.

6.1 Consider Socially Responsible Licensing Conditions for Academia

Research by universities and research institutes is often licensed to the pharmaceutical industry in order to bridge the gap between bench and bedside. Universities and research institutes are adopting pro-active patenting strategies that enable them to license out and generate income. Licensing happens on a voluntary basis and negotiating parties operate under the freedom of contract. However, in various countries principles and toolkits have been developed to stimulate universities and research institutes to impose “socially responsible licensing conditions”. This means for instance that licences should ensure that the price-setting of the final products and/or services do not endanger accessibility. Such conditions may also be imposed by public authorities and funding organizations for (non-

)commercial research projects and innovation studies[312]. Recently such principles were also developed in the Netherlands[313] and operationalized through a Socially Responsible Licensing toolkit.

6.2 Stimulate Voluntary Licensing: Patent Pools and Clearinghouses

A patent pool is an agreement between two or more patent owners owning patents relating to the same technology to license one or more of their patents to one another, or to license them as a package to third parties. Several authors, including Van Zimmeren et al. have explored the potential of patent pools to ensure access to genetic inventions and diagnostics.[314] In those publications, the concept and mechanisms of patents pools, their strengths and weaknesses, incentives, etc. are explained. They draw from experiences with patent pools in other sectors, most notably the ICT and consumer electronics sector. Recently, patent pools are also recommended within the context of the Internet of Things.[315] The World Health Organization (WHO) Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing has also expressed an interest in patent pools to deal with the fragmented ownership for genome editing technologies.[316] Finally, the WHO supports the use of the patent pool model to secure access to essential COVID-19 related inventions.[317] Nonetheless, apart from a few successful cases[318] (e.g. Medicines Patent Pool) patent pools are relatively uncommon in the pharmaceutical sector. For this reason, in the past quantitative empirical research has been carried out in order to better understand the relatively limited use of pools in this sector.[319] Patent owners are often not willing to engage in the establishment of such a pool as they would lose control regarding potentially very valuable patented technologies and the establishment of the licensing conditions, including the setting of the royalties.[320] Moreover, the interests of the

312 See for instance the conditions related to the non-commercial use of studies funded by the KCE Trials Program (Belgium), by ZonMw (the Netherland) and by certain NIHR programs (UK).

313 NFU, Ten Principles for Socially Responsible Licensing, 2020, available at: 19.4511_Ten_principles_for_Socially_Responsible_Licensing_v19-12-2019.pdf (nfu.nl)

314 D. Matthews et al. (2021), The Role of Patents and Licensing in the Governance of Human Genome Editing: A White Paper (2021), Queen Mary Law Research Paper No. 364/2021, available at SSRN: https://ssrn.com/abstract=3896308 B. Verbeure et al. (2006), 'Patent Pools and Diagnostic testing', 3 Trends in Biotechnology, 115-120; G. Van Overwalle (ed.) (2009), *Gene Patents and Collaborative Licensing Models: Patent Pools, Clearinghouses, Open Source Models and Liability Regimes*, Cambridge University Press; G. Van Overwalle et al. (2006), 'Models for facilitating access to patents on genetic inventions', 7 *Nature Reviews Genetics*, 143-148; E. van Zimmeren (2011), 'Patent Pools and Clearinghouses in the Life Sciences', 29 Trends in Biotechnology, 569-576.

315 European Commission's Group of Experts on Licensing and Valuation of Standard Essential Patents 'SEPs Expert Group' (E03600) - Contribution to the Debate on SEPs (2021), available at https://ec.europa.eu/docsroom/documents/45217.

316 World Health Organization (WHO) Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, Human Genome Editing: Recommendations, 2021, available at: https://www.who.int/publications/i/item/9789240030381 and D. Matthews et al. (2021), The Role of Patents and Licensing in the Governance of Human Genome Editing: A White Paper (2021), Queen Mary Law Research Paper No. 364/2021, available at SSRN: https://ssrn.com/abstract=3896308.

317 WHO COVID-19 Technology Access Pool; E. Billette de Villemeur et al. (2021), 'Pool patents to get COVID vaccines and drugs to all', 591 *Nature*:529

318 For more information, see https://medicinespatentpool.org/ and E. Burrone (2018), 'Patent Pooling in Public Health', in: *The Cambridge Handbook of Public-Private Partnerships, Intellectual Property Governance, and Sustainable Development*, Cambridge University Press (2018), 93-108.

319 E. van Zimmeren (2011), 'Patent Pools and Clearinghouses in the Life Sciences', 29 Trends in Biotechnology, 569-576.

320 We note, however, that such a position of patent owners might be harder to maintain if CL mechanisms would effectively be used by governments.

heterogenous players in the pharmaceutical sector are rarely aligned, which is required for the smooth operation of a patent pool.

In the literature regarding pools, also some other collaborative licensing mechanisms tend to be included, such as clearinghouses.[321] Clearinghouses can be depicted as platforms or intermediaries bringing together owners and users of goods, services and information to lower transaction costs. There are many types of clearinghouses ranging from mere databases of information to technology exchange platforms and royalty-collecting organizations performing many functions. The clearinghouse operates as a neutral intermediary or platform for a wide variety of licensable technologies (a type of 'supermarket' for licensable technologies) with substantial expertise in licensing. It matches patent owners and licensees by delivering standard or one-stop-licenses.

Both patent pools and clearinghouses are licensing mechanisms which are particularly helpful to overcome situations where the patent landscape is very fragmented. Though not necessarily applicable to all drugs, fragmentation of the patent landscape may also play a role in the pricing for complex medicines. More particularly, if the commercialization of a product is subject to one or more licenses from third parties, this is likely to increase the price thereof.

To address a given public health problem, an initiative could be taken at an international level to negotiate with the patentees for joint public-health driven licences. Many have argued that this is a more sustainable option protecting almost all parties' interests. This would potentially be more efficient than CLs which would have to be granted on a case-by-case basis and country by country. Nevertheless, patent pools and clearinghouses are typically voluntary measures and thus rely on the goodwill of the parties involved. Typically the goodwill to contribute patents to a patent pool is higher when (a) the need for third party technology is reciprocal and (b) it is a generic part of the final product and/or (c) none of the parties have a product in development covered only by the relevant patent. While definitively of interest to promote the development of multiple solutions to a health problem, it remains unlikely that patent pools could replace the use of CLs altogether.

6.3 Increase Collaboration & Coordination with National and European Competition Authorities in the Pharmaceutical Sector and in particular for Excessive Pricing

It seems desirable that Ministries work more closely together with competition authorities in dealing with high prices. The rationale for this collaboration is the sharing of expertise and the variety of remedies available for the Ministries and the competition authority. This collaboration could occur with a national competition authority, such as the Belgian competition authority or with DG COMP of the European Commission, depending on the facts of the case and the scope of the company behaviour. Collaboration may occur within the context of formal investigations, informal advice or even temporary outsourcing and exchange of staff members. In Belgium, for instance, when a formal competition investigation would be pending related to a given product, the Ministry concerned (Economic Affairs/Health) may wait for the outcome of the formal investigation, which may consist of an obligation to issue a license. The Ministry could also request the Belgian competition authority for formal advice on an alleged abuse of a dominant position, which may or may not lead to a formal investigation by the competition authority. Or the Ministry could request the competition authority for informal advice on an alleged abuse of a dominant position. The advice may strengthen the position of the Ministry in the negotiations with the company or it may provide support for the motivation of the grant of a CL. Such collaborations could ensure that expert staff members from competition authorities familiar with the pharmaceutical industry provide

[321] E. van Zimmeren et al. (2011), 'Patent Pools and Clearinghouses in the Life Sciences', 29 Trends in Biotechnology, 569-576; E. van Zimmeren at al. (2006), G., 'A clearinghouse for diagnostic testing: the solution to ensure access to and use of patented genetic inventions?' 84 *Bulletin of the World Health Organization IP Theme Issue* 352-359.

input on the determination of whether or not pricing is excessive (see also Section 5.2.2.5 and Appendix 1).

6.4 Increase Transparency on Data and R&D Costs

Transparency is essential for providing the relevant authorities (health ministries, medicine agencies, competition authorities etc.) with the necessary data to assess the costs that were involved in the development of a drug and, thus, to inform decisions on excessive pricing. Transparency is, however, also crucial for ensuring public trust in medicines and the pricing of medicine, safeguarding public health and the protection of patient-safety. The increasing transparency requirements in CTD Regulation EU No. 536/2014, as well as the emerging new mechanisms and platforms for disclosing and sharing CTD are a step in the right direction as far as clinical transparency is concerned. However, the transparency of CTD is less relevant for assessing whether the price of particular medicines is excessive. A lot of the relevant data may still be shielded by the confidentiality of negotiations and trade secrets protection as could be recently experienced during the COVID-19 pandemic. Any future policy must find ways to balance these dynamics and make sure that data transparency in the pharmaceutical sector is increased.

6.5 Impose Conditions on Access & Pricing in Case of Public Funding

The COVID-19 pandemic and the dependency on the pharmaceutical sector has reinvigorated the discussion on access to results of publicly funded research. Many are questioning the fact that public funding is provided in this sector without strict requirements in terms of access and affordability of the resulting products. While it indeed appears justifiable to add clear contractual conditions regarding access to and affordability of products and methods funded with public resources, it will be difficult to make such conditions clear and generally applicable[322]. For instance, while these conditions could for instance contain requirements to license out on the condition that fair and equitable/low-cost pricing is ensured for all resulting products, criteria for what is fair and equitable/low-cost pricing would need to be determined (and detailed provisions on resolution mechanisms in case of conflicts would need to be included). Moreover, while such conditions could include the requirement to only license out on a non-exclusive basis, such a requirement would likely have a significant impact on the interest of industry to develop medicines covered by this technology. In addition, imposing such requirements may enable national protectionism. Finally, such a measure, if not taken in an international context could significantly disadvantage Belgian research organizations and universities from getting licensing deals with industry.

6.6 Increase Coordination on Pricing & Reimbursement

Various EU countries have started collaborations regarding pricing and reimbursement mechanisms. However, it would be desirable to stimulate these activities of groups of countries at the EU level to ensure that all resources are employed in an optimal manner.

In Belgium, both the KCE and the Rekenhof /Cour des Comptes have recommended to improve the transparency and efficiency of the Belgian legislation on price-setting for medicines. So far, those recommendations have not been followed (see Appendix 5).

322 Note however that NIHR in the UK has experience in this field https://www.nihr.ac.uk/explore-nihr/funding-programmes/invention-for-innovation.htm.

7 CONCLUSIONS

Globally serious concerns exist about the availability and affordability of medicines today and even more so in the future in view of the increased personalization of medicines, the complementarity of diagnostics and treatments and the complexity of new drugs, such as biologics. CLs have been presented as a suitable tool to control excessive pricing of medicines. The possibility to ensure competition in the market (or at least the ability to threaten with this during pricing negotiations) is expected to help prevent patent owners from abusing their position.

Whether or not the envisaged use of CL to address excessive pricing situations is at all advisable from an economic perspective is addressed in the economic study. The present legal study is aimed primarily at identifying the legal mechanisms for CL that can be developed under TRIPs and their limitations.

From a legal perspective, it appears that the present provisions in the Belgian law for issuing CLs will only in particular circumstances be able to help address the high cost of medication. While the development of new provisions would thus be required, the provisions of Article 31 may be too restrictive. Nevertheless Article 30 TRIPs does offer a broader basis for exceptions to rights conferred to patent owners, such that introducing specific provisions more directed at countering excessive pricing into the Belgian legislation is possible.

The question however remains to what extent this would be effective and sufficient. One of the key conclusions of the present study is that it is impossible to assess the effect of a CL while ignoring the 'bigger' regulatory picture and institutional and governance framework. Thus, complementary mechanisms may be required to address the exclusivity mechanisms that these provide. The regulatory framework for medicines is actually highly complex and strongly interrelated, so any envisaged change thereof should of course be given thorough consideration. If one starts to tweak certain elements of this regulatory framework or initiates new governance experiments, this will also have implications for the operation of other parts of the regulatory framework and this complex ecosystem. Moreover, the actual effects of such modifications and experiments are often difficult to foresee and disputed by some experts and stakeholders.

Under the current EU system for regulatory exclusivities, such exclusivities could have an impeding effect on the use of national CL regimes to address excessive pricing. At the same time, regulatory exclusivities offer interesting policy options to tailor innovation incentives more carefully than possible through patent law due to the flexibilities enshrined in Article 39(3) TRIPs. This flexibility does also provide a certain leeway for policy-makers and legislators to consider alternative regimes, such as schemes compensating the originator of the data for the use by third parties. However, there is a need to ensure more coherence in the current EU regime for regulatory exclusivities with national laws on CLs. Several legislations in non-EU countries, as well as provisions in FTA agreements and in voluntary licensing agreements (e.g. Medicines Patent Pool) provide arguments for waiving regulatory exclusivities in case a CL is granted and offer examples as to how that could be achieved. Furthermore, in order for a CLs to be effective (even if only as a bargaining tool) any proposal for reform of CLs aiming to allow market entry of other parties to influence pricing should be accompanied by complementary enabling initiatives, such as increased clinical trials transparency, and needs to address other potential barriers to the effectiveness of CLs, such as the protection of trade secrets and know-how.

Most CLs that have been granted in the past were granted in developing countries and emerging economies and only a few examples exist where CLs were granted for health reasons in high-income countries. These cases did not necessarily relate to high prices, but rather the availability of the medicines. It should be emphasized that the situation in developing countries that are faced with limited access to many therapeutics is very different from that in developed countries. As indicated in the economic study, the extension of CL provisions may ultimately have a significant impact on the economy in different manners.

Several relevant competition cases exist that deal with excessive pricing and can be taken into account in determining how to identify what should be

considered as “excessive”. The fact that these cases relate to off-patent drugs does mandate some caution in the comparison.

In case a CL system to address excessive pricing would nevertheless be considered opportune, the *substantive* and *procedural* requirements for granting such CLs should, hence, be carefully assessed and optimized to ensure that these mechanisms are appropriate to obtain the desired result; ensuring access to and affordability of medicines and stabilizing health budgets. Having sound procedures to assess what is considered as ‘very expensive/excessive’ for patented pharmaceuticals (in the scope of CLs) is also very important. Nonetheless, the grant of CLs should not be “mainstreamed” and should remain the ‘exception’ rather than the ‘rule’ and in order to ensure a sustainable and resilient health system.

More particularly, in order to address the issue of excessive pricing, we propose a multilevel toolbox of action points, in which the use of CLs remains a solution for use in exceptional circumstances, but which also ensures the effectiveness of the CL mechanisms such that they are considered a credible, powerful tool (e.g. for prize negotiations) within the broader toolbox which can help ensure access and affordability of medicines for patients in Belgium.

Multilevel toolbox - legal and governance recommendations

Mechanisms regarding the CL for Excessive Pricing

R1.1. Develop guidelines in a working group with health (economic) experts, patent and competition experts on how to assess the conditions and existence of “excessive pricing” on the basis of elements taken into consideration in CL cases in other high-income countries, expertise and experience of competition authorities with excessive pricing and economic modelling. Factors that are taken into consideration by competition authorities are amongst others: (1) the way the relevant market operates - actual and potential competition (e.g. price elasticity, entry barriers, agreements to prevent entry); (2) the disproportion between the applied price and the benchmark price; (3) the disparity between the price and the “economic value” (e.g. age product, therapeutic value); (4) whether R&D investments were made and commercial risks were borne; (5) the awareness amongst the companies of the adverse effects of the pricing practices on the health system and patients; (6) whether similar pricing practices were introduced in other countries.

R1.2. Increase the effectiveness of the Belgian CL procedure by clarifying and modifying certain *substantive* and *procedural* requirements to ensure that the use of CLs is considered an effective and powerful negotiation tool by negotiation parties - ***legal intervention required*** (see specific recommendations in Section 5.3.4 on the legislative proposal for CL, e.g. CL v. government use, ground, thorough consideration of criteria, role and expertise of the Advisory Committee on Bioethics, advice on licensing terms, public procurement competition procedure).

R1.3. Develop guidelines in a working group with health experts, economists, patent and industry experts on determining what is an “adequate/reasonable” remuneration based on disclosures of drug development expenditures (see also recommendation regarding transparency, R3.1).

R1.4. Stimulate collaboration regarding the grant of national CLs in case of excessive pricing in various EU Member States to strengthen the negotiation position of health authorities.

R1.5. Explore opportunities for ‘unitary’ CLs , in addition to national CLs, within the context of the Unitary Patent Package or at least increase the coordination at the EU level regarding the grant of national CLs.

Mechanisms regarding Regulatory Exclusivities

R2.1. Call for greater coherence on the EU level and amendments to EU Regulations and Directives to harmonize national legislation with regard to CLs and regulatory exclusivities, e.g. limitations to the regulatory exclusivity periods in case a CL is granted (art. 14(11) Regulation 726/2004).

R2.2. Call for a debate at the EU level to allow for waivers to regulatory exclusivities that are tied to the issuance of CLs and subsequently an amendment to Belgian law. Such waivers may also involve adequate remunerations and may be based on existing examples, such as existing waivers in the EU Regulation No. 816/2006 on CLs for patents for the

manufacture of pharmaceutical products for export to countries with public health problems, the waiver applicable to the MPP and various provisions in FTAs.

R2.3. Consider enhancing CTD transparency requirements at the national medicine authorities and at the EMA in accordance with the *ratio legis* of the relevant provisions. This could include the introduction of specific requirements for plausible evidence and enabling data for regulatory approvals and safe manufacture (even if that would mean that such data might need to be redacted from the public disclosure clinical trials data to safeguard trade secrets and commercially confidential information).

R2.4. Commission a study that investigates potential incentives for voluntary full disclosure of data mentioned in R2.3, for example by offering rapid approval pathways and increased support in the MA process, cf. EMA PRIME scheme.

R2.5. Commission a study to investigate the potential replacement of regulatory data exclusivity regimes by regulatory data protection and compensation regimes in selected areas of critical importance. Involuntary disclosures of data could be linked to adequate remunerations based on audited disclosures of drug development expenditures.

Complementary mechanisms

R3.1. Improve transparency in R&D and marketing costs and price-setting strategies in the pharmaceutical sector.

R3.2. Consider conditions on access to and fair pricing of medicines in case of public funding invested in pharmaceutical research; this could also involve links with initiatives such as the MPP.

R3.3. Consider adopting socially responsible licensing conditions for universities and research institutes; similar to initiatives in the US and the Netherlands – this could also involve links with initiatives such as the MPP.

R3.4 Improve collaboration and exchange of expertise between the Ministries of Social Affairs and Public Health, the Ministry of Economy and Employment and the Belgian Competition Authority by organizing expert meetings, requesting for formal and informal advice or enabling temporary secondments.

R3.5 Further stimulate the exchange of information regarding pricing negotiations at the European level and of expertise and HTAs between health authorities (e.g. BeNeLuxA) and enhance collaboration between competition authorities (e.g. Bilateral cooperation, OECD Competition Committee, European Competition Network).

R3.6 Commission a study regarding the role and operationalization of the pharmacy exemption in Belgium and increasing awareness by informing pharmacies about the opportunities offered by this exemption and by updating the applicable guidelines. For instance, due to practical and legal constraints, the production of drugs in pharmacies will only possible for certain drugs (e.g. those that are not too complicated to prepare), in specific circumstances (non-industrial production) and depends on the availability of raw materials.

SUPPLEMENT

APPENDIX 1. COMPETITION CASES EXCESSIVE PRICING

In this Appendix we list a number of recent excessive pricing decisions issued by competition authorities. However we note that in several Member States similar cases are still pending. For instance, below we report on the Leadiant (CDCA)-decision issued by the Dutch Authority for the Consumer and Markets. In Belgium, Spain and Italy, this case is also pending. In addition, the Belgian and Italian competition authority started investigations against Biogen, the MA holder of Spinraza used to treat spinal muscular atrophy, a rare genetic disease that causes weakness and wasting of the muscles, including the lung muscles. Apparently, the European Commission is supporting these investigations by national authorities behind the scenes based on the assumption that national competition authorities are better positioned to assess such conduct considering the national structure of the markets and the impact of local regulation. These cases are particularly interesting as they relate to medicines with an orphan drug designation.

These very short summaries are meant to give a non-exhaustive overview of the key facts and some interesting insights in the light of the assessment of what are “excessive” and “unfair” prices and the methods used for carrying out that assessment.

European Commission – Aspen (2021)

According to the Commission, Aspen, a large pharmaceutical producer of several off-patent anti-cancer medicines, had imposed significant and unjustified price increases of up to several hundred percent and had withdrawn medicines from certain Member States.[323] The investigation did not cover Italy, because the Italian competition authority already adopted an infringement decision against Aspen in 2016 (see below).

The Commission applied the two-limb *United Brands* test (see Section 5.2.2). For the first excessiveness limb, the Commission relied on a profitability analysis; although the Commission noted explicitly that various ways exist to assess the excessiveness of the profits.[324] Aspen's profits were compared to a benchmark comprised of the profit-margins of 23 comparator companies selected because they had similar profiles and were selling off-branded or generic medicines with similar active substances targeting cancer patients.[325] Once it established the benchmark, the Commission identified a proxy for a reasonable profit margin referred to as the cost-plus level for the six Aspen medicines.

Relying on this proxy, the Commission found that Aspen earned persistent levels of excess profits "very significantly" over the cost-plus level; on average 280-300% in excess. In other words, on top of the reasonable return, Aspen earned additional profits roughly three times the level of cost-plus.[326] Aspen had argued that the price increases were necessary to recover its investment in light of the acquisition price Aspen had paid to GSK. However, according to the Commission Aspen had not accounted for any specific tangible or intangible assets acquired by Aspen (e.g. no patent protection). Therefore, the identification of the underlying capital would be a complex exercise, which in the present case was not required according to the Commission.[327] To assess the "unfairness" of the prices, the Commission focused on whether the prices were unfair "in itself" rather than comparing with "competing products". The Commission concluded that Aspen had not offered material improvements of the products through R&D and designed and implemented a strategy to exploit health systems and patients.[328] The price increases were

323 European Commission (2017), 'Antitrust: Commission opens formal investigation into Aspen Pharma's pricing practices for cancer medicines', Press Release, 15 May 2017, available at: https://ec.europa.eu/commission/presscorner/detail/sl/IP_17_1323

324 *Ibid*, para. 104.

325 The Commission took into account direct costs and indirect costs attributable to the Products. Direct costs are all costs incurred in the production, supply and distribution of the Products, which can be directly attributed to their sales. Indirect costs are common costs (for example, operating costs) that Aspen incurred in the supply of more than one product (including the Products). The Commission considered methods based on revenue, volume and cost of goods sold ('COGS') for the allocation of indirect costs. Moreover, there are also several profitability measures that can, in principle, be suitable to assess suspected price abuses, depending on the factual circumstances of each case. These include, in particular, gross margins, EBITDA margins and EBIT margins (also known as operating profit margins). In the present case, the Commission has focused on two measures of profitability, namely gross margins (that is net sales minus direct costs, and thus not considering indirect costs) and EBITDA margins. EBITDA margin is a net profitability measure that takes into account all direct costs and all indirect costs, with the exception of depreciation and amortisation costs (that cover impairment costs, which are thus also excluded). For more information, see paras. 108-121, 127-131.

326 *Ibid*, paras. 139-143

327 *Ibid*, para. 155.

328 *Ibid*, paras. 165-195. In this respect the Commission also drew on some internal documents to demonstrate the strategies used, see for instance: "Take it or leave it. No other alternative. If the local MOH [Minister of Health] doesn't accept the new price, we will either sell with no reimbursement or not supply at all. No place for negotiations. No time for reference to the other countries." (see para. 192 and footnote 128).

disproportionate to the limited increases in its costs of production[329] and no legitimate reasons existed for Aspen's high prices.[330]

In February 2021, the Commission issued a so-called Commitment Decision fixing the price that Aspen is allowed to charge for six cancer drugs in most EEA Member States and to continue supplying the medicines for a guaranteed five-year period.[331]

Italian Competition Authority – Aspen (2016)

On 29 September 2016, the Italian Competition Authority (ICA) delivered its decision in the Italian Aspen case imposing a fine of 5,2 million euros.[332] Aspen had purchased the marketing rights for various generics from GSK in 2009 and sharply increased the prices up to 300-1500%. It also threatened to discontinue the supply of the generics to the Italian market. The ICA applied the two-limbed test from the *United Brands* case in line with the established case-law on excessive pricing and acknowledging that there is no single method established by law to carry out the test.[333] For examining the excessive disproportion between the cost actually borne for the production of the good and the actual price requested by the company,[334] the ICA used several methods in parallel in line with economic theory and the case-law which shows a lack of one uniform common method.[335]

In line with the case-law of the CJEU and the Commission's later Commitment decision in the Aspen case, ICA emphasized that there are no quantitative thresholds or precise arithmetic relationships that define what measure should be used in examining the disproportion between prices and costs.[336] The assessment needs to take into account the circumstances of the actual case and the "absence of 'reasonableness'" in the relationship between price and economic value of the product. The ICA listed the following elements that can be taken into consideration in determining the economic value: "1) a comparison between the prices imposed by the undertaking and prices applied previously or in other markets by the same undertaking for the same products or with reference to prices of competing drugs and the amount of the resulting gap; 2) with reference to demand, qualitative factors not directly reflected in the costs borne by the undertaking such as, for example, improvements of the product from a therapeutic viewpoint (pharmaceutical formulation, chemical composition, dosage, packaging, etc.) or from a distribution viewpoint and, more in general, the level of service provided to purchasers, that can affect the economic value; 3) the presence or absence of economic justifications for the price levels imposed; 4) with

329 *Ibid*, para. 179.The unit cost of the product had only faced modest increases in the 10-40% range, while the prices had increased in the 180-430% range.

330 *Ibid*, paras. 155.

331 European Commission (2021), Case AT.40394 - Aspen, February 2021, available at: https://ec.europa.eu/competition/antitrust/cases/dec_docs/40394/40394_5350_5.pdf

332 Italian Competition Authority, Case A-480, Incremento Prezzo Farmaci Aspen, available in English at: https://en.agcm.it/dotcmsDOC/pressrelease/A480_eng.pdf.

333 *Ibid*, paras. 128-129.

334 *Ibid*, paras. 132-133. The ICA referred to direct and indirect costs: variable direct costs (in the financial statements defined cost of sales or cost of goods sold - COGS) and a quota of fixed direct costs as well as a quota of indirect costs borne by the undertaking, deemed reasonably related to the production of the good under exam. It also took into account a "fair remuneration" for which it referred to various indicators of the undertaking's profitability ranging from indexes of return on capital employed (ROI, ROE, ROCE, WACC) to sales profitability rates (ROS, contribution margin).

335 *Ibid*, para. 138.

336 *Ibid*, para. 134.

reference to supply, the presence of a potential competitive pressure capable of conditioning the undertaking's behavior in defining the price; 5) the nature of the product, with particular reference to the existence of substitutes; 6) the undertaking's characteristics, with particular reference to possible research activities carried out and the bearing of related investments in innovation".[337] Different from AG Wahl in the Latvian copyright society case (see Section 5.2.2), the ICA notes that "given the peculiar nature of the products under exam (life-saving drugs), the determination of their value cannot be carried out taking into consideration consumers' willingness to pay: the willingness to pay for life-saving drugs lacking therapeutic alternatives can only tend to infinite, potentially justifying any price increase".[338]

The ICA applied different methods: (1) analyzing the percentage gross margin (gross margin/revenue%) and concluded that the new price increased the margin between 300-1500%, when the original prices already generated profits; (2) finding that the revenues were between 150-400% higher than cost-plus price (based on direct variable costs, indicated fixed costs and a measure of profitability); and (3) by comparing the net cash flows during a 20 years' time span. The ICA concluded that the price increase obtained through the negotiations with the Italian medicines agency, AIFA, were excessive and unfair and hence abusive. As the medicines had been on the market for a long time, it argued that the R&D and other related costs had already been sustained by GSK. Moreover, Aspen had not made any substantial improvements to the products. The counterarguments raised by Aspen to justify the price increase regarding price differences with other Member States and the costs related to pharmacovigilance were also rejected. In appeal Aspen also did not succeed to convince the court.[339]

The UK Competition and Markets Authority (CMA) also issued several decisions in excessive pricing cases over the last 6 years.

UK Competition and Markets Authority – Pfizer & Flynn [Phenytoin] (2016)

In December 2016, the CMA fined Pfizer and Flynn Pharma for their price increases regarding an anti-epileptic drug, Epatunin (Phenytoin active ingredient).[340] Although relatively few newly diagnosed patients are prescribed these drugs, there is a community of established users stabilized and thus dependent on the treatment. Phenytoin has long been off-patent. In 2012, Pfizer transferred Epatunin's UK MA to Flynn and became its upstream manufacturer. Flynn started to sell the product as a generic, rebranded it and started marketing it under a new name. Pfizer increased the prize for which it sold the drug to Flynn, which also increased the price significantly from £2.83 to £67.50 for a pack of 84 capsules. Similar to the Commission and the ICA, the CMA applied the *United Brands* two-limb test recognizing the methodological challenges involved. It adopted a cost-plus method and calculated the reasonable rate of return calculated by using the Return on Sales (set at 6% based on the UK's "Pharmaceutical Price Regulation Scheme"[341]) and by cross-

337 *Ibid*, para. 136.

338 *Ibid*, para. 137.

339 Regional Administrative Court Lazio (2017), N 12806/2016 REG.RIC., 14 June 2017

340 CMA, Unfair pricing in respect of the supply of phenytoin sodium capsules in the UK Case CE/9742-13 https://assets.publishing.service.gov.uk/media/594240cfe5274a5e4e00024e/phenytoin-full-non-confidential-decision.pdf

341 In this respect, it is relevant to have a basic understanding about the "debranding practices" that are typical for the UK National Health Service. The NHS publishes tariffs for all approved drugs on the basis of which it reimburses pharmacists for dispensing prescriptions. The method of determining these prices is different for branded and generic drugs. Under the Pharmaceutical Price Regulation Scheme (PPRS), the government imposes a cap on profits from prescription drugs sold to the NHS after making

checking the results with the calculation by the Return on Capital Employed (ROCE).[342] The CMA took into consideration (1) the substantial disproportion between the applied price and benchmark price; (2) the way the relevant markets operated; (3) the age of the drugs and the lack of R&D investments and commercial risk; (4) the awareness amongst the companies of the adverse effect of the price increase on the health system and patients; (5) Pfizer's involvement of Flynn into the supply chain to avoid adverse publicity and reputational damage, rather than genericizing the drugs itself, and (6) the fact that similar price increases were not introduced in other EU countries.[343] On appeal, the Competition Appeals Tribunal (CAT) struck down the decision of the CMA stating that the CMA should not have relied only on the cost-plus method and to exclude other methodologies rather than seeking to establish a benchmark price. Moreover, the CMA should have investigated unfairness by comparing the price with those of comparable products.[344] The Court of Appeal partially allowed CMA's appeal and dismissed Flynn's appeal entirely.[345]

Importantly, it clarified that the CAT was wrong to require the CMA to go beyond a cost-plus calculation.

Although, this case was a missed opportunity to refer the question to the CJEU for a more harmonized application of the *United Brands* test in the pharmaceutical sector and to create more legal certainty (in particular in the pre-Brexit context), its persistent relevance for the EU is reflected in the fact that the Commission decided to intervene before the Court of Appeal. After the judgement of the Court of Appeal, the CMA re-investigated the case and issued a new Statement of Objections in August 2021.[346] The case is still pending before the CMA.[347]

allowances for R&D expenditures. Thus, a company can increase the price of its branded drug, but only as long as the total profit from the portfolio of drugs for the company does not go above the maximum allowed profit. In reality, it may even mean that to increase the price of one drug, a manufacturer has to decrease the price of another drug in its portfolio. Generic drugs, on the other hand, are not covered by the PPRS and are priced using a different set of rules. For these drugs, the government samples generic prices via wholesalers, computes an average price for each drug, and then sets a reimbursement rate based on that average value, while also allowing for a dispensing fee for the pharmacist. The logic behind this mechanism is that the pharmacists will always try to purchase from the cheapest generic provider and this will keep prices low for the NHS. But if the generics firm is the sole supplier on the market he can charge whatever he want, because the average is his price. For more information, see e.g. F. Bokhari & B. L. Lyon (2017), 'Can drug price hikes via debranding be prevented?', *Prescriber*, 43-46.

342 *Ibid*, paras. 5.3-5.57.

343 See summary provided in OECD (2018a), p. 16.

344 CAT, 7 June 2018, Flynn Pharma Ltd and Flynn Pharma (Holdings) Ltd v Competition and Markets Authority [2018] CAT 11, available at https://www.catribunal.org.uk/sites/default/files/2018-08/1275-1276_Flynn_Judgment_CAT_11_070618.pdf.

345 Court of Appeal, 10 March 2020, Competition and Markets Authority v. Flynn Pharma Ltd and Flynn Pharma (Holdings) Ltd (hereinafter 'Phenytoin') [2020] EWCA Civ 339, available at https://www.catribunal.org.uk/sites/default/files/2020-04/1275-76_Flynn_CoA_Judgment_100320.pdf.

346 CMA, 'CMA accuses pharma firms of illegal pricing', Press release, 5 August 2021, available at: https://www.gov.uk/government/news/cma-accuses-pharma-firms-of-illegal-pricing.

347 For the most recent status of the case, see: https://www.gov.uk/cma-cases/investigation-into-the-supply-of-pharmaceutical-products#statement-of-objections.

UK CMA Advanz Pharma [Liothyronine] (2021)

End of July 2021, the CMA fined Advanz Pharma (former Concordia) and several investor firms in total more than £101 million for increasing the price of generic thyroid tablet packs used to treat thyroid hormone deficiency from £20 in 2009 to £248 in 2017.[348] The CMA applied the *United Brands* test referring to earlier cases of the Commission and national competition authorities, the CJEU in AKAA/LAA, older case-law of the High court and the CAT and the Court of Appeals in the Pfizer & Flynn (Phenytoin) case. It also acknowledges again the complexity of the assessment of excessive pricing cases by emphasizing that: "[w]hile the competition authority bears the legal burden of proof and must take a rigorous reasoned approach to the legal and factual questions,[…] it is not required to apply an approach or methodology that is so complex and time-consuming that the relevant authority has neither the time nor the resources to deal with cases of alleged unfair pricing".[349] Although the CMA acknowledges that other methods than the *United Brands* test have been used by EU and domestic courts for determining whether a price is unfair[350], it emphasizes that there is, however, no rule of law requiring competition authorities to use more than one test or method to assess an unfair pricing abuse.[351] Moreover, the CMA relies on the decision of the Court of Appeal in *Phenytoin*, which stated that there is no need to establish a benchmark price or a range of prices, beyond a cost-plus calculation, in order to determine whether the prices charged are excessive.[352] Neither does the case-law prescribe a particular methodology for measuring cost. When establishing the costs actually incurred it will normally be necessary to allocate a reasonable rate of return to cover the cost of capital. Again it is not necessary to adopt any particular approach to the determination of the 'plus' part of the cost plus calculation. It is considered a question of judgement and appreciation on which experts may well take differing views and for which regard may be had to the interests of patients and the NHS.[353] In specifying whether a margin is excessive, the CMA agrees that a "material difference" must be shown, but it does not indicate a particular threshold as this assessment 'involves a proper degree of discretionary judgment by the decision-maker'.[354] According to the CMA, it also has a considerable margin of appreciation when assessing whether an excessive price is also unfair: a price which 'significantly exceeds' the economic value of the product supplied will be prima facie excessive and unfair. The CMA highlights that the economic value of a product may exceed cost-plus as a result of non-

348 CMA, Decision Excessive and unfair pricing with respect to the supply of liothyronine tablets in the UK, Case 50395, July 2021 (non-confidential version December 2021), available at: https://assets.publishing.service.gov.uk/media/61b8755de90e07043f2b98ff/Case_50395_-_Non-confidential_decision_.pdf.

349 CMA, Liothyronine Tablets, para. 5.53 referring to Court of Appeal, 10 March 2020 [2020] EWCA Civ 339, paras. 243-246.

350 Examples are an analysis of "prices charged by (i) the dominant firm at a different point in time; (ii) non dominant firms; and (iii) the dominant firm or other firms in different geographical markets. For instance, in cases involving IP rights, a comparison across different geographical markets has been the method most often used, but the facts of those cases were quite different from the pharmaceutical sector. In such cases, when a company was holding a dominant position and was imposing fees for its services which were appreciably higher than those charged in other Member States, and where a comparison of the fee levels had been made on a consistent basis, that difference had to be regarded as indicative of an abuse of a dominant position. It was then for the undertaking in question to justify the difference by reference to objective dissimilarities between the situation in the Member State concerned and the situation prevailing in all other Member States." CMA, Liothyronine Tablets, paras. 5.97-98.

351 CMA, Liothyronine Tablets, para. 5.99

352 *Ibid*, paras. 5.52-54 referring to CoA, Phenytoin, para. 254.

353 CMA, Liothyronine Tablets, paras. 5.62-63.

354 *Ibid*, paras. 5.65-66 referring to CAT, Albion Water II [2008] CAT 31, paras. 193–194.

cost related factors including, for instance additional benefits not reflected in the costs of supply or any particular enhanced value from the customer's perspective.[355] Nonetheless, economic value is not simply whatever price a product or service will fetch or what the market will reasonably bear. The fact that a consumer will or must pay the price that a dominant undertaking demands is not therefore an indication it reflects a reasonable relationship with economic value. Here the CMA refers to the Opinion of the Advocate General in the SABAM-case, which is also highlighted in the main text of this report[356] and which mentions the particular situation of 'life-saving drugs'. In fact, in such cases customers have no real choice when purchasing the products in question.[357]

The CMA then argues that Advanz's prices were excessive, because the comparison of the prices with the costs of supplying Liothyronine Tablets plus a reasonable rate of return[358] (cost-plus method), the amounts by which Advanz's prices exceeded cost plus ranged from 900% to around 2,500%. Even when a number of issues/limitations are taken into consideration i.e. alternative approaches with regard to the allocation of common costs, the valuation and amortization of product rights and a higher rate of return, the differential was at all times material, ranging from above 300% in 2009 to almost 2,000% by 2017.[359] In assessing the unfair nature of the prices, the CMA highlighted that Advanz faced limited or no competition (despite the fact that the case relates to generics and the patents had expired) and that the significant price increases had significant adverse impact on patients and the NHS. Moreover, substantial disparity existed between Advanz's prices and the economic value of its Liothyronine Tablets (taking account the age of the liothyronine tablets and their therapeutic value). In addition, there was no reason to consider that Advanz's prices were fair when compared to competing products. The price increases were not driven by any meaningful innovation or investment, volumes remained broadly stable, and the cost of producing the tablets did not increase significantly. The CMA did not accept the justifications put forward by the companies.

In Fall 2021, Advanz Pharma, Cinven and HgCapital filed appeals in the CAT against the CMA's findings in the infringement decision.[360]

355 CMA, Liothyronine Tablets, paras. 5.86-5.87.

356 Opinion of AG Pitruzzella C-372/19, SABAM v. Weareone.World, ECLI:EU:C:2020:598, para. 25.

357 CMA, Liothyronine Tablets, paras. 5.92-94 referring to – amongts others - CoA, Phenytoin, para. 154-155.

358

359 CMA, Liothyronine Tablets, para. 5.104.

360 For the most recent status of the case, see: https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-conduct#:~:text=15%20December%202021%3A%20The%20CMA,liothyronine%20tablets%20in%20the%20UK.

UK CMA – Accord-UK [Hydrocortisone] (2021)

In July 2021, CMA fined Accord-UK (former Auden McKenzie/Actavis UK) £155 million for charging the NHS excessive and unfair prices for hydrocortisone tablets for almost 10 years, from 2008 to 2018[361]. The non-confidential version of the infringement decision was only recently published, so after the *Liothyronine* case.[362] This is why this case is discussed after the *Liothyronine* case even though this case was actually decided earlier. The standards and methods applied in this case and the reasoning developed by the CMA are very similar to the ones applied in the *Phenytoin* and the *Liothyronine* cases. The CMA employs the cost-plus method and ascertains a reasonable rate on return while emphasizing the degree of discretion in making the assessment based on the *United Brands* test and the challenges involved in many steps of the assessment, such as determining the costs incurred. As the decision is more than 1000 pages long, we refer to the decision for more insights regarding the methods used and challenges encountered. A more detailed analysis goes beyond the scope of the current report.

The CMA found that Auden Mckenzie and Actavis UK increased the price of 10mg and 20mg generic hydrocortisone tablets by over 10,000% compared to the original branded version of the drug, which was sold by the drug's previous owner until 2008. To protect its position as sole provider of the tablets, and enable it to continue to increase prices, Auden Mckenzie paid off would-be competitors AMCo and Waymade to stay out of the market.

In Fall 2021, whereas Waymade decided to pay its fine, several other companies involved in the case filed appeals in the CAT against the CMA's findings in the infringement decision. The case is currently pending before the CAT.[363]

Danish Competition Council – CD Pharma (2018)

On 31 January 2018 the Danish Competition Council (DCC) ruled that CD Pharma had abused its dominant position by charging unfair prices for the drug Syntocinon.[364] Syntocinon contains oxytocin an active substance given to pregnant women in connection with childbirth. It is used by public hospitals in Denmark, has existed since the 1950s and its patent expired a long time ago. During 2007-2014, the price of Syntocinon was stable around DKK 44, but in 2014 CD Pharma increased its price from DKK 45 to DKK 945, i.e. a price increase of 2,000%. Amgros, a wholesale buyer for hospitals paid almost six million DKK in excess of the price set in the tender contract with another company Orifarm, a parallel importer and

361 CMA, Hydrocortisone tablets: alleged excessive and unfair pricing, anti-competitive agreements and abusive conduct (50277), last updated 31 March 2022, available at: https://www.gov.uk/cma-cases/hydrocortisone-tablets-alleged-excessive-and-unfair-pricing-anti-competitive-agreements-and-abusive-conduct-50277

362 See: https://assets.publishing.service.gov.uk/media/624597bbe90e075f0b5a3da4/Case_50277_Decision.pdf (31 March 2022).

363 For the most recent status of the case, see: https://www.gov.uk/cma-cases/hydrocortisone-tablets-alleged-excessive-and-unfair-pricing-anti-competitive-agreements-and-abusive-conduct-50277.

364 Danish Competition Council (Konkurrence- og Forbrugerstyrelsen), 31 January 2018, CD Pharma, Press Release, 'CD Pharma has abused its dominant position by increasing their price by 2,000 percent', available at https://www.en.kfst.dk/nyheder/kfst/english/decisions/2018-cd-pharma-has-abused-its-dominant-position-by-increasing-their-price-by-2-000-percent/. For more information, see also OECD (2018a), p. 18 and B. Kianzad & T. Minssen (2018), 'How Much is Too Much? Defining the metes and Bounds of Excessive Pricing in the pharmaceutical Sector', 3 EPLR, p. 8-9.

competitor of CD Pharma. Orifarm was however not capable of providing the full amount of Syntocinon for the Danish market.

Kianzad & Minssen briefly summarize the case explaining that the DCC applied the *United Brands* test pointing to profit margins of around 80-90%, with few substantiated claims regarding the cost side.[365] Apparently, the DCC used seven (!) financial analyses and the UK Pharmaceutical Price Regulation Scheme. Comparing the price charged by CD Pharma to previous prices set by former providers showed a gap of 2,000% and the price was also substantially lower in other Member States.[366]

The DCC decided to submit the case to the Danish State Prosecutor for Serious Economic and International Crime. On 2 March 2020, the Maritime and Commercial Court has confirmed that CD Pharma abused its dominant position.[367]

Dutch Authority for the Consumer and Markets (ACM) – Leadiant (2021)

In July 2021, the Dutch Authority for the Consumer and Markets ACM Imposed a EUR 20 million fine on Leadiant, manufacturer of the orphan drug CDCA-Leadiant.[368] CDCA-Leadiant is a vital drug for patients suffering from cerebrotendinous xanthomatosis (CTX), a rare genetic metabolic disorder. Without proper treatment, the health of CTX patients deteriorates severely, and they will die prematurely; so they are heavily dependent on the drug. Since the 1970s, CTX is treated in the Netherlands with chenodeoxycholic acid (CDCA), which was originally used for the treatment of gallstones. Since 2008, Leadiant offers a CDCA-based drug on the Dutch market, Chenofalk. This drug was not developed by Leadiant itself, but was acquired from another manufacturer. In the Netherlands, the maximum price of this drug at the time was 46 euros per pack of 100 capsules. In 2009, Leadiant changed the name of the drug into Xenbilox, and it raised the price to 885 euros. In 2014, Leadiant decided to apply for an MA and an orphan drug designation for its CDCA-based drug for the treatment of CTX and again raised the price of Xenbilox; this time the selling price became 3,103 euros. After being granted an MA and an orphan drug designation Leadiant released CDCA under the name CDCA-Leadiant, and it stopped selling CDCA under the old trade name Xenbilox. The two drugs are molecularly identical. Since then Leadiant started charging a price of 14,000 euros for CDCA-Leadiant. This new price is over 15 times as high as the price of Xenbilox before applying for orphan drug designation.

This price increase cannot be explained by the costs associated with the MA and the orphan drug designation, since Leadiant had already recouped those costs. The pharmacy of the Amsterdam University Medical Center (UMC) manufactured CDCA for a few months in 2018 for the treatment of CTX. Following a complaint from Leadiant however, Amsterdam UMC had to stop this production, because the raw material contained impurities. In January 2020 Amsterdam UMC managed to relaunch the manufacturing of CDCA, which resulted in lowering the price. Leadiant argued that it had always been its intention, after negotiations, to agree on a much lower price than the price of 14,000 euros it charged.

365 B. Kianzad & T. Minssen (2018), p. 9.

366 *Ibid*, p. 9.

367 DCC, The Maritime and Commercial Court: CD Pharma has abused its dominant position by charging an excessive and unfair price for the drug Syntocinon, Press Release, available at: https://www.en.kfst.dk/nyheder/kfst/english/judgements/20200302-the-maritime-and-commercial-court-cd-pharma-has-abused-its-dominant-position-by-charging-an-excessive-and-unfair-price-for-the-drug-syntocinon/#.

368 The official decision has not yet been published. Therefore, this text is based on the summary provided by ACM, see: ACM, 'Summary of decision on abuse of dominant position by Leadiant', ACM/20/041239, 1 July 2021, available at https://www.acm.nl/sites/default/files/documents/summary-of-decision-on-abuse-of-dominant-position-by-leadiant.pdf.

However, according to ACM it never entered into effective negotiations with the Ministry of Health, Welfare and Sport and health insurers.

ACM stated that as an undertaking with a dominant position, Leadiant had a *special responsibility* to negotiate effectively and seriously, and not to charge and collect an excessive price. Different from the other cases described here, in this case regulatory exclusivity was playing a role. Similar to what ACM officials had argued in several academic papers (see also below),[369] ACM claims that a price may also be considered excessive and the *United Brands* test can be applied if the price is charged for an orphan drug in a situation of market exclusivity, such as in this case. Not the regulatory exclusivities are debated, but rather the way in which Leadiant uses this exclusivity. A higher price can be justified if the manufacturer must recoup high costs or if the product offers many benefits or is innovative. For assessing the costs, the ACM took into account the investments Leadiant has made since the start of this project in 2014, all costs that Leadiant incurred in order to manufacture and distribute the drug and the risk that the project could fail. ACM found low costs in comparison with the revenues, low risks, and a very high return even on the basis of conservative assumptions (required rate of return of 15%, reasonable return for investors). ACM comes to the conclusion that the price it charged was not only excessive, but also unfair. In fact, Leadiant had obtained the orphan drug designation because of the very limited number of CTX patients. Moreover, Leadiant did not introduce any innovation, and CDCA-Leadiant does not have any therapeutic added value compared with the previous CDCA-based drugs. Finally, Leadiant's price is also far higher than the prices of Chenofalk and Xenbilox a few years earlier, even though they are molecularly identical, and considerably higher than the price of CDCA compounded by Amsterdam UMC.

In the meantime, Leadiant has filed a complaint against the health insurers arguing that they were unwilling to enter into negotiations with Leadiant about a possible price reduction. ACM has suspended the payment of the fine during the investigation of this complaint.

369 C. Fonteijn et al. (2018), 'Reconciling competition and IP Law: the case of patented pharmaceuticals and dominance abuse', ACM Working Paper, in: G. Muscolo & M. Tavassi (ed.), The interplay between competition Law and Intellectual Propperty – An International Perspective', Kluwer Law International, available at https://www.acm.nl/sites/default/files/documents/2018-03/acm-working-paper-reconciling-competition-and-ip-law-2018-03-07.pdf; I. Akker & W. Sauter (2021), 'Excessive Pricing of pharmaceuticals in EU law: balancing competition, innovation and regulation', December 2021, available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3991903.

APPENDIX 2. TABLE COMPARATIVE ANALYSIS CLS IN OTHER COUNTRIES

Jurisdiction	Failure to work/insufficient working	Public non-commercial use	Public interest/public health	Excessive Pricing	National emergency/extreme urgency	Anti-competitive practices	COVID-19 CL regime	Legislation
Austria	Section 36 (2)	x	Section 36(3)	x	x	x		Section 36 (2) of the Patents Law 1970 (BGBl. No. 259/1970)
Belgium	Article XI.37§1(1°)	x	Article XI.38	x	x	x		Articles XI.37 and further of the Belgian Code of Economic Law
Brazil	Article 68(1)	x	Article 71	x	Article 71	Article 68(3)	x	Articles 68-74 of the Industrial Property Law No. 9.279 of 14/05/1996
Denmark	Section 45	x	Section 47	x	x	x	x	Sections 45-50 of the Consolidate Patent Act No. 91 of 28/01/2009
Finland	Section 45	x	Section 47	x	x	x		Sections 45-50 of the Patents Act No. 550 of 15/12/1967 as last amended by Act 684/2006
France	Article L.613-11	Article L.613-18 and L.613.19	Article L.613-16	Article L.613-16	x	x	x	Articles L.613-11 to L.613-22-1 et seq. of the French Intellectual Property Code.
Germany	Sections 24(1)(5)	Section 13	Sections 24(1), 85a	x	x	x	x	Sections 13, 24 and 81-85a of the Patent Law of 16/12/1980.
India	Article 84 (1)(a)(c)	Art. 92 (3)(iii)	Article 84 (1)(a)	Article 84 (1)(b)	Art. 92 (3)(i)(ii)	x		Sections 82-85, 88-94 and 99-101 of the Patent Act No. 39 of 1970
Ireland	Section 70 (1)(a)	Sections 73 (1A) (b), 77-78	Section 73 (1A) (a)	x	x	x		Sections 70-78 of the Patent Act No. 1 of 27/02/1992, as last amended by Law No. 31 of 2006
Italy	Article 70 (1) (2)	x	X	x	x	x	x	Articles 70- 72, 141 of the Industrial Property Code, Legislative Decree No. 30 of 15/02/2005
The Netherlands	Article 57(2)	Article 59	Article 57(1)	x	x	x		Articles 57-59 of the Patent Act of 15/12/1994
Poland	Articles 68(1); 82(1)(ii)	x	Article 82 (1)(i)	Articles 68(1); 82(1)(ii)	Articles 69(1)(ii); 82 (1) (i)	Articles 68(1), 82(1)(ii);(3)		Articles 68, 69, 82-83 and 88 of the Industrial Property Law of 30/06/2000, as amended by Act of 23/01/2004 and Act of 29/06/2007

South-Africa	Article 56 (2)(a)(c)	x	Article 56 (2) (d)	Article 56(2)(e)	x	x	Sections 55-56 of the Patents Act No. 57 of 1978 as last amended by Act, No. 58 of 2002
Spain	Article 83; 86(a) 91(a)/92	x	Article 86(d); 90	x	x	x	Articles 83-86, 88-90 and 101-104 of the Law about Patents of Invention and Utility Models No. 11 of 20/03/1986 as last amended by Law No. 10 of 29/04/2002
Sweden	Article 45	x	Article 47	x	x	x	Sections 44-49 of the Patents Act No. 837 of 01/12/1967 as last amended by Law No. 159 of 01/04/2004
Switzerland	Article 37	x	Article 40	x	x	Article 40c - diagnostic product/procedure & anti-competitive practice	Articles 36-40e of the Federal Patents Law of 25/06/1954 as on 01/07/2009
Thailand	Section 46 (1)	Section 51	Section 51	Section 46(2)	Section 52	x	Sections 45-47 bis and 50-52 of the Patent Act B.E. 2522 of 11/03/1979.
United Kingdom	Article 48A (1); Article 48B (1)	Article 55(1) - crown use	Article 55(1)	x	Articles 55(1); 59 crown use	Article 51 (1)	Sections 48-51, 55, 57 and 59 of the Patents Act of 1977
United States	x	28 U.S.C § 1498(a)	X	x	x	x	Title 28, part IV, Chapter 91, paragraph 1498 letter a) of the USC - 28 U.S.C § 1498 (a) - sui generis regime for government use; see also 35 U.S.C. § 203 Bayh- Dole Act of 1980

APPENDIX 3. INFORMATIVE CL CASES

For a brief summary of a few CL cases granted by courts in several EU countries, we focus systematically on the following issues: (1) ground for granting the CL; (2) arguments case-by-case analysis; and (3) adequate remuneration.

Denmark: Case No. I 194/1964 (U.1966.566H) Supreme Court, 17 June 1966

Ground: failure to work

Arguments: the patent for a medicinal product (phenylbutazone) had not been sufficiently exploited in Denmark considering the demand for it and without there being any legitimate reasons for it (decision Patent Commission confirmed by the Maritime and Commercial Court and subsequently by the Supreme Court)

Adequate remuneration: 5% of the sales price ex works. The compensation level in the decision has since been considered the standard level in this type of cases in Denmark if another compensation level is not substantiated to be more relevant.

Germany: Interferon-gamma/Polyferon, BGH - GRUR 1996, 190 (192)

Ground: public interest – CL not granted

Arguments: The patentee had a patent on the active ingredient Interferon-gamma. The applicant found a new use of this active ingredient for the treatment of rheumatoid arthritis and was granted a patent for that specific use and an MA for the medicine Polyferon. The court found that neither the fact that a patent had been granted for a new use of the active ingredient nor the authorisation as a medicine could constitute a public interest. The patentee was also exploring the use of Interferon-gamma to treat rheumatoid arthritis and it was not sufficiently proven by the applicant that Polyferon was the only available medicine for any subset of patients.

Adequate remuneration: not applicable

Germany: Merck Sharp and Dohme Limited v. Shionogi German Federal Court of Justice, 11 July 2017, BGH GRUR 2017, 1017 Rn. 22 f.

Ground: public interest

Arguments: The applicant of the CL distributes the medicine Isentress that includes the active ingredient Raltegravir. This medicine can be used for the treatment of HIV. The patent owner also offers a medicine for the treatment of HIV within the scope of the patent. The court stated that there was a public interest in the continued availability of a medicine for HIV, even though only a small group of patients would have been affected. If the patentee would have been successful with its infringement suits and the applicant would have had to stop selling Raltegravir, patients undergoing treatment with Raltegravir would have had to change the treatment to different medicines with a considerable risk of side effects, interaction or therapy failure for the patients. Therefore, the public interest condition was met.

Adequate remuneration: 4% of the net sales price.

The Netherlands: Appeals Division Dutch Patent Council 19 July 1972, BIE 1972, nr. 72, p. 236

Ground: abuse, public interest

Arguments: a CL can only be granted in cases where the behaviour of the patent owner constitutes a misuse of patent rights and the refusal to grant a licence created a situation that is clearly contrary to public interest. The mere fact that the applicant of the CL could provide the products for a lower price was not sufficient to establish that the public interest would dictate the grant of a CL. The applicant would have to show that the patentee charged “exorbitantly high prices” to the effect that it was abusing its patent rights. Higher prices as such are insufficient since the patent owner needs to have an opportunity to earn back R&D costs.

Adequate remuneration: not applicable.

APPENDIX 4. SUMMARY OF THE LEGAL FRAMEWORK FOR PHARMACY PREPARATIONS IN BELGIUM

Compounding pharmacy preparations[370] is one of the core missions of pharmacists working in pharmacies open to the public and hospital pharmacists. In some cases, particularly for patients with rare diseases, hospital pharmacies have even started making these preparations long before they were patented, industrialised and marketed by a pharmaceutical company[371].

Due to the shift towards personalised medicines, including advanced therapy medicinal products (ATMPs[372]), pharmacy preparations are increasingly being promoted as a means to respond to certain patient needs, especially the needs of the patients with ultra-rare diseases. Indeed, in some situations, such as very small patient groups, it is not sufficiently profitable for industry to develop those medicines or to maintain them on the market[373]. In addition, pharmacy preparations are sometime presented as a possible alternative in case of pressure on national healthcare budgets by highly priced medicines or in case of medicinal product shortages[374].

As mentioned earlier in the report (section 3.5), Belgium has implemented, **in its patent law**, a patent exemption for "*the preparation of medicines extemporaneously and per unit in pharmacies, on medical prescription* " (art. XI.34(c) BCEL). Like all exceptions, the pharmacy exemption must be interpreted in a strict manner. Even though no Belgian case law exists that has clarified this provision, the parliamentary discussions preceding its introduction in the law in 1980 state that the preparation shall be made 'in a pharmacy' (and not in industrial facilities) and shall exclude the preparation of 'significant quantities' 'for several patients'[375]. Despite these statements, the pharmacy exemption under Belgian patent law remains relatively vague, especially with regard to preparations which, although not industrial, would be outsourced by a pharmacist to a manufacturing unit (authorised to prepare medicines under Belgian law). It should indeed be highlighted that, at the time this exemption was introduced (1980), ATMPs and personalised medicines requiring very specific precautions were not as developed as they are today. Following the development of highly complex preparations requiring special precautions, the quality standards for preparations were tightened in Belgian legislation and outsourcing practices developed. It seems therefore desirable that the current patent exemption for pharmacy preparation evolves or is clarified through guidelines to address this new situation.

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370 The term 'pharmacy preparation' is not uniformly used throughout Europe. For this appendix, the term 'pharmacy preparations' shall encompass all pharmacy made preparations (e.g. magistral preparation, officinal preparation, hospital ATMPs preparations) excluding reconstitutions of authorised medicines and preparations in the context of clinical trials.

371 The following commercial medicines were for instance already prepared in pharmacies prior to their industrialisation: Cystadane®, Cystadrops®, Gliolan®, Granupas®, Jorzeva®, Pedea®, Peyona®, Wilzin®. See M. Dooms, M. & Carvalho, 'Compounded medication for patients with rare diseases' *Orphanet J. Rare Dis.* 13 (2018), available at: https://doi.org/10.1186/s13023-017-0741-y. P

372 In essence: medicines that are based on genes, tissues or cells.

373 This has been illustrated by several market withdrawals of cell therapies after the holder of an MA failed to obtain the requested reimbursement conditions (for instance Skysona® & Zynteglo®).

374 See for instance European Association of Hospital Pharmacist's Position Paper on Pharmacy Preparations and Compounding https://www.eahp.eu/practice-and-policy/compounding.See also the position paper of the Belgian Cancer foundation : https://www.kanker.be/sites/default/files/white_paper_-_cell_therapy.pdf . See also the position of the Dutch authorities summarized in section 5.5 of this report.

375 *Doc. Parl.* Sess. 1980-81 n°919/1, p. 15, available at: https://www.dekamer.be/digidoc/DPS/K2029/K20293330/K20293330.PDF

In addition to patent law which is the main focus of the report, this appendix briefly summarizes the regulatory framework under which pharmacies are allowed to compound medicinal preparations in Belgium. While the basic conditions of these preparations are defined in EU law, their regulation are not harmonized at the EU level (in particular with regard to the identification of the industrial threshold triggering the application of rules for industrial medicines and to the implementation of quality rules).

The reimbursement of these preparations (including the reimbursement of the raw materials) and the availability of the raw materials and facilities are also two essential conditions for the pharmacy preparations to be efficient. These aspects are however not covered by this appendix.

Appendix 4.1. European and Belgian legislation on non-industrial preparations

Directive 2001/83/EC specifies that it applies to "*medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process*"[376].

For products that meet this definition, the EU legislator has provided, by way of derogation from the general product regime[377], a harmonised system of prior authorisations (incl. marketing authorisation, manufacturing authorisation, wholesale authorisation, …). Indeed, for those industrialised products a stricter regulation was deemed necessary to ensure the highest level of protection of public health while guaranteeing their free circulation[378].

However, according to article 3 of Directive 2001/83/EC, the Directive does not apply to certain preparations, including[379] magistral formulas, officinal formulas, and advanced therapy medicinal products used in hospitals (ATMPs).

Directive 2001/83/EC imposes specific conditions for these three situations to fall outside the scope of the rules for industrial medicines. Provided that these conditions are met and that relevant Community rules are not undermined, the Member States are free to define the rules applicable to these preparations (industrial threshold, qualifications, quality, traceability etc.).

4. Magistral formulas

The magistral formula is defined in article 3 of Directive 2001/83 as the preparation of a medicinal product "in a pharmacy", "in accordance with a medical prescription", which must be "intended for a specific patient". In Belgian law, magistral formula is defined in the same way in Article 6*quater* § 3 of the Belgian law of 25 March 1964 on medicinal products.

These conditions are assessed on a case-by-case basis. However, the CJEU clarified that *"the production, in a standardised manner, of significant quantities of a medicinal product with a view to its storage and wholesale, as well as the large-scale or mass production of magistral formulae in batches, are characteristic of an industrial preparation or of production by a method involving an industrial process*".[380]

In essence, a magistral formula must be prepared in "non-significant" quantities and for a specific patient identified prior to preparation. The magistral exception therefore excludes "*a system of supply by 'subscription',*

376 Article 2, § 1 Directive 2001/83/EC

377 See the 'Blue Guide' on the implementation of EU products rules 2016 (2016/C 272/01), available at: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52016XC0726(02)&from=FR

378 Articles 168.4 and 114 of the Treaty on the Functioning of the European Union (TFUE) constitutes the legal grounds of the Directive 20001/83/EC.

379 Medicinal products intended for research and development trials, intermediate products intended for further processing by an authorized manufacturer, radionuclides in the form of sealed sources and blood, non-industrial plasma or blood cells of human origin are also excluded. These are out of scope of this Appendix.

380 CJEU, Joined cases C-544/13 and C-545/13, Abcur AB v Apoteket Farmaci AB and Apoteket AB (Abcur), ECLI:EU:C:2015:481, para. 51.

taken out by a non-hospital pharmacy, on the basis of an estimate of its short-term needs for a medicinal product which is not prepared specifically for a patient identified in advance." [381]

Provided that those conditions are complied with (and that the patent exemption conditions and quality rules are met – see below under 4.2), pharmacies can prepare a magistral formula, even if there is an alternative with a MA.[382]

Some preparations may require special precautions or expertise. Therefore, under Belgian law, certain magistral preparations may be delegated to another pharmacy or to the holder of a preparation authorisation[383]. It is also possible for hospital pharmacies to pool their work by organising an association for the pharmacy function[384].

5. Officinal formulas

According to article 3 of Directive 2001/83/EC and article 6*quater* § 3 of the Belgian law of 1965 on medicines, officinal formulas are "*medicinal products prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and intended to be supplied directly to patients served by the pharmacy in question*".

According to the Court in the above mentioned *Abcur* judgment, there can be no officinal formula when the medicinal product is prepared by a pharmacy and then sold by that pharmacy to a third party who delivers it to its own patients.

Furthermore, in another judgment of 26 October 2016, the Court added that the quantity must be produced in the normal course of business of the pharmacy (which is the case, according to the Court, of a pharmacy that produces 213 boxes in a year, whereas German law limits the maximum authorised production of officinal preparations to 100 boxes per day) [385].

Like magistral formulas, officinal formulas can be prepared even if there is an alternative with an MA. In addition, no prescription is required but the officinal formula must be prepared solely on the basis of a "validated recipe" (a pharmacopeia) and can be supplied only to the patients of the pharmacy preparing it (which excludes outsourcing between pharmacies).

6. Advanced therapy medicinal products prepared on a non-routine basis and used in a hospital

An advanced therapy medicinal products as defined in Regulation (EC) No 1394/2007[386] can also fall outside the scope of the Directive 2001/83/EC if they are prepared on an *ad hoc* basis, according to specific quality standards, and used within the same Member State, in a hospital, under the exclusive liability of a medical practitioner, to fulfil a specific medical prescription for a product specially designed for a specific patient[387]. Each

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381 CJEU, Abcur, para. 64.

382 See article 6 quarter § 3 of the law of 25.03.194. This was also confirmed in § 55 CJEU*, Abcur.* In contrast, two administrative guidelines from 2008 and 2010 on outsourcing of magistral formulas seem to consider that if authorised alternatives are available, this outsourcing cannot happen. (https://www.fagg.be/sites/default/files/downloads/ozb-514-2008-04.pdf and https://www.fagg.be/sites/default/files/downloads/ozb-567-2010-05-12.pdf). It would be desirable to update and clarify these guidelines in accordance with the Belgian law on medicines and with the European case-law.

383 AR du 21.01.2009 portant instructions pour les pharmaciens (officines), art. 33 et AR du 30.09.2020 portant sur la préparation et la délivrance des médicaments et l'utilisation et la distribution des dispositifs médicaux dans les établissements de soins (pharmacies hospitalières), art. 22 (not yet entered into force).

384 AR 30.09.2020, art. 23.

385 CJEU, Case C-276/15, Hecht-Pharma GmbH v. Hohenzollern Apotheke, Winfried Ertelt, ECLI:EU:C:2016:801.

386 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, [2007] OJ L 324, 121–137.

387 Article 3 of the Directive 2001/82/EC. See also article 6 quarter § 3 of the Belgian law of 25 March1964 and Royal Decree of 08 January2017.

Member State defines its quality standards and specific rules to be allowed to prepare such ATMPs (conditions, timelines for authorisation, level clinical evidence required, etc.).

According to the Belgian legal framework, such preparations require a prior authorisation by the FAMHP for each product (this authorisation is called hospital exemption for ATMPs). While this is not a requirement under European law, the Belgian regulations impose that such an authorisation is refused if a MA was delivered for the same product, provided that this product is '*available for the patients',* including in the context of a medical need program or clinical trial[388]. As such the text of the Belgian regulation does not explicitly exclude an ATMP preparation in cases where there is a product authorised but this alternative is unavailable for the patients due to an excessive price (and lack of reimbursement).

Additionally, Belgium has defined particularly strict requirements for this type of preparation, such as the requirement to present specific clinical data to justify their preparation and use and the conformity of the preparation with Good Manufacturing Practices (GMP). GMP are indeed the highest quality standard for the preparation of medicines. They are also mandatory for the manufacturing of all industrial medicinal products in Europe.

Several countries make use of "hospital exemptions". France (11 authorisations), Germany (7) and the Netherlands (11) use them quite often. Up to now, only one hospital exemption has been issued in Belgium. According to the several Belgian cancer foundations, this can be attributed to stringent clinical data requirements to be authorised to prepare[389] and a lack of capacity to comply with conditions such as GMP in academic centres[390].

Appendix 4.2. Quality rules preparations by pharmacies in Belgium

Both magistral and officinal formulas must be prepared in compliance with high quality standards. Pharmacists must comply with stringent rules for their preparations, including to comply with national Good Practices for pharmacies[391], control the quality of their preparations and have the appropriate equipment. They are also only allowed to use authorised and/or certified raw materials[392].

In the future, hospital pharmacies that make preparations will even have to comply with PIC/S[393] standards (already applicable for investigational medicinal products)[394]. Hospital pharmacies that are unable to meet these standards may delegate magistral formulas (officinal formulas cannot be delegated because their definition limits their use to the pharmacy that manufactures them) to a pharmacy with the required facilities[395].

As mentioned previously, the preparation of ATMPs is even more controlled as it is mandatory to have a prior authorisation issued by the FAMHP and to

388 A.R. 08.01.2017, article 5. The authorisation is also refused if an hospital exemption was already granted to another applicant.

389 In some countries such as Austria, Finland, France and Italy, a HE can be granted without clinical evidence. How academic development of cell therapy can benefit Belgian patients, White paper, February 2022, available at: https://www.kanker.be/sites/default/files/white_paper_-_cell_therapy.pdf

390 *Idem.*

391 These practices are containted in AR du 21.01.2009 portant instructions pour les pharmaciens (officines) et AR 30.09.2020 (pharmacies hospitalières) (only available in French and Dutch).

392 For more details see : https://www.fagg.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/procedures_vhb/ziekenhuisvrijstelling_voor and https://www.afmps.be/fr/humain/medicaments/preparations_magistrales_et_officinales

393 https://picscheme.org/en/about

394 AR du 24.12.2020.

395 AR 30.09.2020.

comply with Good Manufacturing Practices (GMP)[396], in contrast with other countries.

Appendix 4.3. Different practices in the European Union

The Directive 2001/83/EC only contains certain general conditions to prepare magistral and officinal formulas and ATMPs. The regulation of pharmaceutical preparations is therefore not fully harmonized at the EU level.

Differences in regulations between the EU Member States concern for instance:

- **The possibility to outsource preparations**: outsourcing is not permitted in certain States, whereas it is a frequent practice in other, especially when the procedure is considered to be too difficult (advanced therapy medicinal products) or dangerous (cytotoxic and radio-active agents and vaccinations)[397]. In Belgium, pharmacies are allowed to outsource magistral formulas to another pharmacy or to the holder of a specific national 'preparation authorisation'. The preparation of ATMPs in the context of pharmacy exemption is not explicitly limited to the pharmacy, they can therefore be prepared by a pharmacy or by GMP compliant facilities.
- **The threshold to reach an industrial production** (disqualifying the preparation as magistral or officinal formula): in some Member States the legislation or the guidlines identify a maximum number of preparations per day or per patient[398] and in other States there is no specific threshold. In Belgium, there is no specific limitation in quantities. However in the regulation regarding ATMPs pharmacy exemption it is stated that this element will be evaluated as one component of the "non routine" production[399].
- **The absence of authorised therapeutic alternative** : despite the case-law of the CJEU which confirms that this is not a pre-condition, some Member States consider that certain preparations can only be compounded by pharmacies in the absence of an available or suitable authorised medicinal product[400]. In Belgium, the legislation does not impose that condition for magistral and officinal formulas but adds it for ATMPs under the pharmacy exemption.
- **Quality rules :** Members States are completely free to determine which quality rules are applicable to pharmacy preparations. Belgium is for instance particularly strict for the preparation of ATMPs by pharmacies as it requires the compliance with GMP rules (also applicable to industrial medicines) for such preparations while the Netherlands does not require compliance with GMP rules.

In the context of excessively priced medicines, the case of the Netherlands is particularly interesting because the public health authorities explicitly support the use of pharmacy preparations in this situation (under specific conditions)[401]. In addition, in the Leadiant-case (summarized in Appendix 1), the Dutch Competition authorities convicted a pharmaceutical company, for abuse of dominant position (including because they applied excessive prices for a specific product). At the time, these authorities had also announced that they will carefully monitor unjustified barriers to pharmacy production for

396 https://www.fagg.be/sites/default/files/guidance_atmp-he_1.pdf.

397 https://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0741-y#citeas

398 See for instance in the Netherlands https://www.parlementairemonitor.nl/9353000/1/j9vvij5epmj1ey0/vkxilye6j6qv (50 patient short term and 150 long term)

399 RD 8.01.2017, appendix 2.

400 See for instance French Public Health Code (art L. 5121-1). https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000044628485/.

401 https://www.raadrvs.nl/documenten/publications/2017/11/09/development-of-new-medicines---better-faster-cheaper
and
https://www.parlementairemonitor.nl/9353000/1/j9vvij5epmj1ey0/vkxilye6j6qv

example by restricting access to raw materials or by setting unreasonable conditions.

Key points

- **Under Belgian patent law, preparations that are prepared "in the pharmacy" fall under this Belgian patent exemption. As this Belgian patent exemption was introduced in 1980, it would be useful to clarify its application with regard to new "outsourcing" practices (through amendment of the legal text or via guidelines).**
- **In addition, the Directive 2001/83/EC imposes certain specific conditions for the pharmacy preparation to fall outside the scope of the rules for industrial medicines. Provided that these conditions are met, Member States are free to define the rules applicable to these preparations (industrial threshold, quality rules, outsourcing conditions)[402].**
- **Under European law pharmacies are not strictly prohibited to prepare a magistral or an officinal formula or an ATMP, even if there is an alternative with a marketing authorisation 'available' for the patients but certain Member states added this condition sometimes (differently, for different type of preparations) in their national legislations.**
- **In Belgium the quality rules for the preparation of ATMPs in pharmacies are stricter than in other countries. This can possibly explain why until now there only 1 ATPM is currently being prepared and used under the hospital exemption in Belgium.**

402 https://medicineslawandpolicy.org/2019/02/faced-with-unreasonable-medicines-prices-the-netherlands-introduces-pharmacy-exemption-in-patent-law/

APPENDIX 5. BRIEF OVERVIEW OF THE DRUGS PRICING CRITERIA IN BELGIUM [403]

The **maximum ex-factory price** of a drug is determined by the Minister of Economic Affairs. Applications for price setting or price increase must be introduced by the pharmaceutical company. To take the decision, the Minister of Economic Affairs is advised by the Committee of Pricing for Pharmaceutical Specialties (Commission des Prix des Spécialités Pharmaceutiques (CPSP) –Prijzencommissie voor de Farmaceutische Specialiteiten (PFS)).

For each application, the pharmaceutical company must provide different information, including a justification of **the price based on the following cost elements**: production, import, analysis, transfer, research and development costs (called the part KP1 or PR1[404]) and labour, advertising and information, and selling and general costs (called the part KP2 or PR2). [405]

However, as pointed out in 2013 by the highest administrative court controlling the budget spending in Belgium (Cour des Comptes – RekenHof), the information provided by the firms to set the price does not allow for "*a realistic approach to costs and profit margins*"[406]. Despite this report and the discussions announced in 2017[407], the Federal Public Service (FPS) Economy has still **not enough tools to verify cost elements given by the manufacturer**.

The pricing decision should in principle depend on the added therapeutic value of a drug (if a comparator is available). However, **the issues reported in previous KCE report are still observed today**[408]:

- The maximum pricing decision is made before the added therapeutic value has been discussed at the RIZIV-INAMI (reimbursement authorities)[409]. As a consequence, the maximum price is usually based on the prices of other products in the same therapeutic cluster as the new product (internal reference pricing) and on the prices in other countries (external reference pricing).
- The ministry does not dispose of an estimate of the return on investment. According to the companies, it is impossible to grant more transparency in the pricing. Therefore, the ministry uses prices in other European countries as a reference. A similar process is applied in other European countries. The fact that all countries are looking at each other's prices is not very helpful, as this practice will only lead to companies starting off with asking a high price in the first country, they submit their reimbursement request to and to negotiate with the government to keep the high facial price. As companies know that the only direction in which the price decision goes is downwards, they are actually given an incentive to ask a high price.

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403 This section was drafted on basis of the KCE reports 288B (2017) and 147 C (2010).

404 KP : kost prijs (Nl)/ PR : prix de revient (Fr).

405 A.R. 10.04.2014 fixant les conditions de recevabilité, les délais et les modalités pratiques des demandes de fixation de prix, des demandes de hausse de prix, des notifications de prix et des communications (de prix) des médicaments, des objets, appareils et substances assimilés à des médicaments, et des matières premières, tels que visés dans le livre V du Code de droit économique, M.B. 01.07.2014.

406 Rapport de la Cour des Comptes sur le remboursement des médicaments, décembre 2013. See https://www.ccrek.be/FR/Publications/ApercuChronologique.html?year=2013

407 See KCE report 288B. https://kce.fgov.be/fr/publication/report/pistes-pour-am%C3%A9liorer-le-syst%C3%A8me-belge-de-conventions-article-81

408 KCE reports 288B (2017) and 147 C (2010).

409 In France, the pricing system was reformed and the HTA authority (HAS) issues an opinion on the medical service rendered before the price is set.

In accordance with the EU Transparency Directive, the price decision must be communicated to the applicant within 90 days following the application.

The Minister also fixes the maximum distribution margins for the wholesaler and the pharmacist, as well as the maximum public price including T.V.A. (6%). The maximum prices or margins set by the Minister are imperative: they cannot be exceeded. On the other hand, it is always possible for a company to apply prices lower than these maximums.

COMPULSORY LICENSING FOR EXPENSIVE MEDICINES

ECONOMIC CONSEQUENCES

WALTER VAN DYCK, JEROEN LUYTEN, ROSANNE JANSSENS, LIESE BARBIER, STEVEN SIMOENS

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ART	Antiretroviral therapy
CL	Compulsory licensing
EBITDA	Earnings before interest, taxes, and depreciation
ENPV	Expected net present value
HIC	High-income country
IPR	Intellectual property rights
LMIC	Low- or middle-income country
R&D	Research and development
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
WACC	Weighted average cost of capital

1 PROBLEM DESCRIPTION

The current and future market entry of very expensive medicines in high-income countries puts pressure on the limited pharmaceutical budget and threatens the affordability and sustainability of pharmaceutical expenditure in the long term [1]. High prices are observed for a variety of medicine classes, including orphan medicinal products, hepatitis C medicines, oncology medicines, and advanced therapy medicinal products. In high-income countries, numerous media items, reports and academic publications have brought this issue to the fore and have called for measures to address high prices of medicines [2, 3].

However, there is no conceptual consensus on what a 'fair' price for a medicine is [4] A fair price can be set based on historic cost (a 'cost-plus' approach) where a 'reasonable' profit margin is added to the costs required to produce and distribute the product. Of course, which profit percentage is reasonable is a matter of debate, as well as which types of costs can be included. Also, a cost-plus approach does not provide an incentive to pharmaceutical companies to be efficient. Alternatively, a price can be based on the 'value' of the product sold in which case the connection with historic costs is cut. For medicines this would mean that the additional benefits (mostly health but also broader benefits and cost-savings) would need to be 'monetized' in order to determine the 'fair price'. Both approaches have practical difficulties, with a cost-based approach requiring adequate data on drug development costs and their breakdown [5], and value-based pricing requiring monetary estimates of a medicine's benefits.

A discussion of how medicine prices are or should be set falls outside the scope of this report, but we focus on CL as one possible mechanism to influence medicine prices in HICs. Under CL, a third party is authorised to produce and market the medicine subject to restrictions in geographical scope and duration, and with the requirement to pay remuneration to the patent holder. The use of CL for medicines has been primarily debated in relation to developing countries and access to for example HIV medicines [6], but European politicians and policy makers have also put CL on the agenda in recent years. For instance, the Dutch Minister of Health Bruins has discussed the option of CL for expensive medicines. Additionally, some have argued in favour of CL in the context of COVID-19 vaccines and therapies [7]. To date, CL has been occasionally applied by HICs in the context of combatting high medicine prices, but has rarely led to price reductions [8]. Therefore, there is uncertainty about using CL to tackle the issue of very expensive medicines in HICs in terms of its economic consequences for the innovation, investment and industrial climate (for medicines and for other goods or services), for the market entry of new medicines, and for the competitiveness of local and international pharmaceutical markets.

The economic consequences of CL for medicines discussed in this report should not be evaluated in a vacuum, but they must be compared to the consequences of **alternative policies**. Such alternatives include: a 'business as usual' scenario in which patent holders are free to exert their intellectual property rights, voluntary licensing, cost-plus pricing, tiered pricing, procurement on the international market, pooled procurement involving multiple countries, various arrangements regarding price transparency and mandatory cost disclosure [9, 10]. For instance, a literature review of the impact of CL on medicine prices argued that it was not clear that CL always leads to greater price reductions than voluntary licensing, price negotiations or the lowest global price [11]. Finally, competition authorities may investigate high medicine prices in the context of alleged 'misuse of a dominant position' [12]. These policies may have different consequences and which of these policies emerges as the 'best' one depends on what is valued by decision makers and how they want to make trade-offs.

2 OBJECTIVES

The aim of this study is to assess the economic consequences if Belgium would implement CL for very expensive medicines. To this effect, a narrative review of the existing literature is conducted with a view to evaluate CL as an instrument to address high medicine prices. This study is structured as follows: the first part specifies the methodology of our literature review; the second part compiles available studies exploring economic theories, empirical evidence and remuneration models in the context of CL; and the third part investigates the pros and cons of CL for medicines and discusses remuneration for CL based on the literature.

3 LITERATURE REVIEW METHODS

Our narrative literature review is based on the principles of the 'realist review' methodology [13, 14], in particular with respect to: a) understanding the consequences of compulsory licensing; b) combining theory with practice; c) applying a flexible and purposive search strategy; d) extracting and synthesising data; and e) interacting with the commissioner of this study (i.e. KCE).

3.1 Understanding the consequences of compulsory licensing

The 'realist review' methodology allows to investigate the consequences of CL by gaining a deeper understanding of why and how CL works for which stakeholder when implemented in a specific form for a particular purpose in a specific context or setting. Instead of applying a traditional review methodology which is likely to find that the evidence on the consequences of CL is mixed, the realist review methodology is suited to provide insight in the mechanisms by which CL works under which circumstances.

3.2 Combining theory with practice

Our review consists of two phases, i.e. a theoretical foundation and an empirical state of the art.

The first phase examines economic theories with a view to explain the use of intellectual property rights (such as patents, data and market exclusivities, trade secrets) to reward investment in innovation, and to describe the expected economic consequences of CL. The review considers generic economic theories about R&D of goods and services, and also focuses specifically on models related to medicines if available. Hence, this review of economic theories identifies and discusses the theoretical framework(s) that allow us to explain why and how CL might work and what its expected consequences are.

The second phase reviews empirical studies that draw on quantitative or qualitative data to investigate the consequences of CL for medicines on macro-economic indicators (such as the innovation climate, foreign direct investment, competitiveness of the national pharmaceutical market and health expenditure, competition within the pharmaceutical market, market availability and access to medicines, medicine prices and reimbursement) and identify the underlying mechanisms. This phase serves to corroborate, refute or adapt the theories generated in the first phase of the review.

3.3 Applying a flexible and purposive search strategy

An extensive and varied body of evidence is relevant to inform our understanding of the mechanisms and consequences of CL for medicines. Therefore, a flexible and purposive search strategy is run until saturation is reached.

Relevant material is sourced from the peer-reviewed literature (by searching the databases PubMed, EMBASE, EBSCO Business Source Complete, and RePEc [Research Papers in Economics]), from the grey literature (including books, websites of relevant organisations [e.g. World Trade Organisation, World Intellectual Property Organisation, World Health Organisation, World Bank, Organisation for Economic Co-operation and Development, South Centre, pharmaceutical trade associations], reports from consultancy agencies and advisory bodies [e.g. ABDTOPConsult], policy and legal documents) and by searching Google. Also, relevant material is identified by searching the bibliographies of references ('snowballing method'). Search terms consist of legal terms (e.g. intellectual property rights, march-in rights [i.e. right of the US government to assign license to another party when patent holder received public funding], patent), regulatory terms (e.g. compulsory licensing, pricing, reimbursement), economic terms (e.g. innovation, investment, competitiveness) and terms related to study approach (e.g. theory, empirical study, economic model) alone and in combination with each other. No restrictions are placed on geography or time of publication, but only material written in Dutch, English, French or German is considered. Details of the search strategy are provided in Appendix 1.

3.4 Extracting and synthesising data

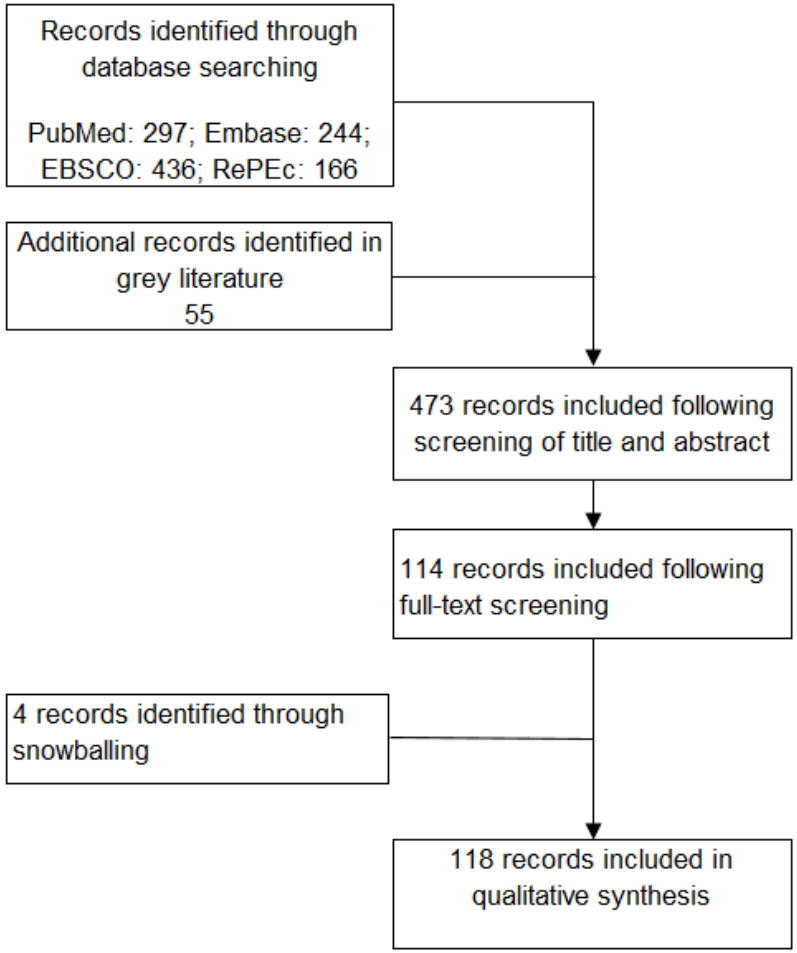
Data from included records are collected in data extraction forms related to economic theories, empirical studies and remuneration (with a record contributing data to multiple data extraction forms if relevant). In light of the varied relevant literature, no standard quality assessment tool is applied. Instead, each record is critically appraised by the review team in terms of its rigour, which is a modus operandi commonly applied in realist reviews. Data are synthesised in a narrative report describing the use of CL worldwide to date and examining the consequences of CL from an industrial policy perspective and from a health policy perspective.

3.5 Interacting with the study commissioner

Regular meetings between the KCE and the review team are organised over the course of the study to delineate the large and diverse body of potentially relevant literature, to refine approaches, and to discuss which additional issues emerging from the literature to examine.

4 LITERATURE REVIEW RESULTS

4.1 Search flow diagram



4.2 Data extraction

4.2.1 Theoretical studies

Mechanism	Consequence	Context	Goods/services	Reference
CL threat aids in reducing the price during negotiations **CL serves to break up monopoly and support technological progress (incremental innovation)**	-	-	Goods/services, drugs	[15]
Intellectual property protection stimulates R&D in innovation but it can also slow down innovation when the scope of application of the technology is broad. The paper argues that CL can increase innovation but only when appropriate levels of royalties are being paid.	To minimize the loss in dynamic efficiency in generating new knowledge and innovation though issuing CL, patent holders should be paid a high enough royalty.	R&D in general	Goods/services	[16]
CL diminishes monopolistic power and enables the sharing of knowledge required to produce new knowledge	CL supports innovation	-	Goods/services	[17]
The consequences of CL are different in a small country: there will be static gain as prices will go down and the negative impact on innovation will be limited as this will be determined on bigger markets such as US or Japan. **The mere possibility of a CL can lead to a loss in dynamic efficiency (i.e. lower propensity to future innovation). The threshold for using CL must be high enough so that the static gains outweigh the dynamic cost.**	CL can be useful, particularly for small countries.	CL can be useful, particularly for small countries, not having the innovator company on their territory. Regulatory economics literature arguing that some forms of intellectual property are like 'essential facilities. In a country, these are input factors for which there's no viable substitute, so that the input factor owner can exercise market power so consumers may experience welfare loss.	Goods/services	[18]
CL reduces incentive to innovate, but increases access to drugs	Society needs to find socially optimal point where CL cost in terms of reduced innovation equals benefit of increased access	Although there is less incentive to innovate, this may not translate in less innovation or current investment levels in research may exceed socially optimal level	Drugs	[19]
CL can promote innovation - if governments can credibly commit to using it only in exceptional cases of emergencies.	CL may be particularly effective in promoting invention by increasing the threat of competition in fields with low pre-existing levels of competition, which will motivate incumbents to invest more in R&D. However, transposing this to pharma, the credibility of national government to apply CL is	German chemical industry 1900-130 period following CL imposed by US in Enemy Act	Chemicals	[20]

Mechanism	Consequence	Context	Goods/services	Reference
	only there when they can invoke emergencies, seen as a 'one-shot' event.			
Foreign direct investment is determined by three factors: Ownership, Localisation and Internalization (ILO-theory). CL can – depending on the local circumstances – affect all three aspects and can therefore influence foreign direct investment.	Countries issuing a CL risk reduced foreign direct investment. This 'cost' is long-term and needs to be compared to the immediate benefit of saving lives through CL.	Brazil and Egypt are compared. Brazil is a success case of CL, Egypt not.	Drugs	[21]
CL can lead to (1) reduced foreign direct investment, (2) reduced activities in the licencing country, (3) increased litigation costs, (4) do not necessarily lead to lower prices (5) can lead to broader economic sanctions	The challenge for low- and middle-income countries is how to minimize the side effects of CL.	Drug access in low- and middle-income countries	Drugs	[22]
Price control in combination with CL threat ensures consumer access to (lower-quality) good, reduces voluntary license price, can incite company to enter the market instead of engaging in voluntary licensing, but can delay access in the case of CL	Price control and CL complement each other	A company decides whether to enter the market or engage in voluntary licensing subject to price controls set by a country	Drugs	[23]
If a drug is subject to CL, there may be price spillover effects to other countries	Price reductions reduce company profits	Impact depends on extent to which price spillover happens	Drugs	[24]
Does CL replace market entry or voluntary licensing?	Under high fixed costs of market entry, CL grants access to a drug and generates royalties for the company from a market in which the drug would otherwise not have been available Under intermediate entry costs, a company prefers not to enter but wait for CL and CL reduces welfare of the country (delayed access to lower-quality drug) when the company would have entered in the absence of CL Under low entry costs, a company will enter and CL does not impact welfare	The impact of CL depends on the size of market entry costs and the decision of the company whether to enter the market in the absence of CL	Drugs	[25]
Without TRIPS: When patent holder does not enter the market, CL can be positive for patent holder (due to royalties). Imitation is cheaper for a country than CL because no royalty payment needed. **With TRIPS: low- and middle-income countries have incentive to issue CL to make medicines**	Depending on prior existence of patent protection, CL can be a rational outcome for both low- and middle-income countries and patent holders.	The South has an incentive to offer patent protection if and only if it is necessary for inducing the patent holder to serve its market and the quality of the imitated local product is sufficiently low.	Goods/services	[26]

Mechanism	Consequence	Context	Goods/services	Reference
cheaper. But CL can also make patent holders better off: less imitation and counterfeit.		Patent protection (instead of CL) becomes more likely when the South can negotiate a price below the optimal monopoly price.		
In a bargaining between a company that considers product launch in a country, when the latter has the option of a CL, when there can be negative spill-overs from entering that market (e.g. through international reference pricing) it can be worthwhile for high valuation firms to enter immediately and for the lower valuation firm to wait for the CL to be issued.	CL can be an important weapon for countries to enforce entry in a market by a patent holder. Depending on the firm and the product, it can be strategic for them to wait or to enter.	Patent holders decision to enter a market or not, applicable to patented drugs entering low- and middle-income countries	Goods/services	27
Paper develops a supply and demand scheme for DDP-4 inhibitors sales in India and analyses and quantifies the welfare effects of voluntary licencing, tiered pricing and CL. CL leads to maximal consumer surplus in the short term but in the long-term it will be reduced when companies stop launching new products because sales are not profitable anymore or because they want to influence policy.	Consumer welfare can increase in the short term due to lower prices but may decrease in the long term when innovators response is to not enter or delay entry into markets with weak IP protection.	DDP-4 inhibitors in India.	Drugs	28
CL that are short-term/unpredictable or affect insignificant markets do not necessarily have an adverse impact. Otherwise, they are more risky. Level of compensation may be equally important.	Small countries issuing a CL with substantial compensation could be attractive.	All economic sectors but focus on pharma	Goods/services	29
CL can also be used to produce for other (low- and middle-income) countries. Canada does this. Its generic sector grows potentially to produce for export	CL can make export generics industries grow	All drugs	Drugs	30
A less studied consequence of CL is that it facilitates the entry of less efficient producers on the market. In a cournot (quantity) competition with a threat of CL, monopolists will compare the loss of income through CL with a lower price with the situation without CL but a lower price (to avoid CL). The latter option is more efficient from social welfare perspective because there is no need for costly extra production capacity. A royalty per	Under a royalty arrangement, CL might work as a disciplining device to improve short term social welfare as it would lead to lower prices without needing inefficient producers entering the market. When there is a small cost disadvantage with the patent holder, A CL would be the preferred choice.	The static efficiency effects of CL	All products	31

Mechanism	Consequence	Context	Goods/services	Reference
unit (and not a fixed fee) will increase the deterring effect.				
Tiered pricing with marginal cost pricing in low- and middle-income countries could be the way to reconcile access to medicines with incentives to innovate. CL only makes sense when local production has a cost advantage over originator firms or when there are price spill-overs to other countries (making it impossible for originators to price at marginal costs). CL can also be useful in systems without large public negotiator so that many products will compete and put downward price pressure. Risk is that many countries follow and that no one pays for the R&D costs anymore. A second consequence of CL is industrial policy: promoting local industries at the expense of originator firms	A case is made for differential pricing between low- and middle-income countries and high-income countries, with the former only paying marginal cost prices, as long as parallel imports or external reference prices can be stopped. Confidential rebates may be a solution.	Drug access in low- and middle-income countries	Drugs	32
Price reductions and encroachment of intellectual property rights caused by CL can have multiple consequences	5 theoretical consequences: Impact of lower profit margins on innovation Impact on direction of innovation Pharmaceutical companies are less likely to locate in CL country, do not introduce new medicines or introduce them later, are less likely to conduct clinical trials	-	Drugs	12
Alternatives exist for CL: targeted negotiations, challenging unfair pricing by competition authorities, mandatory disclosure of economic data and facilitating voluntary cross-border purchasing arrangements.	CL is the 'nuclear option'. Alternatives such as abuse of a dominant position but mostly, collaborative cross-border negotiations are more promising and less risky.	Gene therapies and other high-price drugs	Drugs	10
CL can also be used as a tool to protect competition, to avoid antitrust, but many legal questions remain	It is difficult to judge when valid intellectual property rights become an impediment to competition and innovation in the later years.	Intellectual property in general	Goods/services	33
To compensate for the loss of income due to CL, a pharmaceutical company is unlikely to raise drug prices, reduce expenditure on advertising or return on investment; but can reduce expenditure on research and development	CL has a negative impact on pharmaceutical innovation	-	Drugs	34

Mechanism	Consequence	Context	Goods/services	Reference
Corporate social responsibility can be seen as a practice of dynamic negotiation and interaction between different actors	Providing drugs at low cost or allowing CL can be viewed as corporate social responsibility from originator firms. However, they will need governments pushing them into this direction.	Anti-retroviral drugs in Brazil	Drugs	[35]
In markets with high income inequality, monopolists have an incentive to price their product much higher than in more equal income markets, so that they serve only the price-inelastic part of the (often convex) demand curve. This leads to large 'deadweight losses' and could be an additional argument for using CL.	In markets with high income inequality, mostly low- and middle-income countries, there is an incentive for monopolists to ask higher prices than in markets where the same income is more equally distributed. This is a rationale for why companies may charge the same prices in low- and middle-income countries as in high-income countries, because demand curves are more convex in the former.	Drugs in general, but mostly in low- and middle-income countries	Drugs	[36]
Patents can be used to block sales of an essential facility and to limit competition. Therefore a CL can be a useful tool to incentivize competition. Paper also discusses magnitude of compensation payment. **Two ways in which CL reduces incentives for R&D: (1) reduces profits, (2) it increases profit perspectives for competitors who can use the progress without having made investments themselves.** **CL may lead to an under but also an overinvestment in R&D.**	CL in case of refusals to produce can in some cases lead to higher efficiency. In other cases it can reduce efficiency. Effects of CL are a priori unknown but it can be a very costly public policy instrument. CL is only worth it if the benefits of equal access outweigh the regulatory costs and the long-run disincentives for investment and innovation.	-	Goods/services	[37]
Incentives to innovate depend on the costs of innovation, the risks of innovation, the potential payoff and the ability to imitate the product. It may also be driven by the prospect of having spectacular profits, not just modest profits above R&D cost recouping. CL reduces these profits because royalties are likely lower than the normal market price, plus there will be more competition between manufacturers which will drive down prices.	In theory, CL should make innovation less attractive. Many of the sensitivities that drive innovation and dependencies on the patent system are present in the pharmaceutical industry. The paper suggests 'regulated licensing' in which originator firms have more input in the licensing arrangement, as an alternative to CL.	Innovative products in high-income countries	Innovative products	[38]
Expected effects of TRIPS on low- and middle-income countries are that prices would increase or that more investments would be made in R&D. This paper argues that this is not the case and that TRIPS will have limited effects on availability of medicines in low- and	The author argues that the real reason why intellectual property rights in low- and middle-income countries is important for pharma is 'global reference pricing'. A second reason is the fear for	The welfare effects of intellectual property rights in developing countries	Drugs	[39]

Mechanism	Consequence	Context	Goods/services	Reference
middle-income countries because of insufficient distribution networks and demand. This would justify CL. **The welfare effects of patent protection depend on the particular country conditions in a multi-country economy.** **Five ways in which low- and middle-income countries are different from high-income countries: (1) households are poorer and drug expenditures lower, (2) individuals are less insured, (3) burden of disease is different, (4) patients have different preferences (5) different regulations around prescriptions**	parallel imports from low- and middle-income countries into high-income countries. Diminished intellectual property rights in developing countries can be efficient. The effects of CL are always 'case-dependent'.			
CL leads to market entry of less expensive version of the drug	The less expensive version of the drug could be exported to a high-income country, thus reducing the profitability of the company marketing the originator drug in that country	-	Drugs	40
The patent length that maximizes the social welfare is finite, even if the royalty rate can be controlled by CL.	-	Proof delivered in economic theory	Product and process innovations	41
Objective of CL can be health policy (access to medicines, assurance of a reliable supply and greater affordability) and industrial policy (establishment of a domestic generics industry and learning-by-doing). Implementation should enable rapid CL, otherwise generic producers will have less time to recoup start-up costs.	CL can be a rational strategy but its success depends on many contextual factors and the way CL is implemented in concrete policies.	Drugs in general, but mostly in low- and middle-income countries	Drugs	42
Could CL be a way to produce cheap HPV vaccines? Paper highlights that vaccines are biologics and more complex to develop than traditional chemical products. There is also different regulatory requirement as bioequivalence may not be sufficient for approval of generic biologics. Additional clinical trial data will be necessary. However new legal frameworks are emerging worldwide. CL require political support. The more CL is used, the lower the cost in terms of retaliation will become.	CL are an important tool for governments to keep medicines prices affordable. They are a viable option also in cases of non-emergency. For more complicated biological drugs there are a number of requirements in terms of generic production capacity and regulatory requirements. These are serious but not insurmountable obstacles.	HPV vaccine	Vaccines	43

Mechanism	Consequence	Context	Goods/services	Reference
CL leads to market entry of less expensive version of the drug	A gray market may emerge leading to export to countries in which the higher-priced originator drug is marketed	-	Goods/services	44
An analysis of R&D investments in the US by domestic and foreign companies after the trading with the enemy act after World War 1 shows an increase in R&D investments and inventions in the US.	The purported negative effects of issuing CL on incentives to innovate was not found in a large analysis of patented technologies in the US and instead showed positive effects on the innovation climate. This however may be the result of the fact that CL were an exceptional measure as a result of an emergency situation (war). Patent holders may have done additional efforts to maintain their leading position in a changing market.	R&D after World War 1	Technologies and chemicals	45
Historical evidence suggests that CL may encourage innovation by allowing a new set of firms to produce a patented technology, and possibly by increasing competition to improve the technology.	Overall, the weight of the existing historical evidence suggests that patent policies, which grant strong intellectual property rights to early generations of inventors, may discourage innovation. On the contrary, policies that encourage the diffusion of ideas and modify patent laws to facilitate entry and encourage competition may be an effective mechanism to encourage innovation.	Historical narrative economic perspective analysis starting from the Renaissance period to now	Goods/services	46
CL requires royalty payments. Paper argues that an international panel should determine whether pharmaceutical companies are being over or undercompensated for their innovations. Without this, there will also be inequity in how the R&D cost is spread across countries. Pharmaceutical companies that challenge CL will also pay a cost in terms of public relations, making them vulnerable to unfair compensations.	An international body that oversees the use of CL and adequate royalty payment would benefit both pharmaceutical companies (higher income but also lower public relations costs) and issuing countries (lower impact on rare diseases and other innovation sensitive health problems and also lower counterfeit markets).	Adequate remuneration for licenses of drugs	Drugs	47
The threat of a CL can be as effective as an actual CL. This would be the case in countries with sufficient manufacturing capacity but, under the Doha declaration, also through import.	Countries, mostly low- and middle-income countries but also high-income countries, can effectively reduce prices by threatening with a CL	Drug access in low- and middle-income countries	Drugs	48
CL requires domestic manufacturing capacity to fully function in terms of being a credible threat but also in terms of enjoying the industrial policy benefits.	Most African countries lack this capacity and rely on Asian manufacturers.	Essential medicines in Africa	Drugs	49

Mechanism	Consequence	Context	Goods/services	Reference
CL and royalties paid to the patentees affect the innovator's profit share in the market after a successful imitation (i.e., patent breadth).	It is shown that the stronger the externality in production relative to R&D is, the slower the optimal growth rate, the larger the optimal proportion of duopoly industries, and the longer and narrower the optimal patent.	The government can control patent length by the requirements for accepting a substitute for a patented good, and patent breadth by imposing CL and royalties for the patentee after a successful imitation.	Goods/Services	50
Three factors play a role in the outcomes of CL: local manufacturing capacity, import possibilities and political pressure/retaliation. **If the technology cannot be licensed or independently developed by local firms, one possible solution is to negotiate for a price drop with the patent holder in lieu of issuing a CL.**	Possible consequence of CL is not launching new drugs or not including the country in clinical trials for drug development or broader trade retaliation and cutting back investments. Game theoretic bargaining model showing that CL does not occur under complete information. A CL can be rational but only when there is incomplete information about the options to retaliate (by the patent holder, not the public agent).	CL for essential drugs in low- and middle-income countries CL should not be considered as a tool to promote long-term sustainable access to critical medicines, but rather a short-term fix for market conditions that exclude patients from receiving the right treatment	Drugs	51
Paper presents a narrative review of all the arguments pro and con CL. **Pharma companies are reluctant to offer low prices in low- and middle-income countries because of (1) reference pricing and (2) convex demand curves. Governments hence need to force them to act in the public health interest instead of the private interest, e.g. through CL.** **Government needs however to be prepared to face political pressures and there are many restrictions on CL. There can be diminished foreign direct investment. Domestic firms may still ask high prices. There can be reduction in innovative activity and there is a risk of trade sanctions.** **There is little empirical evidence for the claim that CL will reduce foreign direct investment, particularly in countries where there remain attractive market opportunities. Vice versa, the benefits for a country of starting a CL-induced generic industry can be very large.** **Short-term impact of CL in low- and middle-income countries on innovation will be very limited, however, as these markets expand, it will affect development of new drugs. On the other hand, this innovation will not necessarily**	In low- and middle-income countries, companies need to be forced from a low volume-high margin strategy into a high volume- low margin strategy. Alternatively, governments should create mutually exclusive market segments so that price discrimination can occur. In low- and middle-income countries, the economic promise of CL can be very large, as it can become the hub for generics production. An alternative is to use competition law, however that is technically complicated. Many of the drawbacks of CL can be avoided through careful design of the license. Another alternative is to pool demand across countries in order to negotiate lower prices, without needing to issue CL. Governments issuing CL need to be willing to stand up for their rights in the face of retaliation (threats) by other countries. In that case, it is likely that the threatening country loses because of WTO-trade law violation.	A summary of a symposium on CL	Drugs	52

Mechanism	Consequence	Context	Goods/services	Reference
be the innovation that low- and middle-income countries need (neglected diseases).				
Patents consist of two elements: the right to a high remuneration and the right to exclude others. The value of exclusivity (and the cost of licensing) depends on these two elements and their relation to the annual cost of renewal. The value of the right to exclude others is very skewed and grows with age of the patent. For most, this element is very valuable. **A CL would imply substantial losses to the patent holder and would undermine the incentive effect of the patent system.**	A compulsory license leads to lower income due to lower prices but it also takes away the right to exclude other producers, which is valuable in its own right. A CL would also affect that latter part (which is not compensated through royalties).	German patent system – license of right	Goods/Services	[53]
CL is studied as a dynamic phenomenon (with generic producer and originator interacting over time), with potential royalties to be paid during the first year, and a classic pricing game in the subsequent years. **A sufficiently high royalty can make the patent holder invest in R&D while boosting the generic sales (rather than competing itself).** **When originator is perceived as high quality, it can still ask high prices for the price-inelastic part of the demand curve. This effect will play more when royalty is high enough.**	Through setting royalties, policy makers can decrease prices of patented drugs while steering the R&D incentives for patent holders. As such, the negative effects of CL can be reduced. Price sensitivity of consumers and height of royalty will play a big role in social and economic effects of CL.	The role of royalty in the strategic interaction between patent holder and generics producer. Context is the one of a patent holder entering a low- and middle-income country market.	Mainly drugs	[54]
CL can be waived for inventions with high ex post private benefit-cost ratios on the condition the patent recipient exhibited exceptional creativity or undertook unusual technical and/or commercial risks in the invention's development.	The patent recipient bears the burden of showing why his patent should not expire or be licensed at modest royalties to all applicants after its issue	A "best of both worlds" policy, rooted in the logic of economic theory, recognizing that CL would tailor the life of each patent to the economic characteristics of its underlying invention. It can be waived when the market is small relative to the costs of research, or because the social welfare savings are modest in relation to research costs	Product and process innovations	[55]
CL generates consumer surplus, but has negative impact on innovation expenditure	CL has uncertain impact on total welfare, but is more likely to raise total welfare in less competitive industries CL promotes competition per se	Welfare implications depend on competitiveness of industry	Goods/services	[56]
In an innovation race, CL disincentivizes winning the R&D race. **The total welfare effect of CL depends on the underlying degree of competitiveness of the**	Since what matters in determining the hazard rates is the difference in profits from winning and losing the innovation race, the incentives of the leader (avoiding paying under a voluntary licensing	Derives necessary and sufficient conditions for CL to increase consumer surplus and total welfare, considering both static (technology transfer) and dynamic (innovation) effects.	Electronics, health information services	[57]

Mechanism	Consequence	Context	Goods/services	Reference
industry and is more likely to be positive when the industry in question is naturally less competitive	deal if the follower wins) are now exactly equal to those of the follower (to win so as to earn the voluntary licensing fee).			
CL is recommended to be used in low- and middle-income countries when there can be parallel trade (to compensate the losses caused by high-income countries), the fixed cost of a CL is low and the market relatively small. CL should therefore not be used for neglected diseases.	Innovation impact of CL can be reduced through banning parallel trade.	Trade relations between North (high-income countries) and South (low- and middle-income countries)	Mainly drugs	58
In a model between a 'leader' and a 'follower' under several market and technological circumstances, compulsory licensing may improve social welfare but it will limit innovative activity due to reduced incentives to invest in R&D. These negative effects can however be diminished trough control over licensing fees and state guarantees for inventors. It is possible that this even increases R&D investment incentives.	There is a trade off in terms of static and dynamic efficiency and its effects on social welfare. Policy should guard that competitors are not avoiding voluntary licenses and wait for CL to be issued in order to pay lower royalties. In particular, when the market of the innovation is relatively small and production costs low, CL in addition with substantial royalty can even increase innovative investment.	R&D in general	Goods/Services	59
CL can affect profits directly but also indirectly in other countries through: (1) parallel trade and (2) international reference pricing. **It is costly for governments as well: legal and administrative costs plus costs related to reputational loss, sanctions because of violations of international law and possible retaliation.** **Also for export of a CL drug, parallel trade can force the patent holder to reduce the drug price in expensive markets (international spill-overs).**	After Thailand's introduction of a CL for Abbott's Kaletra® the firm withdrew their activities from Thailand and said it would not introduce any new drugs there. Brazil has made large price reductions through threatening with CL. Theoretical model results show that CL can be welfare enhancing and that the negative impact on innovation is outweighed by other factors. Important is the international exhaustion of IPR.	CL in low- and middle-income countries and possible effects for high-income countries	Drugs	60
The threat of parallel trade under CL does not induce firms to market inferior versions of their products in poor countries.	Parallel trade is less likely to be detrimental to welfare when there are price caps, since CL can mitigate the innovator company's refusal to supply a poor country market)	Parallel trade is much less likely to enhance overall welfare, which implies that parallel trade in products intensive in R&D, such as pharmaceuticals, is less desirable than in fields such as branded consumer products.	Goods/Services	61
Proposes the notion of royalty rates that optimally trade off the negative incentive effects of licensing with the positive consumer	Preliminary calculations suggest that the use of CL may lead to substantial welfare improvements, even if the patent life is left unchanged at 17	Patents create monopolies, but there seems to be no effective way of eliminating the associated deadweight losses. It is argued that CL could	Product and process innovations	62

Mechanism	Consequence	Context	Goods/services	Reference
price effects. So, CL may, at least theoretically, lead to increased welfare. Generalized CL might lead to less "inventing around" which might increase welfare benefits.	years. However, it is likely to reduce firm's propensity to patent and keep their inventions secret.	serve to reduce them. Opponents, however, have argued that forced licensing would reduce or even eliminate the incentive for R&D-intensive firms. Theoretical model acknowledged to be highly stylized and quite impractical. Also, the use of secrecy instead of patenting is predominantly impossible in life sciences reducing the applicability of the theory to Life Sciences		
CL (threat) increases bargaining power of developing country in price negotiations with pharmaceutical company	CL (threat) reduces drug prices	The impact of CL (threat) on price negotiations depends on local manufacturing and import capabilities, and on the likelihood of sanctions	HIV/AIDS drugs	63
CL promotes local industrial development and subsequently innovation **CL discourages foreign investment and hence local innovation**	-	-	Drugs	64

4.2.2 Empirical studies

Objective	Country	Drug(s)	Data period	Design	Results	Context	Conclusion	Rigour	Reference
To quantify impact of CL on innovation	Germany	79,591 patents for chemicals	1900-1930	Regression analysis controlling for unobservable variables	There was 30% increase in innovation by companies subject to CL There was increased entry by companies into domains subject to CL	CL impact was larger in less competitive industries Impact of CL is likely to depend on the frequency of its use	CL increases competition threat, inciting companies to innovate more to stay ahead. This effect may disappear when CLs are issued repeatedly. CL should only be used in exceptional cases.	Rigorous statistical analysis, but outdated evidence	65
To investigate the use of CL	TRIPS	Most CL episodes occurred between 2003 and 2005, involved drugs for HIV/AIDS, and occurred in upper- and middle-income countries. Aside from HIV/AIDS, few CL episodes involved communicable disease, and none occurred in least developed or low-income countries	2000-2011	Historical descriptive analysis	While upper- and middle-income countries have high CL activity and strong incentives to use CLs compared to other countries, there were considerable countervailing pressures against CL use even in upper- and middle-income countries	-	Authors conclude that there is a low probability of continued CL activity. Highlight the need for further systematic evaluation of global health governance actions	Rigorous descriptive analysis. Outdated (-2011). Acclaimed negative trend in CL in need of verification	66
To investigate whether prices obtained through international procurement (e.g. global fund) lead to	Brazil/Malaysia/Zimbabwe/Indonesia/Zambia/Thailand/Rwanda/Ecuador	Anti-retroviral drugs	2003-2012	Observational	CL prices exceeded the median international procurement prices in nineteen of the thirty case studies	Drugs	There can be alternatives for CL. Pooling and international collaboration are important steps to investigate before resorting to CL.	Letter sent to journal	67

Objective	Country	Drug(s)	Data period	Design	Results	Context	Conclusion	Rigour	Reference
lower prices than compulsory licensing.									
To describe experiences of Egypt and Brazil with using CL and its effect on foreign direct investment	Egypt/Brazil	Anti-retroviral drugs + Viagra®	1990-2005	Observational	Egypt: negative effects on foreign direct investment Brazil: successful use of CL: increased access and domestic activity	Drugs	There is a range of conditions under which CL can be successfully used	-	21
To describe experiences with CL in various countries and discuss strategies to minimize the harmful side effects	Thailand, India, Egypt, Argentina, South Africa	Drugs	90s-2000s	Narrative review of empirical studies	Five strategies are suggested: (1) CL should be issued in consultation with firms and their affected interests, (2) narrowly tailor compulsory licenses to further genuine humanitarian goals, (3) capture the moral high ground in the public debate over access to medicines, (4) remove stifling tariff barriers and other cost-increasing aspects of drug trade, (5) remove cultural and social barriers to Western medicines	Low- and middle-income countries	CL can be a powerful tool for low- and middle-income countries and many of the side effects are preventable or reducible through careful design.	-	22
To describe South Africa's experience with CL	South Africa	Drugs	1998	Case study	South Africa faced severe threats from the US (watch list, withholding preferential tariff treatment in the generalized system of preferences).	Drugs	CL-issuing countries will face severe and high-level political and economic pressure from pharmaceutical industries and countries such as the US.	-	68

Objective	Country	Drug(s)	Data period	Design	Results	Context	Conclusion	Rigour	Reference
To describe the likelihood that CL will be used as a pharmaceutical policy measure in the US, after the EBay CL.	US, India, Brazil	Drugs	2000s-10s	Case study	Four factors matter to the effect of CL on innovation: the price at which the CL is set, markets significance to the producer, availability of alternative sources of non-patent protection, predictability of a CL.	US and low- and middle-income countries	Considerations in US are different from those in developing countries and impact would be much bigger. However, after the Ebay precedent, although unlikely, it may be that CL will be used in the US as well. A sporadic use of CL would be smart so that it can serve as a credible threat.	-	69
To investigate impact of CL on R&D spending	US	Fibrin sealant, dicyclomine, HSV-tk, CD4, insulin, rabies vaccine	1980s and 1990s	Description of 6 cases where CL have been used in antitrust cases	No effect on R&D in 5/6 cases. In a majority of cases R&D efforts even increased.	Drugs	CLs that are issued in predictable manner in big markets may reduce R&D but the general belief that CL categorically harms innovation is wrong. CL issued in smaller markets may not reduce R&D.	Limited and anecdotal evidence	29
To describe Brazil's experience with CL	Brazil	Drugs/anti-retroviral drugs	-	-	Through the clause in TRIPS that production must be 'domestic' Brazil justified a threat to CL which resulted in substantially lower prices. Brazil faced heavy pressure from US (trade sanctions and tariffs)	Drugs	One of the key success factors in brazil's negotiation was that it had a substantial domestic production capacity. Prices were reduced up to 65%.	-	30
To analyse Canadian Access to Medicines Regime (allowance for Canadian generic producers to produce for low- and middle-income	Canada	Essential drugs	2006	interviews	Although the initiative is good in intention, in practice there are too many restrictions to make it a useful tool for low- and middle-income countries	Generics export to low- and middle-income countries	Canadian Access to Medicines Regime is symbolically meaningful but in practice limited.	-	70

Objective	Country	Drug(s)	Data period	Design	Results	Context	Conclusion	Rigour	Reference
countries which issue a CL but can't produce themselves)									
To quantify impact of CL on drug prices	Zimbabwe, Malaysia, Mozambique, Zambia, Indonesia, Eritrea, Ghana, Thailand, Brazil, Ecuador	All	2002-2009	Before-and-after studies	CL led to substantial drug price reductions	-These were large developing countries with capacity to produce drugs locally, thus threatening international pharmaceutical industry (with Brazil and Thailand facing external political pressure) -These countries had little or restricted foreign investments -CL is part of local industrial policy	CL reduces drug prices	Collection of case studies with qualitative interpretation	[71, 72]
To quantify impact of CL on drug prices	Global	All	-	Literature review of impact of price regulation on innovation	Price reductions have negative impact on innovation, but there may be positive impact in certain cases	When implementing CL, coordinate with other countries Role for competition authorities of multiple countries to act in case of suspected price abuse	There is a need for an assessment framework to explore potential consequences of CL	Not a comprehensive review of the literature Personal opinion of chair of Dutch CL commission	[12]
To quantify impact of CL on drug prices and pharmaceutical industry	Canada	70 drugs	1969-1983	Descriptive evidence	CL led to growth of companies in Canada manufacturing CL drugs CL increased price competition in Canada	This study did not consider retaliatory economic sanctions by other countries	CL has a positive impact	Outdated evidence	[73, 74]

Objective	Country	Drug(s)	Data period	Design	Results	Context	Conclusion	Rigour	Reference
					Drug prices in Canada are among the lowest in the world No impact on profitability and growth of pharmaceutical industry in Canada, although some individual companies are impacted				
To describe how the 'Brazilian model' can be an example for how to use CL effectively	Brazil	Anti-retroviral drugs	1990s-2000s	Opinion article	Practical details and circumstances are essential aspects of CL and their success: no one size fits all.	Low- and middle-income countries	CL can be effective but there are conditions	-	[75]
To quantify impact of CL	Canada	All ethical drugs	1968-1980	Before-and-after price studies of CL policy	Canada implemented in 1968 CL in an effort to significantly reduce their drug prices in comparison to the US	CL led to a significant price drop for those ethical drugs affected by the legislation. This while the prices of CL-unaffected drugs remained constant relative to those in the US for the studied period.	CL leads to a substantial reduction in drug prices	Peer-reviewed empirical evidence	[76]
To investigate for the US what the effect is of CL on prices and levels of innovation	US	Drugs	-	Review of case studies and anecdotal evidence	Measures such as the Hatch-Waxman Act and the 'Bolar provisions' act as a sort of CL. These have largely increased the supply of generics (access) and reduced prices. It also increases competition. The evidence on the effects on innovation is inconclusive. However, the effect may be larger in the pharmaceutical	US	The paper suggests that innovation in the pharmaceutical industry is particularly sensitive to CL because here many of the determinants of innovation would be affected (costs and risks of innovation, potential payoff, ability to imitate). But also the need for access to patented products is higher. The paper suggests that 'regulated licensing' (sort of CL but with much more choice for the patent	-	[38]

Objective	Country	Drug(s)	Data period	Design	Results	Context	Conclusion	Rigour	Reference
					industry than in other industries because of the particular characteristics of that industry.		holder in terms of production and royalty) is a solution.		
To quantify impact of CL on foreign investment	Global	All	2000-	Descriptive analysis of evolution in foreign investment over time	There was no association between CL and foreign investment	Impact depends on predictability of CL use and market size	CL did not have negative impact on foreign investment	Design did not allow for causal relationship to be demonstrated	[77, 78]
To provide a framework to evaluate CL in developing countries and to evaluate experiences of Thailand and Brazil	Thailand and Brazil	Drugs	1990s and 2000s	Observational	CL brought health and industrial benefits to both Thailand and Brazil	Low- and middle-income countries	CL brought down prices substantially and increased access to essential medicines for large parts of the population. Although there were initially logistic problems with setting up domestic production capacity, in the end the CL brought industrial benefits as well.		[6]
To quantify impact of CL on drug access, health gains, trade and foreign investments	Thailand	Efavirenz, lopinavir/ritonavir, clopidogrel, imatinib, erlotinib, letrozole, docetaxel	2006-2008	Impact assessment over 5 years	CL increased number of patients with access to these drugs and generated associated QALY gains CL led to withdrawal by US of trade advantages to Thailand No impact on foreign investments	Study relates to drugs imported under CL Impact depends on whether other countries or companies take retaliatory trade/investment measures Selection of drugs is important	CL has positive impact on public health and little impact on trade and investments	Did not consider impact beyond 5 years Limited generalizability to other countries	[79]
To examine impact of 1987 changes in Canadian Patent Act on pricing of ethical drugs.	Canada	Sample of 82 drugs from the British Columbia Pharmacare Programme pre- and post-1987	Before and after CL period	Regression analysis of market price behavior	Despite evidence of significant first mover advantages which resulted in higher brand prices, competition from generics succeeded in reducing overall market prices prior to 1987. However, after 1987, the	From 1969 to 1987, Canada opted to control pharmaceutical prices by promoting competition between branded drugs and their generics. In 1987, the Act was amended to guarantee patent	Following CL abandonment after 1987 brand-generic competition was reduced by retarding generic entry and suggests that ceteris paribus, after 1987 pharmaceutical prices increased relative to pre-1987 prices.	-	[80]

Objective	Country	Drug(s)	Data period	Design	Results	Context	Conclusion	Rigour	Reference
					efficacy of generic competition was reduced and both brand and market prices increased.	holders an extended period (7±10 years) of protection.			
To describe experiences of Canada and Thailand with using CL	Canada / Thailand	Drugs	2000s	Case study	CL are a powerful tool to reduce prices. In addition, the threat itself is important. However, success lies in nuanced social, political and economic environments.	-	CL can be a success if there is (1) a clear policy purpose for why CL might be used, (2) adoption in legislation, (3) remuneration system must be clear and (4) there must be political interest and commitment	-	81
To investigate impact of CL on R&D	Canada	CL has not resulted in active price competition since, in Canada, price of the generic product is generally fixed at 70 per cent of the branded drug and all the prices of the subsequent generics are also invariably fixed at this level	1870 - 2004	Qualitative case study	A sizeable amount of R&D investment is focused on applied research rather than basic research, which is, reflected in the number of real breakthrough drugs that appeared in the market	-	R&D in Canada has increased because of withdrawal of the CL, the foreign payments made by the pharmaceutical companies are also increasing indicating their dependence on import	Outdated analysis in need of extension to present day. Acclaimed relation between CL presence and pharma investment is not quantitatively proven. Study is a narrative.	82
To review Canadian and Thai experiences with CL	Thailand and Brazil	Drugs	1990s and 2000s	Narrative review of policy documents	Canadian experience was no success because too many restrictions and lack of profitability for generics producers. Thai experiences and its relatively high prices suggests that industrial policy objectives play a role. Health consequences of CL are	Drugs	CL (and export of generics) is a legal possibility in many countries but rarely used. The mechanism is not fully understood. The paper outlines a framework for successful CL. Experiences of Thailand and Canada are different but both highlight the complexity of CL in practice.	-	42

Objective	Country	Drug(s)	Data period	Design	Results	Context	Conclusion	Rigour	Reference
					not necessarily positive in Thailand where patients have often access to lower quality products.				
To examine impact of absence of patent protection on innovation	US	Random sample of 100 firms from 12 industries (excluding very small firms) in the US.	1981-1983	Estimate of proportion of a firm's inventions developed in 1981-83 that would not have been developed without patent protection	The impact of having no expected patent protection would be a 14 percent decrease in the number of innovations introduced. Pharmaceutical companies were an exception in this study, with reductions of 60 percent in the United States.	-	-	Detailed investigation of a sample of firms. Now outdated evidence.	83
To describe the effects of the 'trading with the enemy act' after World War 1 in which a large number of CL were allowed in the US over German patents	US	Technology and chemical compounds	1920s	Difference in difference analysis comparing changes after 1918 in patent issues per year for 336 technologies with CL, with changes for a control group of 7,248 technologies without licensing	Domestic investment in R&D and invention of patent holders increased after CL. Positive effects occur however with a time lag of about 8 years after the CL.	Chemical industry	Analysis suggests that issuing CL on foreign products encourages domestic invention. Also negative effects on investment by foreign patent holders was limited but this may be the result of the context of the CL: a one-shot response to an emergency situation (World War 1).	Robust statistical difference-in-differences analyses analysis based on verifiable historical data. Now outdated evidence.	45
To examine effects of CL on drug prices	Ecuador	Drugs	2011-2017	Price comparisons for products before and after CL	CL had mixed results in Ecuador. For many products there was insufficient capacity and prices did not drop.	Essential drugs	CL requires more than political will. A competent local pharmaceutical industry is required.	-	84

Objective	Country	Drug(s)	Data period	Design	Results	Context	Conclusion	Rigour	Reference
To describe and evaluate Thailand's anti-retroviral drug policy in the battle against AIDS	Thailand	Anti-retroviral drugs	2000s	Modelled costs and effects of different anti-retroviral drug policies	A 90% reduction in the future cost of second line therapy through CL would save the government $3.2 billion and would halve the cost per life-year saved.	Anti-retroviral drugs	CL are predicted to lead to large savings in public expenses, money which can be used to save other lives.	-	[70]
To analyse impact of patent strengthening on corporate R&D spending in Canadian pharmaceutical industry	Canada	Pharma	1987-1992	Time trend analysis	R&D spending has increased but there were other factors to explain this than patent protection only (e.g. structural change in the industry worldwide). Partly it is attributable to increased IP protection but also it was related to an agreement between the industry and government to increase R&D spending should Canadian patents become stronger.	Pharmaceutical R&D	The Canadian data show an increase in R&D spending after patent protection became stronger but it is difficult to translate this association into a causal effect.	-	[85]
To quantify impact of CL on drug access and prices	Thailand	Efavirenz, lopinavir/ritonavir, clopidogrel, letrozole, docetaxel	2008-2010	Descriptive evidence	CL increased number of patients with access to these drugs and reduced drug prices	-	CL is effective in increasing drug access and reducing prices	Focus on evolution in access and prices without control group	[86]
To analyse use of CL in price negotiation episodes for anti-retroviral drugs in Brazil	Brazil	Anti-retroviral drugs	2007-2012	Case study	Price discounts by MNEs for their patented drugs improve access, but they slow down catch-up, because it becomes more challenging for local firms to become equally competitive. Similarly, following a CL, while there will be catch-up, access might be	Local technological capabilities and import possibilities have an important influence on outcomes of price negotiations evoking CL	Brazilian Ministry of Health was able to negotiate better prices – on average, 1.7 times the lowest international price. This was possible because, in 2001, Ministry of Health authorized reverse engineer the production technology of these three active pharmaceutical ingredients to strengthen its position in the	Case study analysis	[87]

Objective	Country	Drug(s)	Data period	Design	Results	Context	Conclusion	Rigour	Reference
					improved more by importing cheap generics than by procuring costlier locally produced drugs.		negotiation with pharmaceutical MNEs.		
To describe how Thailand and Brazil made use of CL	Thailand/Brazil	Drugs	2000s	Case study	Population pressure made call for CL louder, leading to domestic regulatory changes that allowed CL. Large international alliances were made that could counter pharmaceutical lobbies.	Essential drugs	Successful use of CL requires broad alliances and support to create the right climate. A war of perceptions needs to be won.	-	[88]
To quantify impact of CL	Canada	-	-	Descriptive evidence	Pharmaceutical R&D expenditure decreased during CL and increased after CL ended CL undermined Canada's competitiveness in worldwide pharmaceutical market During CL, pharmaceutical prices in Canada increased more than in USA	-	CL has a negative impact	Anecdotal evidence from various sources	[89]
To examine economic feasibility of CL and its potential to act as a price-leveraging instrument in markets in developing and least	India	-	Post-2005	Industry survey	-	The focus has been on India's TRIPS compliance and emerging firm strategies for both R&D and business	Although their business models are different, generic companies share with the research-based industry the common motivation of serving the interests of their shareholders. CL will not be used if the financial incentives for participation, taking account of the risks involved, are deemed inadequate. Whether this mechanism can make supplies of lower cost drugs available to developing countries with	-	[90]

Objective	Country	Drug(s)	Data period	Design	Results	Context	Conclusion	Rigour	Reference
developed countries							inadequate manufacturing capacity remains to be seen. So far no developing country has sought to make use of it.		
To quantify impact of CL on innovation	-	Goods/services	-	Evidence related to 700 companies	Companies subjected to CL invest 36% more in R&D than companies in the same industry which are not subjected to CL	-	In order to remain competitive, CL induces companies to invest in innovation	Outdated evidence	91
Patent protection is viewed positively by the stock market, but only when measured with hindsight	US-Canada	-	1960s with CL vs 1980s without CL	Comparative response studied in 1960s and 1980s	Despite the small size of the Canadian market, the US-based NYSE share price response to the passage of Bill C-22 abandoning CL was strong to amount up to +8.5%.	-	Patent protection does allow appropriation of gains from knowledge by firms in pharmaceutical industry. Thus, pharmaceutical companies would benefit from international agreements to provide more stringent levels of patent protection.	Allows to compare results based on foresight with those relying on hindsight.	92
To analyse time after drug launch that a CL is issued, and to investigate whether this affects time to CL for other drugs	Worldwide	Drugs	1995-2014	Regression analysis, Kaplan Meier curves	After Doha-declaration, countries were faster in issuing CL, mostly for HIV but less for oncology. Previous experiences with CL triggers CL in other countries but also accelerates CL for other drugs within the country	Drugs	Issuing a CL affects the probability that other CL will be issued	-	27
To investigate whether CL is a legitimate part of a country's patent system	WTO countries	Among 139 WTO countries across Asia, Africa, Latin America, 24 attempted CL, while 115 did not		Descriptive analyses to present the difference between two groups, including the CL-attempted group and non-CL-	CL could be a potential alternative or complement to achieve access to medicines in health systems through manufacturing and exporting patented pharmaceuticals	-	A mature intellectual property system is positively associated with attempting CL	-	93

Objective	Country	Drug(s)	Data period	Design	Results	Context	Conclusion	Rigour	Reference
				attempted group					
To quantify impact of CL on drug prices	Brazil, Ecuador, India, Indonesia, Thailand, Malaysia, Rwanda, Zimbabwe	Mostly HIV/AIDS drugs	2003-2012	Before-and-after price studies of actual CL event	Mean price reduction of 66.2-73.9% for 24 CL events Mean price reduction of 67.1-79.4% for drugs imported under CL Mean price reduction of 65-66.8% for locally produced drugs following CL	Not clear if CL leads to greater price reductions than voluntary licensing, price negotiations or the lowest global price CL is feasible if country has local technological and manufacturing capabilities	CL leads to substantial reduction in drug prices	Peer-reviewed articles only Review excluded studies that quantify impact of CL threats Price data originated from multitude of sources	11
To quantify impact of CL	Global	All	-	Evidence from peer-reviewed and grey literature	CL reduced drug prices in Thailand, Brazil and Malaysia CL threat contributed to negotiating lower drug prices in Brazil Following CL, a company did not register its pending and new drugs in the country There was economic and political pressure from governments and companies against CL in Brazil, Colombia, India, South Africa and Thailand	-	There are too few empirical studies about impact of CL to derive robust conclusions	Anecdotal evidence	94

4.2.3 Remuneration

Mechanism	Consequence	Context	Goods/services	Reference
-Royalties should not be determined in relation to the good/service, but in relation to the new knowledge generated to create the good/service **-Royalties should be set at the level of the research costs spent to generate new knowledge**	-	-	Goods/services	17
Even though the marginal cost of supplying access to intellectual property is zero, some unit charging using socially optimal licensing fees (a combination of fixed fee and royalties) is likely to be efficient	Royalty payments offer a greater range of choices to a regulator than fixed fees because it connects to marginal value rather than to marginal cost	CL used when some forms of intellectual property can be seen as 'essential facilities' to a country	Drugs	18
-Proportion of sales **-Fixed amount** **-Tiered royalty method (based on originator drug price (4%), but adjusted for income level of country)**	-Links remuneration to drug volume sold -Independent of drug volume, can depend on income level of country		Drugs	95, 96
For Tamiflu®, the US Government would have to pay "reasonable and entire compensation" to Roche for time that it produced the antiviral medication. If the government chooses to infringe on Roche's Tamiflu® patent through the issuance of a CL, a court must determine a reasonable royalty	The US government could force a license for a domestic medical patent and face an action for damages by the patent owner under 28 U.S.C. § 1498 as long as the government compensates the owner. US Courts have interpreted reasonable compensation to fall within two categories: lost profits and reasonable royalties	Market access for Roche's Tamiflu®	Drugs	97
Royalties need to be based on value of patent and on revenue for licensee	-Value of patent can be determined by means of future income generated by patent, by value of similar market good/service, or by costs of generating the patent -Remuneration needs to be linked to drug volume sold	Remuneration also needs to account for CL purpose (lower remuneration if abuse of monopolistic power or for humanitarian purpose)	Drugs	96, 98, 99
In issuing a CL for efavirenz, Thailand cited its own laws and the declaration WTO TRIPS agreement.	In the US, a one-year supply of efavirenz costs about $6,000. In 2006, Merck's official price for the 600-mg formulation in the least developed countries was $277 per patient per year. In middle-income countries with an HIV prevalence rate	Thailand's action has received considerable attention while the country has a leadership role in fighting AIDS, it has a domestic pharmaceutical industry, and it has licensed a high-profile medication. The government simply	Drugs	100

	among adults of 1% or greater, such as Thailand, it was also $277. Merck has objected to Thailand's unilateral action and wants the Thais to consider other options. For example, Merck might sell efavirenz at a lower price or it might provide a voluntary license to produce a generic version, as it has done in South Africa.	announced the "public use" of the patent without discussing the matter with Merck first.		
US Secretary of Health and Human Services sets remuneration based on multiple considerations (according to Public Health Emergency Medicines Act proposed to, but not enacted by House of Representatives)	-	Remuneration can be set taking into account: -risks and costs of invention and product development -efficacy, innovative character and public health importance of drug -extent of public funding for drug -requirement to maintain incentives for innovation -public interest considerations -population health benefits -benefits of drug availability -need to address anti-competitive practices	Drugs	101
Tenofovir disoproxil fumarate is a first line HIV treatment registered in 2001, Initially only available in developed countries at a cost of US$5 000 per person per year. Gilead's Access Programme has extended the use of the product to 2.4 million patients in low- and middle-income countries in a voluntary licensing programme.	The 2001-2011 programme has two components: distribution of the branded product at reduced prices and licensing partnerships with generic manufacturers. The licensing partnerships now supply 75% of the market by volume, at a treatment cost of US$57 ppy (1% of the branded cost).	From Gilead's perspective, Gilead's Access Programme must be considered a huge success. It has enabled the company to maintain high prices in developed countries whilst reducing its input costs and deflecting criticism of its failure to provide essential medicines for the poor, hence risking the possibility of compulsory licensing.	Drugs	102

5 EXAMINING THE ECONOMIC IMPACT OF CL FOR MEDICINES

Economic consequences of CL can be interpreted narrowly in terms of only financial gains or losses to all affected parties, but should be viewed broader, considering the potential impact on wealth, health, and wellbeing of the population. We will adopt a broader approach. Our literature review has highlighted several pathways through which compulsory licenses can sort effects on all these broader outcome measures (see Table 1). **Given the limited empirical evidence base predominantly focused on the use of CL in low to middle-income countries (LMIC), most of these effects remain uncertain, open for speculation and highly dependent on the specific context (e.g. the country, the product, the companies involved, etc.). For most of the consequences, there is no consensus in the literature about the magnitude or even the direction of the consequence listed.** Therefore, the economic impact of issuing a compulsory license must always be evaluated on a *case-by-case* basis. A CL can be issued for the same product in two different countries with diverging or even opposing consequences. Moreover, although the literature speaks of CL as a well-defined concept, CL can be issued in a variety of forms and modalities (e.g., with different compensation payments for patent holders, with(out) prior negotiations, quality control arrangements for producers, etc.), each with different expected consequences. These modalities will affect the purported costs and benefits of the system and many of the 'side-effects' of CL can be mitigated through careful design [75].

We distinguish between two broad categories of consequence. First, CL can affect *economic activity* within a region and may therefore be a lever of industrial policy. Here, we think of consequences in terms of employment, investment, trade and other aspects generally captured in the measurement of Gross Domestic Product (GDP). Second, and this is particularly relevant in the domain of pharmaceuticals as compared to other R&D-heavy industries (e.g. ICT), CL will also directly affect *patient outcomes and public health*. In economic terms, the latter are highly valuable 'resources' that would be typically ignored in measures of industrial activity such as GDP. Of course, both are not perfectly separable as industrial policy can affect health policy and vice versa. For instance, higher levels of unemployment will have a public health impact and an unhealthy workforce will affect industrial activity. However, for our analytic purpose to explain the differential impacts that CL could have, we think it makes sense to separate both.

Furthermore, a distinction needs to be made between **the use of CL as a negotiation tool and the actual application of CL in practice**. The former can be a smart policy. When the use of CL is credible (i.e. when there is a viable domestic industry able to produce the licensed product, legal possibilities to do so, and when policy makers are willing to use compulsory licenses (perhaps without actually doing so) or when there are credible import possibilities), the bargaining power of a country in negotiations with a pharmaceutical company increases and lower prices or voluntary licenses can be negotiated [48, 49, 63]. For instance, Brazil has negotiated large price reductions for ART by referring to the use of compulsory licenses [60] but it had a large domestic market, sufficient production capacity and a strong moral justification to issue CL. That is not the case in many other countries. Some authors argue that it is a good strategy for governments to, once in a while, issue a CL so that it remains a credible, although rarely implemented tool [69].

Table 1 – Potential consequences of CL

Industrial policy	Health policy
• CL can stimulate economic activity within a region and may therefore be a lever of domestic industrial policy. • Originator companies who are impacted by CL will likely reduce their R&D investment in the issuing country. • The incentives to invest in R&D by other companies and sectors can be affected when the issuance of the CL signals that the investors' 'climate' in a country has changed. • Issuing trade sanctions and increasing tariffs are potential instruments used by foreign governments to influence domestic decision making regarding CL as well as issuing retaliatory compulsory licenses.	• Domestic patients in need of expensive treatments will have better access to these treatments, when a CL is issued succesfully. • Resources spent on the patented medicine will be freed and can now be used to invest in other (health) programs. • Pharmaceutical companies may respond by delaying drug launches or cancelling clinical trials in the CL-issuing country, which would affect domestic patients' access to innovative medicines. • Investors might be less inclined to invest in drug R&D. If this happens on a sufficiently large scale, this would affect the drug pipeline and over time impact the supply of innovative drugs that become available for patient populations worldwide.

5.1 Industrial consequences

5.1.1 Development of a domestic pharmaceutical industry

CL can be used to allow developing economies of LMICs to get access to developed country technologies at sub-market prices. By doing so, it allows developing economies to build up their own domestic competing industries, effectively catching up with developed economy invention and production through learning-by-doing [45, 87]. It is generally acknowledged that CL increases developing countries' bargaining power when negotiating more affordable prices, e.g. from pharmaceutical companies for their novel medicines [15, 66, 87]. As an example, Thailand and Brazil are cited to have issued CLs in 2006 and 2007 for antiretroviral supplies from Merck and AbbVie due to the high prices quoted, which allowed them to import generic versions of the related medicines from India at significantly lowered cost [103].

So, issuing compulsory licenses can have a stimulating catch-up effect on local industrial development [64]. By taking away (some of) the production of medicines from (preferably foreign) pharmaceutical production plants and handing these over to domestic companies, oxygen will be provided to develop new economic activity within country borders. Local firms will receive market share which can make these firms grow, build up a capital stock, develop human capital through learning-by-doing, etc [42]. This can be an attractive strategy with important long-term economic benefits as illustrated by the experiences of **India, Brazil and Thailand [6, 42]. These countries have used CL for patents (mostly held by companies from HIC) to successfully develop domestic pharmaceutical industries, predominantly focused on generic medicines manufacturing.** For instance, some have called India the 'pharmacy of the world' and a substantial share of the global covid-19 vaccine supply is now developed in India [104]. Whereas, initially, Indian pharmaceutical companies were mainly generics producers, set up to meet India's domestic needs for affordable

drugs, now they have become globally competitive suppliers and increasingly collaborators with big-pharma companies from HIC, e.g. through voluntary licenses [104]. Brazil provides another example where a CL-based industrial development policy led to a catch-up trajectory of the local generics industry. In 1996, Brazil initiated universal and free access to highly active antiretroviral therapy. The Brazilian catch-up in highly active antiretroviral production between 2001 and 2010 led [87] to conclude that when domestic manufacturers master generic production, then price discounts obtained from foreign patent holders are likely to be higher.

Such industrial benefits of issuing CL depend on **the domestic economic circumstances, the presence of a local pharmaceutical industry, the type of medicine subjected to a compulsory license, the point in time during a medicine's lifecycle at which a CL is issued, and the presence of other instruments for an originator company to protect its intellectual property rights in addition to patents**. Such aspects and scenarios are identified and discussed here:

1. A country needs to commit to developing a domestic pharmaceutical industry or needs to have an established pharmaceutical industry, otherwise CL risks being a non-credible negotiation tool [49]. For instance, countries such as Brazil, India and Thailand are large developing countries with capacity to produce drugs locally and in which CL is used as an instrument of local industrial policy [71, 72]. However, when the use of CL as a negotiation tool induces the originator company to reduce prices to levels comparable to those under compulsory licenses, and when the production of the medicine already occurs domestically, then society is better off with not having to invest in additional production facilities [31]. A different scenario is when originator drugs are foreign, domestic unemployment is high, and the opportunity cost of developing domestic production capacity is low. In this case, issuing a CL can have positive long-term consequences for the economy. This is particularly true when the domestic market is sufficiently large to sustain a stable long-term demand. In general, the use of CL as a negotiation tool is more credible to the extent the developing country has local manufacturing capacity, has sufficient import possibilities to resist pressure from HIC countries and pharmaceutical firms' threats of market withdrawal, the latter, for instance, not launching future drugs in the developing country, exclude concerned developing countries from clinical trials for drug development or engage in more general trade retaliation (see next sections) [51].
2. The TRIPS agreement in principle allows a country to issue CL and export these medicines to other countries that lack production capacity[1]. Therefore, domestic industries can grow through producing for other countries. For instance, drug producers in many countries (e.g. Canada but also countries in the European Union) have the legal possibility to export generic versions of patented drugs to be used in low- and middle-income countries, although it is disputed whether that is actually a realistic option for these countries as there are many legal and administrative restrictions [30, 70]. So far, to our knowledge, only Rwanda has been able to make use of this pathway [70].
3. The domestic pharmaceutical industry needs to have access to the raw materials, infrastructure, scientific and technical expertise required to produce these medicines. However, local production may face hurdles if for example companies offering active pharmaceutical ingredients restrict supply. Patent holders sometimes have contracts with suppliers of active pharmaceutical ingredients, requiring that the patent holder is the only buyer and that it cannot be supplied to other parties. It also requires pharmaceutical knowledge to produce the medicine domestically and this is likely to depend on the type of medicine: making a medicine from a simple active ingredient is of a different order than making a medicine consisting of complex proteins [43].
4. The domestic industry benefits of CL will be bigger when the CL is issued quickly after launch of the patented drug, instead of being the result of a long bureaucratic process throughout (some of) the years of

[1] Many high-income countries including the EU and its Member States agreed to opt out of using the mechanism as an importer for their own medicines supply (given that it was mainly aimed at supporting access to medicines in developing countries) and are hence, in principle, ineligible to import medicines manufactured in another country under CLs within this system.

patent protection [42]. However, even CL issued closely before the end of the patent term can give domestic producers a head start in comparison to their future competitors.

5. The authorisation to produce a medicine under a CL may not be sufficient to make the product available to patients. For instance, data and market exclusivities may prevent the licensee to receive a marketing authorisation for its product (see Legal chapter). With respect to data exclusivity, this implies that: a) the licensee has to conduct clinical trials to prove that the product is safe and effective (raising the question whether the unnecessary duplication of clinical trials is ethical); b) the licensee needs to pay a remuneration for the use of test data to the holder of the medicine's marketing authorisation if the MA holder agrees to sharing these data; or c) wait for the data exclusivity to be lifted (usually after eight years). These scenarios are likely to raise the price of the medicine produced under a compulsory license and/or delay its market entry. With respect to market exclusivity, orphan medicinal products benefit from a monopoly following marketing authorisation in the sense that no similar medicinal product for the same therapeutic indication can be registered for ten years in the European Union. In such a case, issuing a compulsory licence is legally not possible. When there are other ways for an originator company to protect its intellectual property rights (such as using trade secrets on important production processes), then CL will again become more difficult to execute in a beneficial way [69].

CL has not only been used to allow developing economies to build a domestic pharmaceutical industry, it has also been applied by developed high-income country (HIC) economies such as the United States (see Box 1) and Canada (see Box 2) in the past for the same purpose. Whereas the experience with the Trading with the Enemy Act showed that CL allowed the US to develop an innovative domestic chemical industry, the Canadian experience demonstrated that CL supported the domestic generics industry, but did not encourage innovative domestic R&D and did not allow Canada to be active at the technological frontier [82]. As also quoted by Lexchin [105], the Canadian Eastman Committee observed that "Canada does not now possess either the scientific manpower or the physical infrastructure that would make it a major world centre for pharmaceutical research. Nor in the opinion of the Commission, would it be wise for governments to seek to create such an environment in competition with heavily supported long established centres in other countries".

Box 1 – The Trading with the Enemy Act (1917)

An early historical example of the use of Compulsory Licensing by the US Government to provoke an industrial catching-up effect is provided by the Trading with the Enemy Act. Passed at the US Congress in November 1917 because of World War I, the Act allowed US firms to violate enemy-owned patents if they contributed to the war effort. In the end, it effectively confiscated all enemy-owned patents. Today, Cuba is the only country still affected by the Trading with the Enemy Act. From 1919 onwards, the US Chemical Foundation issued nonexclusive licenses of enemy-owned patents to US firms and allowed the United States, at the time lagging in complex chemical processes, to catch up with Germany in the field of organic synthesis chemistry. The Trading with the Enemy Act had a significant and persistent positive effect on US domestic innovative capacity with the US chemical industry gaining prominence as an originator of knowledge in the 1930s [45].

Box 2 – Compulsory Licensing in Canada (1969-1987)

Following considerable concern that Canada paid excessively high prices for medicines, starting from 1969 the country decided to apply CL to imported products which significantly limited the strength of drug patent protection and encouraged competition to curb the 'excessive monopoly rents on inventions conceived elsewhere' [92]. In the absence of a domestic drug manufacturing industry at the time, it allowed predominantly smaller Canadian owned firms to obtain the CL-based right to produce imported drugs or to import the active ingredient and manufacture the drug [82, 92].

The Canadian Eastman Committee observed that CL saved a $211 million out of a total drug bill $1.6 billion in 1983, and it did not affect the profitability of multinational drug companies active in Canada [73, 74]. Implementing CL combined with provincial product selection legislation led to compulsory licensed drugs sold to the pharmacist in Canada to be priced from about 86% of the US price in 1968 to 45% in 1980 [76]. However, CL did not result in large competition between drugs. Furthermore, CL policy did not promote domestic R&D in Canada [89]. With multinationals dominating R&D in Canada, it is a net importer of intellectual property, with as much as 50% spent on applied research against about 17% on basic research that advances scientific knowledge, as opposed to 24.5% or 36% in the US at the time. This led to an abundance of R&D geared to 'me-too' rather than to innovative drugs [82].

This led to the passage in 1987 of Bill C-22, which significantly relaxed CL conditions, amending the Act to guarantee patent holders an extended period of 17 years of protection (instead of the former 10 years) following which both branded and generic prices increased again [80], which immediately led to gains in NYSE stock market prices of multinational pharmaceutical companies of up to 8.5%. This was not seen to be trivial given the small portion of the Canadian market in the global sales of pharmaceutical multinationals [92].

5.1.2 Reduced investment by originator pharmaceutical companies

When faced with CL, it has been argued that a pharmaceutical company is not likely to compensate for the ensuing loss of income by raising drug prices, by reducing expenditure on advertising or by lowering return on investment. Instead, the company is likely to reduce R&D expenditure [34] Yet, in practice, this is not always what happened in countries that have issued CL. Lexchin et al. argue that, when Canada abandoned its CL practice, this was partly done because the R&D based pharmaceutical industry promised to increase its R&D investments, which however never happened[105].

In general, theories of innovation predict that originator companies will reduce their investment (either financial investment in new R&D projects but also technology transfer) in a country that does not (fully) protect intellectual property rights. There is an increased risk that R&D activity is less securely protected, that future innovations would also be copied and all of this diminishes the expected profits to receive from innovation. The pharmaceutical industry, with its high R&D costs and failure rates, would in theory be sensitive to the disincentivizing consequences of CL on R&D investment and innovation [38].

Reduced incentives to invest can occur through a variety of channels. First, R&D managers may consider other locations with similar labour costs and access to important resources more attractive to develop a product. Particularly multinational corporations will have the ability to cherry-pick the most promising regions for further investment. Second, the disincentivizing effects can also occur indirectly, beyond company managers themselves, when financial observers such as those who sell or recommend a firm's stock may question the firm's projected revenue streams, which can –rightly or wrongly- have impact on the firm's value on financial markets [22]. Third, there is not only the risk of losing revenue in the local market in which a CL would be used, but, and this is perhaps even more important, there is also the risk of international spill-overs. The local product could be exported to other countries but mostly, through the system of External Reference Pricing, where drug prices in other countries are influenced by those in others, compulsory licenses can generate international consequences (at least when the issuing country is a reference) [24, 39, 60].

It is not only the immediate profit motive that could diminish the attractiveness of R&D and hence influence investment decisions. Mere retaliation is also possible, partly as a signal to disincentivize other countries thinking of doing the same thing or because companies want to influence domestic policy decisions in the future [28]. After Thailand's introducing a CL for Abbott's Kaletra the firm withdrew their activities from Thailand and said it would not introduce any new drugs there [60]. One study indeed found that issuing a CL for a product (ARTs compared to oncology products) affects the probability that other CL will be issued [27]. The ability to retaliate will depend on the size and scope of the originator company. A large company with a large product portfolio will have more opportunities to retaliate than a small biotech company focussed on only one product. On the other hand, retaliation (when identified as such) will also likely generate backlash from public opinion, particularly when the grounds for issuing the compulsory license were humanitarian motives. If on the other hand, the motive for the compulsory license was merely one of industrial policy, then perception will be different and retaliating companies would arguably have a moral high ground and incur lower goodwill costs [81].

The issue of reduced investment by originator pharmaceutical companies is especially relevant for an evaluation of CL in HIC.

- It can be argued that pharmaceutical companies are able to offer lower prices for medicines in LMIC because they can recoup R&D costs by applying higher prices for these medicines in HIC. In other words, the pharmaceutical industry compensates lower revenues in LMIC by higher revenues in high-income countries. The impact of CL is therefore of a different nature when used in HIC than in LMIC [32] and the deterring effect of CL on R&D investments can be expected to be higher in HIC [22]. If CL is introduced for medicines in HIC too, this could undermine the system of tiered pricing between LMIC and HIC. On the other hand, also in LMIC, CL can strictly speaking become a threat to pharmaceutical profits obtained in HIC. There is a risk that the less expensive version of the medicine is exported to a HIC through **parallel imports,** thus reducing the profitability of the company marketing the originator medicine in the HIC [40, 44], although this risk will to a large extent be countered through various international trade barriers and custom controls.
- Although this has not been thoroughly investigated in the literature, it can be hypothesised that the impact of CL on investment by originator pharmaceutical companies depends on the **frequency of CL use** (i.e. is it used in exceptional circumstances or is it regularly applied to very expensive medicines?) [65] and the geographical scope of CL use (e.g. does a single country such as Belgium apply CL or do a number of European countries jointly apply CL?). It can be expected that the regular application of CL by a group of countries would have a larger impact on reducing investment by originator pharmaceutical companies.

Despite the previous theoretical arguments, **empirical evidence substantiating the claim that CL reduces R&D investments is scant:**

- Evidence from WWI shows that companies increased instead of decreased their R&D activity. After the 'Trading with the enemy act' after WW1 (see Box 1), where the trade relationships between US and German companies were arranged, US companies were allowed to copy patented German technologies and chemicals. With a time lag of eight years, affected companies invested more, not less in R&D [45]. CL encouraged invention as German inventors produced 30% more patents after 1918 in the fields where CLs were issued. The incentivizing effects were stronger in fields with ex ante higher concentration, and lower in fields with more competition. The explanation for this finding is that the increased threat of competition had led to more investment in R&D in order to stay ahead of competitors and maintain a leading position in a changing market. This effect however may be the result of the fact that CL were an exceptional measure as a result of an emergency situation (war) and it may disappear when CL are issued repeatedly [65].
- Even though this evidence is also outdated, an analysis of 700 companies found that companies subjected to CL invested 36% more in R&D in order to remain competitive than companies in the same industry which are not subjected to CL [91].

- A study that investigated measures of inventive activity (such as patent rate) before and after six cases of compulsory licensing in the US in the 1980s and 1990s did not observe a uniform decline in innovation by those companies affected by compulsory licenses [29].
- The Canadian experience showed that implementing CL for an extended period led the country to obtain a pharma R&D 'free rider' status losing R&D investments from big pharma and having its manufacturing mostly focused on generics [82].

Of course, the potential negative impact on investment (and also other negative consequences) will be softened when **larger royalties or compensation payments** will be paid to patent holders [29]. When the remuneration is sufficiently high, a compulsory license can even be to the advantage of the patent holder, when it is unwilling to invest in production and distribution costs and there is a substantial risk of imitation and counterfeit [26].

5.1.3 Reduced investment from other industries vulnerable to IP protection

Also, the incentives to invest in R&D by other companies can be affected when the issuance of the CL signals that the investors' 'climate' in a country has changed. As such, CL may discourage foreign direct investment [64], the amount of resources invested domestically by foreign investors and an important determinant of economic growth in the recipient country. The empirical literature does not provide an answer to the question of the potential impact of CL on foreign direct investment: a few studies have examined the evolution in foreign investment over time, but such a design does not allow for a causal relationship between CL and foreign investment to be demonstrated [77-79]. It has been argued that this was less of an issue in developing countries with little or restricted foreign investments [71, 72]. When the motivation behind the CL is one of providing lifesaving treatments to patients or other ethical reasons, its effects may be limited to only pharmaceutical investment. It is therefore crucial that policy makers who plan issuing a CL have a clear communication strategy regarding their humanitarian motives, in order not to affect the business climate and scare investors from other industries where these motives are less pertinent.

The only well-developed case study is provided by Canada where a sustained CL policy over almost twenty years (1969-1987) created a thriving generics industry being domestically and globally active in the developing world. However, it also led to retaliatory underspending by US biopharma multinationals in basic biopharmaceutical research in Canada, the latter leading to substantial domestic R&D being focused on developing me-too drugs, rather than on innovative medicines [82, 105].

Paradoxically, patents in themselves can also obstruct investment in innovation. The value of a patent not only consists of the possibility to claim high monopoly prices, but also in a right to exclude others from producing it and develop product-specific know-how [53]. Patents may obstruct the speed of innovation by limiting the dissemination of knowledge and the sharing of innovative production processes [17]. Therefore, CL can also work in a positive way to stimulate R&D activity, particularly when the patent is used to block or diminish the distribution of an 'essential facility' [37] and a sufficiently high royalty is paid [16, 59]. It is notoriously hard to judge when the dynamic benefits of IPR protection in rewarding innovation become outweighed by the benefits of increased competition and short-term innovation [33].

5.1.4 State retaliation

Well-organized pharmaceutical lobby groups will likely pressurize politicians to also retaliate through various levers in international economic affairs. Issuing trade sanctions and increasing tariffs are potential instruments to influence domestic decision-making regarding CL as well as issuing retaliatory compulsory licenses. There is a documented history of countries such as Brazil, South Africa or India facing retaliatory threats from the US government when they were planning to issue CL for essential medicines [68]. Countries that have issued compulsory licenses have been put on the US 'Priority Watch List', a selection of countries that require special monitoring by the US government for their leniency towards protection of intellectual property rights [22]. For instance, the US imposed various WTO complaints and sanctions against Brazil for failing to protect intellectual property rights [22, 30]. When Thailand imported medicines under CL, the United States withdrew trade advantages to the country [79].

The effectiveness of these state retaliation strategies remains to be seen. Often these measures are used as a threat rather than an actual policy. Particularly in humanitarian matters (such as drug pricing), the acceptability in the global public opinion of these retaliation measures remains controversial. There is a 'war of perception' that needs to be won and those in favour of IPR protection are facing an uphill battle. For instance, Brazil is reported to have won this 'war' with the US government ultimately backing down from economic retaliation. Moreover, some also argue that these trade sanctions are in themselves illegal as they go against WTO agreements and are hence not enforceable.

5.2 Health consequences

Apart from the effects CL could have on the economic development of a region, in the context of pharmaceuticals it will also directly and indirectly affect patient and population health. As such, CL can equally well be seen as a measure of health policy instead of industrial policy. We distinguish between four separate pathways trough which CL can affect patient and population health.

5.2.1 Increased access for patients to expensive, innovative drugs

The immediate benefit of issuing compulsory licenses is that, when successfully implemented, patients in need of expensive treatments will now have better access [19]. The lack of access to medicines is especially poignant when local markets are underserved by patent holders, potentially because of insufficient demand or ability to pay (as is often the case in LMIC but increasingly also in HIC when drugs are deemed 'unaffordable' by healthcare payers) or because the patent holder deems distribution networks too costly to develop [39], although the latter will also be a concern to generics producers. To create an assured supply of (essential) medicines, countries can turn to CL [42]. When the Health Intervention and Technology Assessment Program assessed the Thai CL programme, it concluded that CL increased the number of patients with access to these medicines and generated associated health gains [79, 86]. The extent to which CL will increase patient access is of course dependent upon the issuing country's ability to produce local versions of the patented drug to the same quality standard. That is not always evident. For instance, it has been argued that compulsory licensed products in Thailand were of lower quality [42]. So, this concern depends on the quality and safety requirements that will be demanded from CL products (for instance, is new safety testing required for the CL products?), but more stringent safety requirements will also imply more obstacles to production and supply.

Access will mostly be impeded by high prices. In case there is large income inequality, like in certain LMIC, then it can be that the profit-maximizing price for a monopolist is even higher than in countries with more equal income distribution. It can be profitable to only serve the price-inelastic part of the demand curve [36] and when there are more 'convex' demand curves (indicating a non-linear relationship between a rising price resulting in lowered quantity demanded), this price could be higher as the rich fraction of the population may be much less price-sensitive than the rest of the population. This reasoning applies only, however, when there is no reimbursement for the product in question. In case of full or even partial reimbursement, patients' demand will not or only to a very limited extent be influenced by the price of the product. If the product is not reimbursed, the profit-maximizing selling strategy can be a 'low-volume-high margin' one, whereas the population needs a 'high volume-low margin' strategy [52]. For products that have large consequences for health and wellbeing of patients, this prioritization of private interests over public ones could be an additional argument to issue compulsory licenses. Note that in Western countries with public health insurance, products with a major health impact are generally reimbursed.

Although lower prices can be expected with CL, this will also depend on the particular context. One study of 51 cases of issuing a CL in the drug sector showed that issuing a CL is indeed likely to reduce prices (on average with 60-70%)[11]. However, some studies have also shown that compulsory licenses do not necessarily lead to lower prices. Domestic production can be expensive in itself, particularly for complex production processes. The ability to compensate fixed costs of building development capacity depends on the market size that is expected to be served [22]. In Ecuador, CL had mixed results. For many CL-products there was insufficient capacity and prices did not drop [84]. Additionally, it needs to be investigated whether high

drug prices are also not the consequence of other obstacles, such as high import tariffs or other cost-increasing aspects of drug trade [22].

5.2.2 Freeing of resources that can be invested elsewhere

When compulsory licenses lead to lower prices of already funded drugs or when increased access to these drugs reduces the need for alternative (expensive) treatments for patients, this implies that resources will be saved. Those resources that were earlier reserved for paying for these expensive medicines or treatments (through public insurance or private resources) can now be freed to invest in alternatives. When these freed resources are invested in health programs that are safe, effective, and cost-effective this can have an additional positive effect on population health. As such, depending on how freed resources are used, the CL can indirectly improve patient outcomes in other domains as well. One study estimated that in Thailand a reduction of 90% in the future costs of second line treatment for HIV therapy through CL would save the government a discounted 3.2 billion $ and would halve the cost per life year saved through ART, money that can be used elsewhere to help patients [70].

On the other hand, compulsory licenses will also generate certain expenses in themselves. There will be legal and regulatory costs of issuing them (including costs of litigation by the patent holder) and, depending on the prevailing rules of market access in the domestic market, generic products may have to go through a long and costly process of evaluation themselves [22, 60].

5.2.3 Reduced access to innovative drugs through fewer drug launches or fewer trials

The consumer surplus generated through compulsory licensing (i.e. better and/or cheaper access to patented medicines) can be diminished by a reduced or slower access to other medicines in the longer term [28, 56]. One of the benefits of having a well-developed originator industry is that companies will be relatively quick in launching new products in the domestic market. Moreover, before launching drugs, they will also often set up clinical trials in these countries in which domestic patients can enrol. These are pathways through which patients can obtain faster access to innovative medicines. A risk of issuing compulsory licenses is that such initiatives (drug launches or clinical trials) will be delayed or cancelled.

This can be done because companies fear that CL will also be used for these new medicines, or for strategic reasons to retaliate, or both. However, how realistic these scenarios are will largely depend on how attractive the domestic market remains for the innovator company. If not introducing new medicines or not starting up clinical trials is costly to the firm itself, the risk that new drug launches would be delayed becomes less credible, certainly when the motive would be one of retaliation purely to make a statement [52]. Following this perspective, it seems more likely that companies effectively cancel investments, drug launches or trials in relatively small markets where the costs of making a clear ‘statement’ are lower, than in large markets where delays would be costly in terms of forgone profits.

5.2.4 Reduced supply of innovative medicines due to lower investment in R&D

A central theoretical argument used against compulsory licenses is that using CL to make medicines more affordable is a short-term strategy with potentially negative consequences on medicine availability in the long term. Through affecting the pay-off from making risky investments, investors will be less inclined to invest in drug R&D (relative to investing in other more profitable industries and businesses) and, if so, this will affect the drug pipeline and over time impact the supply of innovative drugs that become available for patient populations. This has consequences in terms of industrial activity (see section 5.1.1) but it will also affect the health and wellbeing of the population. Future generations’ health and wellbeing will be sub-optimal in the sense that innovative medicines that would have been developed under strict IP protection, now will not have seen the light of day.

Of course this argument is extremely hard to verify and requires many qualifications. One is that it assumes that the innovation that occurs under IP protection (and that can be expected to diminish through CL, nationally but also internationally) is also the *needed* innovation. This may be true for HIC but for LMIC, which are struggling with neglected diseases for which there are already little investment incentives, the argument that much needed innovation will be hampered by issuing CL will be less compelling[52].

Another qualification is that, in a small country, the effects on general innovation climates worldwide of issuing CL will be limited [18]. Therefore it seems unlikely that there would be a price to pay in terms of future people's health opportunities when a small country (e.g. Belgium) issues a CL [106]. When this happens in large markets such the US or Japan, this argument gains force again. Of course, a small country can also set a precedent for other countries to follow and then the impact would be larger. Third, as mentioned earlier (see sections 5.1.1 and 5.1.3), CL can also have positive effects on industrial development and innovation, which can create innovation benefits on their own. If so, these positive effects would need to be balanced against the negative consequences in terms of stimulating investment in drug R&D. Fourth, although the argument is theoretically coherent, as discussed earlier, the empirical evidence that CL would effectively diminish or enhance innovation is scant. Some studies on post-war industry re-emergence even document positive effects of CL on innovation [45].

5.3 Adequate remuneration for compulsory licenses

The TRIPS agreement legally entitled member countries in its Article 31 to issue a CL requiring the government authority or a court applying for CL to have been unable to obtain a voluntary license from the patent holder on 'reasonable' commercial terms, to adequately remunerate the patent holder under CL. According to the TRIPS agreement, adequate remuneration should be based on the economic value of the authorisation. However, this does not apply when compulsory licensing is used to address anti-competitive practices [107].

As it is up to national law and decided on a case-by-case basis to define what is meant by 'adequate remuneration', there is a need to identify the considerations that can be taken into account when determining the adequateness and to discuss the consequences of different methods of setting remuneration.

One consideration relates to the objective of compulsory licensing [98, 99]. It has been suggested that remuneration can be set at a lower level when compulsory licensing is used in the context of anti-competitive practices or for humanitarian purposes. In the context of excessively priced patented medicines in developed economies, recent proposals suggest applying competition law [108], but then "excessiveness" still needs to be defined and operationalised (cfr. Box 5).

The literature proposes a number of other considerations that can inform the level of remuneration [17, 97-99, 101]. These tend to fall into two categories:

- Industrial considerations, e.g., the risks, costs and innovative character of product development; the extent of public funding for the development of the medicine; the requirement to maintain incentives for pharmaceutical innovation; lost profits for the patent holder and revenues for the licensee.
- Health considerations, e.g., the efficacy and public health importance of the medicine; public interest considerations; population health benefits; the benefits of medicine availability.

Two main methods for setting remuneration have been identified: 1) a fixed amount or 2) a proportion of the price of the medicine, also called a royalty, applied to the volume sold [18, 95, 96]. A distinguishing feature of these two methods is that the former does not link remuneration to the volume sold, whereas the latter does. An adaptation of the latter method has been proposed by the World Health Organisation, the so-called 'tiered royalty' method, which seems to be suited for the specific context of compulsory licensing in low- and middle-income countries. According to this method, remuneration is set at 4% of the price of the medicine in a high-income country, but adjusted to the income level of the country that issues the compulsory license [109]. However, the literature is not clear how remuneration needs to be set in practice in relation to any of these considerations or how these considerations need to be traded off against each other. We subsequently discuss 'adequate remuneration' for the use of CL in developing and developed economies.

5.3.1 Adequate remuneration of CL in developing economies

Until today, CL has almost exclusively been used by LMIC economies to get affordable access to innovative medicines developed by HIC biopharmaceutical firms acting as monopolists. This also explains why antecedents and consequences of adequate remuneration for CL have been predominantly studied conceptually making use of game theory models stylizing negotiations between HIC biopharmaceutical patent holders, developing countries' governmental institutions and their incumbent generics manufacturers [51, 54, 110].

Box 3 – Remuneration in LMIC: Examples from Merck and Gilead

In 2006, Thailand's Ministry of Public Health issued @a CL for efavirenz, a medicine for the initial treatment of adult HIV patients that had become available in the late 1990s. The CL lasted until December 2011. It allowed the Thai government to import generic efavirenz from India, where the drug is not patented, and to produce the drug themselves. At this time Merck still had a patent in Thailand on this drug. In the US, Canada and some EU countries, BMS markets efavirenz as Sustiva, Merck markets it in the rest of the world. In 2006, a one-year supply cost by Merck was about $6000. In LMIC it came at $277 per patient per year. Thailand did not discuss first the public use of the drug with Merck. Brazil took a different approach, negotiating price discounts by referring to the potential use of CL resulting in a voluntary license covering the local manufacture of patented HIV drugs. Thailand imported the drug from Ranbaxy in India and produced it domestically through the Thai Government Pharmaceutical Organization. Merck received a royalty fee of 0.5% of the total sale value of efavirenz that Thailand imports or produces [100].

Gilead followed a separate path marketing tenofovir that had quickly become a mainstay of first line regimens for HIV treatment. Available in developed countries at $5000 ppy, Gilead's global access programme extended the use of the product to 2.4 million patients in LMICs. Licensing partnerships now supply 75% of the market by volume, at a treatment cost of $57 ppy, which is 1% of the branded cost.

Over the period 2001-2011 tenofovir generated a profit of $25 billion in India by issuing nonexclusive licenses to 11 companies, which gave them the right to produce generic versions of the drug and distributing them to 95 low-income countries. Gilead received a 5% royalty on generics sales. As a result, Gilead's global access programme supplied 1.2 million patient-years of tenofovir to patients that would not have been able to afford the branded Western price.

For Gilead, this represented a revenue loss of US$5.9 billion. However, the net benefit of avoiding further price cuts could have been significantly larger [102].

Sarmah et al.'s [12] dynamic model of the use of CL along the drug product lifecycle provides the closest representation of reality in LMIC [54]. Modeling the situation in LMICs, they focus on the situation following a first stage of price- and profit maximization based on patent exclusivity. In their model, in this subsequent stage of the drug life cycle, the exclusive patent holder can be exposed to CL by LMIC generics manufacturers and/or their governments, which will impact the market structure; it now consists of both the HIC branded and LMIC-domestic generic manufacturers, with the latter having to pay royalties to the former. The application of CL in this subsequent stage of the drug lifecycle can lead to profits foregone to be levelled by royalty income. A large enough previously unserved population given unaffordable drugs, in conjunction with a high enough royalty compensation, typically in the order of magnitude of 4-6% [109] could possibly lead to a positive outcome for both innovator firm and social welfare in a negotiated agreement. On the condition that the royalties received by the patent holder from the generics companies now using its technology to reach this patient potential is sufficiently high, the Western innovator can increase its cash flow and thus have an incentive to further invest in R&D. A larger royalty from compulsory or voluntary licensing commanded by the Western patent holder to the LMIC domestic generics manufacturer will limit the latter's capability to set a low price and attract the large potential of price-sensitive patients in LMIC, not being able to afford the initial Western prices. This explains the consistently low royalty rates of 4 to 6% being held by biopharmaceutical companies in LMICs, as in the case of Gilead's global access programme (see Box 3). High revenue levels even at a small

contribution can still lead to marginal profits sufficient to provide an incentive to innovate and to reach larger, previously unserved LMIC patient populations.

5.3.2 Adequate remuneration of CL in developed economies

As mentioned above, CL is most used to improve access and price negotiations in LMIC countries. However, a recent review of the use of CL in HIC countries reveals that here CL is used to ensure access to biopharmaceuticals that have been on the market for many years to more than a decade [8]. Examples include CLs issued pertaining to the export of ciprofloxacin in Canada and Merck's imipenem/cilastatin in Italy. In this latter case, the Italian competition authority forced Merck via CL to allow a generics manufacturer upon their request to produce the drug for export to other EU countries in which the patent had already expired. Furthermore, the review found no cases of the use of CL as a threat during market entry negotiations, although with two exceptions; i.e. pertaining to Orkambi®, an expensive medicine for cystic fibrosis in the UK and an expensive hepatitis C medicine in Italy [8]. In the case of Italy in 2017, no definitive action was taken. In the case of Orkambi® it led the manufacturer Vertex to accept a discount to become reimbursable by the NHS in 2019. So, to date, there is hardly empirical support for the use of CL to positively impact access at affordable prices.

In the past 20 years, CL has been predominantly used in HICs to ensure adequate supply and a lower price, e.g. to stockpile a Bayer-originated antibiotic [8] or to fight potential pandemics like the *avian flu*. Governments in fear of worldwide patent holders lacking the production capacity to respond to sudden large outbreaks of viruses, such as experienced with Roche's Tamiflu, have been using CL to infringe on Roche's worldwide exclusive patent access and have domestic manufacturers, other than the patent holder, produce the necessary quantities for the time needed to fight the outbreak. This on the condition that the rightful patent holder can sue the government if not provided with a "reasonable and entire compensation for such use and manufacture" [97]. Roche, in an effort to avoid the CL and to keep its global market power, negotiated high royalty rates to be paid by licensees producing Tamiflu along with Roche. The advantage of Roche privately negotiating license rates with generic manufacturers is that once a royalty rate has been established, the US government 'may have to pay that same amount as reasonable and entire compensation for infringement' (Mitchell, 2007). Clearly, due to increased generic competition based on voluntary licenses from Roche Tamiflu, prices will have turned down. So, to receive *"reasonable and entire compensation*" as defined by the US government[2], revenue effects from royalty rates might have to compensate for lost profits for Roche to follow this market access strategy. Yet, it is not clear in the US legislation whether "entire" compensation refers to the extent of the compensation for the government use or to the fact that on top of the compensation for the government use, costs to launch a procedure in court also need to be covered. Moreover, it has not been defined in US law what "reasonable" actually means[3]. As explained in box 3 above, this example mirrors the effect of the use of CL in developing economies where Gilead's global access programme followed this market access path with generics licensing revenues in expanded patient populations fighting profit erosion. While generic formulators' margins have been held at typically 15 to 25%, operating margins for Gilead's access products had risen to nearly 60%,

[2] As cited in Mitchell (2007): "28 U.S.C. § 1498 (2006) ("Whenever an invention **...** covered by a patent of the United States is used or manufactured by or for the United States without license.., the owner's remedy shall be by action against the United States in the United States Court of Federal Claims for the recovery of his reasonable and entire compensation for such use and manufacture.")" and further "Conversely, [w]hen an established royalty does not exist, a court may determine a reasonable royalty based on 'hypothetical negotiations between willing licensor and licensee."

[3] Art. 28 U.S. Code § 1498 states that "(…) Reasonable and entire compensation shall include the owner's reasonable costs, including reasonable fees for expert witnesses and attorneys, in pursuing the action if the owner is an independent inventor, a nonprofit organization, or an entity that had no more than 500 employees at any time during the 5-year period preceding the use or manufacture of the patented invention by or for the United States (…)".

mainly due to the falling average and marginal cost of the active product ingredient (API) being needed in larger volumes [102].

Box 4 – Remuneration in HICs: on price setting of innovative medicines

Innovative medicine price setting is primarily unrelated to the costs involved in discovering, developing, producing, and commercializing the product. Instead, it is driven by health market-related factors such as payers' willingness to pay for a societal unmet need or disease category, comparative clinical advantage or competitive differentiation and the comparative cost of the current standard of care. Conforming to the Ramsey distributive justice pricing principle, the global industry price discrimination policy maximizes societal welfare surplus by charging more to countries exhibiting low price elasticity i.e. to the richer countries.[111]

A medicine's price is set following a therapy lifecycle approach, which calculates the expected net present value (ENPV)[4] of the operating cash flow of the novel medicine project. A price should be set so that the ENPV, taking into consideration production and commercialization costs, R&D-related costs (not depreciated investments), and the cost of capital needed to finance the project, is larger than zero. As an example, in Gilead's Annual Reports from 2013 to 2016 it can be verified that the operating margin[5] (operating cash flow as % of revenues) went from 30% in 2013 to 50-60% afterwards. This following the $11Bn Pharmasset acquisition, which moved the company into the treatment of chronic hepatitis C virus with sofosbuvir.

The medicine's operating cash flow, also called EBITDA, is built up during the therapy's life-cycle, which is composed of four periods following Sarmah et al. [54]; (1) pre-market R&D where cash is drained; (2) a first in-patent market period of four years where the full monopoly EBITDA needs to be earned, (3) a second in-patent period where the market will be served by innovative branded products and generics companies having obtained a CL hence featuring a lowered EBITDA contribution, and (4) a third out-of-patent period where generics firms compete with the branded pharmaceuticals, where CL is no longer applicable and the EBITDA contribution is marginalized. Maximizing medicine project EBITDA is necessary to positively influence innovation propensity, so that the probability of a positive ENPV is maximized.

From a societal point of view, while leading to increased innovative activity across Member States, the EU Commission pleads for an increase of the general effective protection period [112]. In contrast, non-governmental organisations, in an effort to fight high medicine prices, point to the negative impact of supplementary protection certificates on medicine prices and plead for its abandoning [113].

Summing up for all projects, the resulting corporate EBITDA indicates the amount of cash the company generates from its product portfolio and can be used for strategic investments (predominantly in R&D) ensuring dynamic efficiency.

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4 Capital investment analysis uses the concept of ENPV to determine the economic feasibility of an investment. The ENPV of a stream of cash flows is the sum of all cash expenditures and net market-based cash flows for a certain product innovation project. In the case of biopharmaceuticals, the cash drains entail the medicine project R&D costs including the costs of failure but excluding non-cash costs such as depreciation from investments made. Net market-based cash flows include product expected revenues minus marginal (i.e., made only for this product at a moment in time) production and marketing costs. Given their uncertain nature, all cash flows (and drains) are probabilistic in nature at project onset, hence the term "Expected". To sum amounts of cash spread in time one needs to correct with a discount factor which is representative for the cost of capital. A riskier project will require a higher discount factor and, representing the higher return commanded by the investor to invest in this project. A higher needed discount factor will reduce the probability of having ENPV>0.

5 The operating margin is the "gross profit", i.e. profit *before* adding investment-related costs. Net profit includes all investment-related non-cash costs (also called depreciations, minus the taxes) and hence is lower.

Both the Bayer antibiotic case and the Tamiflu example pertain to the use of CL as a negotiation tool used by a HIC to a Western patent holder as part of a health policy to protect the population for potential pandemics by reserving medical treatment capacity or resources in a compulsory manner. Dwindling global prices could be seen more as a beneficial side effect of this CL-based health policy. Also, it was the price Roche was apparently prepared to pay to claim global moral leadership in fighting pandemics like the avian flu [97].

Context matters when studying *adequate remuneration* in the case of fighting *anti-competitive excessive pricing* behaviour of innovative drug companies in HIC's developed economies. The context of national payer – industry CL agreements reached in developing economies differs substantially from CL-based negotiations in the context of developed economies. The Sarmah dynamic process model of the drug lifecycle can still be used for the latter context providing the basis for our analysis [54]. However, as mentioned above, almost all examples of the use of CL in HICs pertain to the last phases of their process model (i.e., in-patent with CL and out-of-patent phases in non-originator countries), while we need to study adequate remuneration during the first two market phases (monopolistic in-patent, and in-patent with CL) in developed economies for which, with the exception of Orkambi in the UK[8], in the first phase hardly any empirical evidence is available.

Conducting a negotiation analysis, in the context of LMIC developing economies described above, in the in-patent with CL phase, the potential threat of CL made the pharmaceutical innovator company to find an equilibrium business rationale that compensated for the CL-induced profit erosion. This by creating a revenue effect through licensing generics manufacturers able to serve the most price-sensitive patient population. Then, the net EBITDA loss could cater for the gain in patient welfare in LMICs where otherwise at branded prices this would have led to market failure with no or limited revenues. In contrast, in the context of developed economies, finding such an equilibrium allowing for reasonable remuneration is much harder, if not impossible. This while a positive pharmaceutical business rationale for applying CL in HICs is hard to motivate while only negatively hitting the profit potential of the medicine without any extra reach to markets as in the context of LMICs that were previously unattainable.

Box 5 – On price excessiveness

From an economic standpoint, two arguments are made to judge the excessiveness of medicine prices. From an industry perspective, price-setting for realising the EBITDA of medicines resulting from their investments is deemed to be excessive if it leads companies to making "excess returns", i.e. if the company generates more profits than expected given the risk associated with their investments [114]. The latter risk behaviour is exhibited by the company's *weighted average cost of capital* (WACC). In their recent study, focusing on the 2013 – 2018 period of biopharmaceutical companies featured in the Standard & Poor's S&P 500, excess returns varied between 1.9% lower than S&P 500 for pharmaceutical companies, to 6% above S&P500 for biotech firms, the latter including Gilead and AbbVie. This makes sense given the possibility of the larger pharmaceutical companies to diversify their risks across compounds and disease areas, which smaller more focused biotech companies are less capable of doing.

From a societal perspective, following the conclusions drawn by the European Commission from the United Brands Company landmark case on excessive pricing, Dutch economists Canoy and Tichem apply this case to the particular domain of patented medicines [108]. They propose to consider the price of a patented medicine to be excessive if the price overshoots the goal of patent protection. In healthcare this can be interpreted as when the medicine price leads to a cost-effectiveness ratio which is higher than the societal willingness to pay for health gains (potentially corrected for ethical and other individual country-relevant considerations). Also, they argue that it can be used by competition authorities to relate pricing excessiveness to the propensity to innovate while high drug prices, in their view, can lead to crowding out valuable non-price excessive medicine development projects that are still valuable to society.

This would of course require the payer to be transparent about its maximum willingness-to-pay (WTP) level.

Along the same lines, Fonteijn et al. propose, although still rarely used, the two-pronged United Brands test for excessive pricing of biopharmaceuticals.

Doing so, following their ACM Working Paper'[6] (1) the excessive relationship between costs and prices, and (2) the unfair nature of the prices are the two legs that must be examined cumulatively'. They do believe that the enforcement of the prohibition of excessive pricing should take incentives for innovation into account. Conversely, they rightfully remark in our view that patent protection does not provide a reason to be excluded from excessive pricing prohibition. They plead for including ex-ante probabilities of success, and for the maximum WTP cited before, under the first leg of the test. This is taken into consideration in practice when applying the ENPV reasoning described above. Of course, evaluating the fairness level, then, would require full transparency on all costs and a yet inexistant method to objectively judge their excessiveness given the varying existing perspectives on the concept.

In our analysis, using CL during the earliest in-patent phases (Phases 2 and 3 in Sarmah et al.'s process model) in HIC-based negotiations will have a high probability to be seen to be unacceptable by the innovative industry, which will lead to downturned proposals of remuneration and engender tit-for-tat negotiation strategy behaviour, while not being seen to be rational from an economic logic-obeying business rationale nor from a patient welfare perspective.

In this context, in the same manner as in the developing economies context, applying a CL-based industrial policy will also extend the market structure from one branded manufacturer to include several generic manufacturers paying compulsory or voluntary royalties to the former patent holder. Only now, during these early in-patent stages, both branded and generic manufacturer will be active on the same price-insensitive HIC market. This in contrast to the CL-induced market structure in LMIC where the CL-induced change, as described above, allows to reach the large price-sensitive part of the population and compensate profit erosion by licensing revenues and increased patient welfare. This will inevitably lead to significant uncompensated innovator firm profit erosion while significantly shortening Phase 2 and dividing the total market between branded innovators and generics firms. The lowered average market price resulting from non-branded competition will put a significant downward- and upward pressure on respectively the innovator (now typically in the range up to 60%, see Box 4) and generics manufacturer (now typically in the range of 15-25%, see Walwyn (2013)[102]) operating margin to form an equilibrium which will be unacceptable to the innovator firm. In sum, instead of the WHO recommended royalty rates of 4% charged in the developing economies context, a much higher royalty rate compensating for the profit erosion, speculatively double-digit numbers would be charged by the innovator firms to the generic manufacturers in the context of HIC developed economies.

From a patient welfare perspective, reduced profit in the early in-patent stages will inevitably be compensated by an upward pressure on the late royalties commanded in LMIC making it more difficult for generic firms to have the low price needed to reach those highly price-sensitive patient sub-populations[54]. Within Europe, lowered prices in rich countries will delay access to innovative medicines in poorer countries[111].

This is probably why the WHO/TCM/2005 'Remuneration guidelines for non-voluntary use of a patent on medical technologies' state that '[i]n middle- or high-income countries, systems that result in royalty payments that are the same as they would be in the poorest countries are likely to be underutilized; adjudicators and policy makers will likely be uncomfortable with such outcomes, and thus will be deterred from issuing compulsory licences at all' [109].

[6] Chris Fonteijn is Chairman of the Dutch authority for consumers and markets (ACM). Here we quote the unpublished ACM Working Paper C. Fonteijn, H. Akker, and W. Sauter (undated) *Reconciling competition and IP law: the case of patented pharmaceuticals and dominance abuse*.

Second, to comply with the need to have a credible manufacturing capability [51, 87] the CL-inducing government would need to find a generic manufacturer. Given the unavoidably strong emerging generics competition for such innovative medicines, only when having sufficient volume will a generic manufacturer be found ready to accept such a deal, which may limit the possibilities of a smaller country like Belgium to find a generic manufacturer for its own territory. This makes it necessary to conduct the CL negotiations at a European level where at present there is no forum to discuss drug pricing. This upon explicit request of countries that today and into a foreseeable future are not willing to delegate pricing negotiations to the supranational level.

Finally, excessively priced innovative therapies in the domains of immunology, gene and cell therapy feature extensive patent thickets. The generics manufacturer, to make a profit facing high patent holder royalties and a complex cost structure given these patent thickets would strongly need access to a patent pool. This while having to keep its marginal cost as low as possible in the face of these contingencies. Industrial economic research of this IP strategy shows that the required pool would be of the inverse pyramid style [115]. In such a patent pool, in contrast to regular pyramid sequential pools as found in electronics, all innovators enjoy equal bargaining power while all representing partial but necessary (sub-)solutions to the disease; like AIDS cocktails containing several drugs. But also, more and more, as equally applicable to combination therapies in the domain of oncology. This latter type has shown to render the endogenous formation of the patent pool highly unlikely. Unfortunately, as evidenced by the Medicines Patent Pool backed by the UN in 2010, governments or non-profit organisations had to intervene to facilitate their setup. Hence, this would add an extra institutional cost to the implementation of a CL-based industrial policy.

6 CONCLUSION

The worldwide experience with CL has shown that the economic pros and cons of CL must be evaluated on a case-by-case basis. Indeed, CL can be issued in a variety of forms in different contexts with various objectives, implying that CL can have different advantages and disadvantages. This report has listed key industrial and health policy consequences of CL that need to be judged and balanced by decision makers. The magnitude (and even direction) of these effects is context-dependent and many complex economic dynamics are simultaneously operating. Unfortunately, there is insufficient empirical evidence to give clear answers as to which net economic consequences can be expected when CL is applied to (very) expensive medicines by a developed country such as Belgium.

The literature review also indicated that the economic desirability of CL for very expensive medicines depends on the frequency of use (i.e. use in exceptional circumstances of excessively priced medicines vs regular application to very expensive medicines), the characteristics of the medicine to which CL is applied (e.g. complex biologic medicine vs simple chemical medicine, point in time during drug lifecycle [at market entry vs close to expiry of patents and exclusivities]), and on the characteristics of the country which implements CL (e.g. large vs small country, country with strong presence of innovative pharmaceutical industry vs generic industry).

Although there is no empirical evidence to support the assumption, it is assumed that if CL is regularly applied to very expensive medicines in a country such as Belgium with a strong presence of (inter)national innovative pharmaceutical companies, these companies and other industries might reduce R&D investment, which may have a negative impact in Belgium on the development of sophisticated production capacity, employment, scientific and technical know-how, competitive position, and international trade relationships. Based on the Canadian experience, the frequent use of CL would likely transform the pharmaceutical ecosystem in Belgium into one of generic manufacturers. Also, there may be practical constraints to using CL in terms of having access to raw materials and determining what an ‘adequate’ remuneration for the patent holder is.

With respect to the health consequences of CL, patients can be expected to have better access to otherwise very expensive medicines and the health care system which pays lower prices through CL can use these freed resources to help other patients. On the other hand, there can be fewer trials (and an ensuing loss of income for hospitals involved), delays in new drug launches and in the (very) long term, although open for discussion, a less fertile pharmaceutical pipeline can be expected when CL is frequently used. The potential decrease in the number of trials is especially relevant to Belgium, but this risk may be mitigated by the observation that pharmaceutical companies have an incentive to conduct trials in Belgium in light of the availability of clinical trial experience and capacity in the country.

CL can also serve as an instrument to exert pressure during price negotiations with pharmaceutical companies. For CL to be viewed as a credible negotiation tool, procedures need to be in place addressing legal provisions (with respect to, for instance, data and market exclusivities) and practical issues (e.g. criteria for assessing 'excessive' medicine prices and 'adequate' remuneration for the patent holder). Hence, CL for very expensive medicines needs to be viewed in relation to the broader context of medicine regulation and the availability of alternative instruments to combat excessive pricing behaviour of pharmaceutical companies such as an investigation by the Belgian competition authorities.

Key Points

- **When considering policy actions to address high medicine prices, the economic consequences of CL must be compared to the consequences of alternative policies such as voluntary licensing, tiered pricing, procurement on the international market, pooled procurement involving multiple countries, or various arrangements regarding price transparency and mandatory cost disclosure.**
- **When applying CL to expensive medicines, the practical challenges arise of determining what 'expensive' means and what an 'adequate' remuneration for the originator patent holder is. Both concepts are at present ill-defined and not generally agreed upon to be practically implementable in CL-related decision-making.**
- **For CL to be successful, the local manufacturer must have access to raw materials, infrastructure, scientific and technical expertise required to produce these medicines, and must address a range of issues related to intellectual property rights, or international producers must be found from which the medicine can be imported.**
- **In general, CL for expensive medicines can have various consequences in terms of economic activity within a country, patient outcomes and public health. Decision makers must judge and trade off these consequences when considering CL.**
- **It may be sufficient to use CL as a negotiation tool, but then the application must be perceived as credible (i.e. there must be a viable domestic or international industry able to produce the licensed product, legal possibilities to do so, and policy makers willing to use CL).**
- **CL can be used as a lever of industrial policy in a country that wishes to develop its domestic generic pharmaceutical industry to the detriment of its innovative pharmaceutical industry. In the**

event of CL, originator pharmaceutical companies and other industries may reduce R&D investment, which can negatively impact innovation in the long term. CL may also induce state retaliation against the CL-issuing country.

- **CL increases patient access to expensive medicines and frees up resources that can be invested in other (health) programs. However, pharmaceutical companies may respond to CL by delaying drug launches or cancelling clinical trials in the CL-issuing country or, in general, invest less in pharmaceutical R&D.**
- **Given that there is uncertainty about the magnitude or even the direction of economic consequences of CL in the international economic and empirical literature, the impact of issuing a compulsory license must always be evaluated on a case-by-case basis.**
- **The economic consequences of CL for expensive medicines are likely to be influenced by the frequency of CL use, the characteristics of the medicine to which CL is applied, the characteristics of the country which implements CL, and whether the CL is issued by a single country or a group of countries.**

BIBLIOGRAPHY

1. Vogler S, Zimmermann N, Babar ZU. Price comparison of high-cost originator medicines in European countries. Expert Rev Pharmacoecon Outcomes Res. 2017;17(2):221-30.
2. Kesselheim AS, Avorn J, Sarpatwari A. The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform. JAMA. 2016;316(8):858-71.
3. Luzzatto L, Hyry HI, Schieppati A, Costa E, Simoens S, Schaefer F, et al. Outrageous prices of orphan drugs: a call for collaboration. Lancet. 2018;392(10149):791-4.
4. Luyten J. Wat is een billijke prijs voor een nieuw geneesmiddel? Karakter: Tijdschrift van Wetenschap. 2021;73:9-12.
5. Simoens S, Huys I. R&D Costs of New Medicines: A Landscape Analysis. Frontiers in Medicine. 2021;8(760762).
6. Guennif S. Evaluating the Usefulness of Compulsory Licensing in Developing Countries: A Comparative Study of Thai and Brazilian Experiences Regarding Access to Aids Treatments. Developing world bioethics. 2017;17(2):90-9.
7. Perehudoff K, t Hoen E, Boulet P. Overriding drug and medical technology patents for pandemic recovery: a legitimate move for high-income countries, too. BMJ Glob Health. 2021;6(4).
8. Qunaj L, Kaltenboeck A, Bach PB. Compulsory Licensing of Pharmaceuticals in High-Income Countries: A Comparative Analysis. Milbank Q. 2022;100(1):284-313.
9. World Health Organization. WHO guideline on country pharmaceutical pricing policies, second edition. Geneva: 2020.
10. den Exter A. Fighting Excessive Pharmaceutical Prices: Evaluating the Options. European journal of health law. 2020;28(1):68-80.
11. Urias E, Ramani SV. Access to medicines after TRIPS: is compulsory licensing an effective mechanism to lower drug prices? A review of the existing evidence. Journal of International Business Policy. 2020;3:367-84.

12. de Jong A. Persoonlijke beschouwing over de inzet van de dwanglicenties bij hoge prijzen van medicijnen [Web page].Den Haag: ABDTOPConsult;2020. Available from: https://www.rijksoverheid.nl/documenten/rapporten/2020/06/16/persoonlijke-beschouwing-over-de-inzet-van-de-dwanglicenties-bij-hoge-prijzen-van-medicijnen

13. Pawson R, Greenhalgh T, Harvey G, Walshe K. Realist Synthesis - an Introduction. London: Economic and Social Research Council; 2004. ESRC Working Paper Series

14. Pawson R, Greenhalgh T, Harvey G, Walshe K. Realist review--a new method of systematic review designed for complex policy interventions. J Health Serv Res Policy. 2005;10 Suppl 1:21-34.

15. Abbas MZ. Pros and Cons of Compulsory Licensing: An Analysis of Arguments. International Journal of Social Science and Humanity. 2013;3(3):254-8.

16. Antonelli C. Compulosry Licensing: the foundations of an institutional innovation. Turin: 2012.

17. Antonelli C. Compulsory Licensing: The Foundations of an Institutional Innovation. The WIPO Journal. 2013;4(2):157-74.

18. Aoki R, Small J. Compulsory licensing of technology and the essential facilities doctrine. Information Economics and Policy. 2004;16(1):13-29.

19. Bailey TC. Innovation and access: The role of compulsory licensing in the development and distribution of hiv/aids drugs. University of Illinois Journal of Law, Technology & Policy. 2001;1:193-218.

20. Baten J, Bianchi N, Moser P. Does Compulsory Licensing discourage invention? Evidence from German patents after WW I. NBER Working Paper Series. Cambridge, MA: N. B. o. E. Research; 2015.

21. Bird R, Cahoy DR. The Impact of Compulsory Licensing on Foreign Direct Investment: A Collective Bargaining Approach. American Business Law Journal. 2008;45(2):283-330.

22. Bird RC. Developing nations and the compulsory license: maximizing access to essential medicines while minimizing investment side effects. J Law Med Ethics. 2009;37(2):209-21.

23. Bond EW, Saggi K. Compulsory licensing, price controls, and access to patented foreign products. Journal of Development Economics. 2014;109:217-28.

24. Bond EW, Saggi K. International price negotiations under the threat of compulsory licensing. Department of Economics, Vanderbilt University; 2014.

25. Bond EW, Saggi K. Price controls versus compulsory licensing: effects on patent-holders and consumers. Nashville, TN: Vanderbilt University; 2017. Vanderbilt University Department of Economics Working Paper Series Paper 17-00013

26. Bond EW, Saggi K. Compulsory Licensing and Patent Protection: A North-South Perspective. Economic Journal. 2018;128(610):1157-79.

27. Bond EW, Samuelson L. Bargaining with private information and the option of a compulsory license. Games and Economic Behavior. 2019;114:83-100.

28. Chatterjee C, Kubo K, Pingali V. The consumer welfare implications of governmental policies and firm strategy in markets for medicines. J Health Econ. 2015;44:255-73.

29. Chien C. CHEAP DRUGS AT WHAT PRICE TO INNOVATION: DOES THE COMPULSORY LICENSING OF PHARMACEUTICALS HURT INNOVATION? Berkeley Technology Law Journal. 2003;18(3):853-907.

30. Cohen JC. Expanding drug access in Brazil: Lessons for Latin America and Canada. Canadian Journal of Public Health. 2006;97(6):1-15-1-8.

31. Cugno F, Ottoz E. Static Efficiency of Compulsory Licensing: The Role of Limit Pricing. Journal of Interdisciplinary Economics. 2007;19(1):19-33.

32. Danzon PM, Towse A. Differential Pricing for Pharmaceuticals: Reconciling Access, R&D and Patents. International Journal of Health Care Finance and Economics. 2003;3(3):183-205.

33. Fine F. European Community Compulsory Licensing Policy: Heresy versus Common Sense. Northwestern Journal of International Law & Business. 2004;24(3):619-46.

34. Fisch AM. Compulsory licensing of pharmaceutical patents: an unreasonable solution to an unfortunate problem. Jurimetrics Journal. 1994;34(3):295-316.

35. Flanagan W, Whiteman G. "AIDS is Not a Business": A Study in Global Corporate Responsibility – Securing Access to Low-cost HIV Medications. Journal of Business Ethics. 2007;73(1):65-75.

36. Flynn S, Hollis A, Palmedo M. An economic justification for open access to essential medicine patents in developing countries. J Law Med Ethics. 2009;37(2):184-208.

37. Gilbert RJ, Shapiro C. An economic analysis of unilateral refusals to license intellectual property. Proceedings of the National Academy of Sciences of the United States of America. 1996;93(23):12749-55.

38. Gillat A. Compulsory licensing to regulated licensing: effects on the conflict between innovation and access in the pharmaceutical industry. Food Drug Law J. 2003;58(4):711-40.

39. Goldberg PK. ALFRED MARSHALL LECTURE INTELLECTUAL PROPERTY RIGHTS PROTECTION IN DEVELOPING COUNTRIES: THE CASE OF PHARMACEUTICALS. Journal of the European Economic Association. 2010;8(2/3):326-53.

40. Grabowski H. Patents, innovation and access to new pharmaceuticals. Journal of International Economic Law. 2002;5(4):849-60.

41. Iwaisako T, Futagami K. Patent Policy in an Endogenous Growth Model. Journal of Economics. 2003;78(3):239.

42. Lybecker KM, Fowler E. Compulsory licensing in Canada and Thailand: comparing regimes to ensure legitimate use of the WTO rules. J Law Med Ethics. 2009;37(2):222-39.

43. Maybarduk P, Rimmington S. Compulsory licenses: a tool to improve global access to the HPV vaccine? Am J Law Med. 2009;35(2-3):323-50.

44. McManis CR, Contreras JL. Compulsory Licensing of Intellectual Property: A Viable Policy Lever for Promoting Access to Critical Technologies? In: Ghidini G, Peritz RJR, Ricolfi M, editors. TRIPS and Developing Countries – Towards a New World Order?: American University, WCL Research Paper No. 2014-16; 2014.

45. Moser P, Voena A. Compulsory Licensing: Evidence from the Trading with the Enemy Act. American Economic Review. 2012;102(1):396-427.

46. Moser P. Patents and Innovation: Evidence from Economic History. Journal of Economic Perspectives. 2013;27(1):23-44.

47. Nuno M. A FAIR RETURN APPROACH TO PHARMACEUTICAL COMPULSORY LICENSING. Case Western Reserve Journal of International Law. 2016;48(1/2):395-415.

48. Ooms G, Hanefeld J. Threat of compulsory licences could increase access to essential medicines. BMJ. 2019;365:l2098.

49. Owoeye OA. Compulsory patent licensing and local drug manufacturing capacity in Africa. Bull World Health Organ. 2014;92(3):214-9.

50. Palokangas T. Optimal patent length and breadth in an economy with creative destruction and non-diversifiable risk. Journal of Economics. 2011;102(1):1-27.

51. Ramani SV, Urias E. Access to critical medicines: When are compulsory licenses effective in price negotiations? Soc Sci Med. 2015;135:75-83.

52. Reichman JH. Comment: compulsory licensing of patented pharmaceutical inventions: evaluating the options. J Law Med Ethics. 2009;37(2):247-63.

53. Rudyk I. The License of Right, Compulsory Licensing and the Value of Exclusivity. 2012. Discussion paper No. 415

54. Sarmah A, De Giovanni D, De Giovanni P. Compulsory licenses in the pharmaceutical industry: Pricing and R&D strategies. European Journal of Operational Research. 2020;282(3):1053-69.

55. Scherer FM. Nordhaus' Theory of Optimal Patent Life: A Geometric Reinterpretation. American Economic Review. 1972;62(3):422-7.

56. Seifert J. Compulsory Licensing, Innovation and Welfare. Beiträge zur Jahrestagung des Vereins für Socialpolitik 2013. Wettbewerbspolitik und Regulierung in einer globalen Wirtschaftsordnung - Session: Oligopoly, No. G14-V3; 2013.

57. Seifert J. Welfare effects of compulsory licensing. Journal of Regulatory Economics. 2015;48:317-50.

58. Senra de Morais RP. Compulsory licensing of pharmaceuticals by the developing south. Economics Letters. 2017;161:74-7.

59. Shastitko A, Kurdin A. Incentives for process innovations under discrete structural alternatives of competition policy. VOPROSY ECONOMIKI. 2016;4.

60. Stavropoulou C, Valletti T. Compulsory licensing and access to drugs. Eur J Health Econ. 2015;16(1):83-94.

61. Szymanski S, Valletti T. Parallel trade, price discrimination, investment and price caps. Economic Policy. 2005;20(44):705-49.

62. Tandon P. Optimal Patents with Compulsory Licensing. Journal of Political Economy. 1982;90(3):470-86.

63. Urias E. Improving access to HIV/AIDS treatment in Brazil. When are compulsory licenses effective in price negotiations? [Web page].2015. Available from: https://cris.maastrichtuniversity.nl/en/publications/improving-access-to-hivaids-treatment-in-brazil-when-are-compulso

64. Vastano Vaughan S. Compulsory Licensing of Pharmaceuticals under TRIPS: What Standard of Compensation. Hastings International and Comparative Law Review. 2001;25(1):87-110.

65. Baten J, Bianchi N, Moser P. Compulsory licensing and innovation – Historical evidence from German patents after WWI. Journal of Development Economics. 2017;126:231-42.

66. Beall R, Kuhn R. Trends in compulsory licensing of pharmaceuticals since the Doha Declaration: a database analysis. PLoS Med. 2012;9(1):e1001154.

67. Beall RF, Attaran A, Kuhn R. Compulsory Licenses: The Authors Reply. Health Aff (Millwood). 2015;34(6):1068.

68. Bond P. Globalization, pharmaceutical pricing, and South African health policy: Managing confrontation with U.S. firms and politicians. International Journal of Health Services. 1999;29(4):765-92.

69. Brodsky J. THE HEALTH OF EBAY: THE IMPACT OF EBAY ON THE FUTURE OF TRIPS-LIKE PHARMACEUTICAL COMPULSORY LICENSES IN THE UNITED STATES. Am J Law Med. 2015;41(4):656-79.

70. Cohen-Kohler JC, Esmail LC, Cosio A. Canada's implementation of the Paragraph 6 Decision: Is it sustainable public policy? Globalization and Health. 2007;3.

71. Correa CM. The use of compulsory licenses in Latin America [Web page].2013. Available from: https://www.southcentre.int/question/the-use-of-compulsory-licenses-in-latin-america/

72. Correa CM. Pharmaceutical Innovation, Incremental Patenting and Compulsory Licensing. Geneva: South Centre; 2013.

73. Eastman HC, Fraser RD, Laskin JI, Kennedy WA. Report of the commission of inquiry on the pharmaceutical industry. 1985.

74. Correa CM. Intellectual property rights and the use of compulsory licenses: options for developing countries. Geneva: South Centre; 1999. T.R.A.D.E. Working Papers 5

75. Flaer PJ, Benjamin PL, Bastos FI, Younis MZ. Health care policy and the HIV/AIDS epidemic in the developing world: More questions than answers. Journal of Health Care Finance. 2010;36(4):75-9.

76. Fowler D, Gordon M. The Effect of Public Policy Initiatives on Drug Prices in Canada. Canadian Public Policy. 1984;10(1):64-73.

77. Cherian NG. Using Compulsory Licenses to access pharmaceuticals: A Cross Case Analysis on Outcomes. Oslo: University of Oslo; 2016.

78. Goyal Y. Economic and Procedural Constraints of Compulsory Licences for Medicines. In: Hilty RM, Liu KC, editors. Compulsory licensing: practical experiences and ways forward. Berlin Heidelberg: Springer-Verlag; 2015. p. 438-58.

79. Health Intervention and Technology Assessment Program (HITAP). Assessing the Implications of Thailand's Government Use Licenses issued in 2006-2008 [Web page].2009. Available from: https://www.hitap.net/en/research/17635

80. Jones JCH, Potashnik T, Anming Z. Patents, brand-generic competition and the pricing of ethical drugs in Canada: some empirical evidence from British Columbia, 1981-1994. Applied Economics. 2001;33(7):947-56.

81. Kuek V, Phillips K, Kohler JC. Access to medicines and domestic compulsory licensing: learning from Canada and Thailand. Glob Public Health. 2011;6(2):111-24.

82. Lalitha N. A review of the pharmaceutical industry of Canada. Working Paper Series. Gota, Ahmedabad, Gujarat Institute of Development Research. 2004.

83. Mansfield E. Patents and Innovation: An Empirical Study. Management Science. 1986;32:173-81.

84. Ortiz-Prado E, Cevallos-Sierra G, Teran E, Vasconez E, Borrero-Maldonado D, Ponce Zea J, et al. Drug prices and trends before and after requesting compulsory licenses: the Ecuadorian experience. Expert Opin Ther Pat. 2019;29(8):653-62.

85. Pazderka B. Patent Protection and Pharmaceutical R&D Spending in Canada. Canadian Public Policy. 1999;25(1).

86. Phueksuwan T. Compulsory licensing policy implementation in Thailand [Web page].2014. Available from: http://libdcms.nida.ac.th/thesis6/2014/b185150.pdf

87. Ramani SV, Urias E. When access to drugs meets catch-up: Insights from the use of CL threats to improve access to ARV drugs in Brazil. Research Policy. 2018;47:1538–52.

88. Rosenberg ST. Asserting the primacy of health over patent rights: a comparative study of the processes that led to the use of compulsory licensing in Thailand and Brazil. Dev World Bioeth. 2014;14(2):83-91.

89. Rozek RP. The effects of compulsory licensing on innovation and access to health care. Journal of World Intellectual Property. 2000;3(6):889-918.

90. Sampath PG. India's Product Patent Protection Regime: Less or More of "Pills for the Poor"? Journal of World Intellectual Property. 2006;9(6):694-726.

91. Scherer FM. The economic effects of compulsory patent licensing. New York: Center for the Study of Financial Institutions; 1977. New York University Monograph Series in Finance and Economics

92. Shapiro DM, Switzer LN. The Stock Market Response to Changing Drug Patent Legislation: The Case of Compulsory Licensing in Canada. Managerial & Decision Economics. 1993;14(3):247-59.

93. Son KB. Importance of the intellectual property system in attempting compulsory licensing of pharmaceuticals: a cross-sectional analysis. Global Health. 2019;15(1):42.

94. World Trade Organization, World Intellectual Property Organization, World Health Organization. Promoting Access to Medical Technologies and Innovation: Intersections between public health, intellectual property and trade. 2nd edition ed. Switzerland; 2020.

95. Brebeck S. The Failure of Compulsory Licensing of Pharmaceuticals in Least Developed Countries. Essen: University of Duisburg-Essen; 2014.

96. Lin X. Prior negotiation and remuneration for patent compulsory licensing: practice, problem, and proposal. In: Hilty RM, Liu KC, editors. Compulsory licensing: practical experiences and ways forward. Berlin Heidelberg: Springer-Verlag; 2015. p. 166-90.

97. Mitchell A. Tamiflu, the Takings Clause, and Compulsory Licenses: An Exploration of the Government's Options for Accessing Medical Patents. California Law Review. 2007;95(2):535-59.

98. Välimäki E. Calculation of Royalties in Compulsory Licensing of Pharmaceutical Patents in Europe – How Much is Justified? Nordic Journal of Commercial Law. 2011;Special Edition 2011:1-27.

99. Taubman A. Rethinking TRIPS: 'Adequate Remuneration' for non-voluntary Patent Licensing. Journal of International Economic Law. 2008;11(4):927-70.

100. Steinbrook R. Thailand and the compulsory licensing of efavirenz. N Engl J Med. 2007;356(6):544-6.

101. Thomas JR. Compulsory Licensing of Patented Inventions [Web page]. Congressional Research Service;2014. Available from: www.crs.gov

102. Walwyn D. Patents and profits: A disparity of manufacturing margins in the tenofovir value chain. African Journal of AIDS Research. 2013;12(1):17-23.

103. Wong H. The case for compulsory licensing during COVID-19. J Glob Health. 2020;10(1):010358.

104. Financial Times. How Covid has raised the profiles and fortunes of India's pharma entrepreneurs. Financial Times. 2021;21/11/2021.

105. Lexchin J. Pharmaceuticals, patents, and politics: Canada and Bill C-22. International Journal of Health Services. 1993;23(1):147-60.

106. Lakdawalla D. Economics of the pharmaceutical industry. Journal of Economic Literature. 2018;56(2):397-449.

107. World Trade Organization. Agreement on Trade-Related Aspects of Intellectual Property Rights [Web page].1994. Available from: https://www.wto.org/english/docs_e/legal_e/27-trips_01_e.htm

108. Canoy M, Tichem J. Lower drug prices can improve innovation. European Competition Journal. 2018;14(2-3):278-304.

109. Love J. Remuneration guidelines for non-voluntary use of a patent on medical technologies [Web page]. WHO and UNDP;2005. Available from: https://apps.who.int/iris/bitstream/handle/10665/69199/WHO_TCM_2005.1_eng.pdf?sequence=1&isAllowed=y

110. Avagyan V, Esteban-Bravo M, Vidal-Sanz J. Licensing radical product innovations to speed up the diffusion. European Journal of Operations Research. 2014;239:542-55.

111. Riccaboni M, Swoboda T, Van Dyck W. Pharmaceutical Net Price Transparency across European Markets, Insights from a Multi-Agent Simulation Model. Health Policy. 2022;in press.

112. Copenhagen Economics. Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe. Luxembourg: Publications Office of the European Union; 2018.

113. Hu Y, Eynikel D, Boulet P, Krikorian G. Supplementary protection certificates and their impact on access to medicines in Europe: case studies of sofosbuvir, trastuzumab and imatinib. J Pharm Policy Pract. 2020;13:1.

114. Sood N, Mulligan K, Zhong K. Do companies in the pharmaceutical supply chain earn excess returns? Int J Health Econ Manag. 2021;21(1):99-114.

115. Lampert H, Wettstein D. Patents and pools in pyramidal innovation structures. International Journal of Industrial Organization. 2020;69.

APPENDICES

APPENDIX 1. SEARCH STRATEGY

Appendix 1.1. Search strategy in general

Project number	2020-50 HSR
Project name	Evaluation of the feasibility of compulsory licensing for very expensive medicines
Research question	What are the (possible) consequences for the medicines market (economic)?
Structured search concepts	
Concept 1	On the main terms: Compulsory licensing/march in rights
Concept 2	On government use and alternatives for compulsory licensing (e.g. price control, tiered pricing)
Concept 3	On elements related to economics and competition (e.g. hold-up problem, industrial organization)
Concept 4	On impact (e.g. impact, effect, consequence)
Concept 5	On elements that might be impacted through compulsory licensing/indicators (e.g. innovation, investment, discovery)
Concept 6	On methodological approach (e.g. theory, empirical study)
Concept 7	On context (e.g. mechanism, conditions, infrastructure, county, market size)
Concept 8	On examples of context (e.g. pandemic, COVID, ATMP, extreme price, emergency)
Concept 9	On payment (e.g. royalty, remuneration, payment, compensation)
Connection of concepts in search query:	(Concept 1) AND ((Concept 2) OR (Concept 3) OR (Concept 4) OR (Concept 5) OR (Concept 6) OR (Concept 7) OR (Concept 8) OR (Concept 9))

Appendix 1.2. Search strategy for peer-reviewed literature

Appendix 1.2.1. PubMed

Date	27/09/2021 – 297 results
Strategy	((compulsory licen*) OR (“march in rights”)) AND ((“government* use” OR voluntary OR procur* OR tender* OR purchas* OR “tiered pricing” OR “price tiering” OR “segment* pricing” OR “price control*” OR (group purchasing[MeSH Terms])) OR (economic* OR “industrial organization*” OR externalit* OR “hold-up problem*” OR “hold up problem*” OR “competition law” OR “competition polic*” OR economics[MeSH Terms] OR (competition, economic[MeSH Terms]) OR (competitions, economic[MeSH Terms]) OR (economic competitions[MeSH Terms])) OR (impact* OR effect* OR consequence* OR implement* OR outcome* OR result* OR repercussion* OR fallout*) OR (innovation* OR investment* OR compet* OR ‘R&D’ OR discovery OR development OR research OR medicin* price* OR “drug price*” OR “drug price setting” OR “drug price-setting” OR expenditure* OR “market access” OR “market entr*” OR approval* OR authorisation* OR authorization* OR reimbursement* OR “health technology assessment” OR “health technology assessments” OR HTA OR HTAs OR payer* OR shortage* OR employment OR cost OR costs OR benefit* OR disadvantage* OR advantage* OR (innovation, organizational[MeSH Terms]) OR (innovations, organizational[MeSH Terms]) OR investment[MeSH Terms] OR (activities, research[MeSH Terms]) OR (activity, research[MeSH Terms]) OR (drug discovery[MeSH Terms]) OR (discovery, drug[MeSH Terms]) OR (direct expenditure[MeSH Terms]) OR (access to health care[MeSH Terms]) OR (approval process, drug[MeSH Terms]) OR (approval processes, drug[MeSH Terms]) OR employment[MeSH Terms]) OR (theor* OR framework* OR empir* OR case stud* OR case report* OR experim* OR experience* OR observ* OR explorat* OR (empirical research[MeSH Terms]) OR (research, empirical[MeSH Terms]) OR (case reports[MeSH Terms]) OR observation[MeSH Terms]) OR (context* OR mechanism* OR condition* OR factor* OR influence* OR infrastructure OR ‘know-how’ OR “know how” OR “technical capability” OR capacit* OR countr* OR budget* OR health* OR “market size” OR “market volume” OR segmentation OR sanction* OR medicin* OR drugs OR drug OR pharmaceutic* OR “goods and services” OR (expertise, technical[MeSH Terms]) OR (budget[MeSH Terms]) OR (budgets[MeSH Terms])) OR (pandem* OR COVID OR corona OR COVID19 OR COVID-19 OR coronavirus OR CoV OR SARS-CoV-2 virus OR “extreme urgenc*” OR “national emergenc*” OR “global emergenc*” OR “excessive pric*” OR “extreme* pric*” OR “rare” OR “orphan” OR “ATMP” OR “advanced therapeutic medicinal product” OR “gene” OR “cell-based” OR “cell based” OR “cell therap*” OR “oncolog*” OR “biologic*” OR pandemic[MeSH Terms] OR pandemics[MeSH Terms] OR coronaviridae[MeSH Terms] OR (coronavirus, sars[MeSH Terms]) OR (coronavirus, sars associated[MeSH Terms]) OR (coronavirus, sars related[MeSH Terms]) OR emergency[MeSH Terms] OR emergencies[MeSH Terms] OR (rare disease[MeSH Terms]) OR (rare diseases[MeSH Terms]) OR (orphan disease[MeSH Terms]) OR (orphan diseases[MeSH Terms]) OR (gene therapy[MeSH Terms]) OR (cell therapy[MeSH Terms]) OR (biopharmaceutics[MeSH Terms]) OR (biologics[MeSH Terms])) OR (royalt* OR remunerate* OR pay OR payment* OR paying OR recompens* OR compens* OR restitution* OR reward* OR payoff* OR settlement* OR arrangement* OR agreement* OR contract* OR fee OR fees OR earning* OR damage* OR detriment* OR profit* OR incentive* OR exclusivit* OR (equities, pay[MeSH Terms]) OR (equities, pay[MeSH Terms]) OR (compensation[MeSH Terms]) OR (reward[MeSH Terms]) OR (rewards[MeSH Terms]) OR (incentive[MeSH Terms])))

Appendix 1.2.2. Embase

Date	27/09/2021 – 244 results
Strategy	((‘compulsory licen*’) OR (‘march in rights’)) AND ((‘government* use’ OR voluntary OR procur* OR tender* OR purchas* OR ‘tiered pricing’ OR ‘price tiering’ OR (‘prospective pricing’/exp) OR ‘segment* pricing’ OR ‘price control*’ OR (‘purchasing’/exp)) OR (economic* OR ‘industrial organization*’ OR externalit* OR ‘hold-up problem*’ OR ‘hold up problem*’ OR ‘competition law’ OR ‘competition polic*’ OR (‘economic decision making’/exp) OR economic* OR (‘economic aspect’/exp)) OR ((‘impact’/exp) OR effect* OR consequence* OR implement* OR outcome* OR result* OR repercussion* OR fallout*) OR (innovation* OR investment* OR (‘economic incentive’/exp) OR compet* OR ‘R&D’ OR discovery OR development OR research OR medicin* price* OR ‘drug price*’ OR ‘drug price setting’ OR ‘drug price-setting’ OR expenditure* OR ‘market access’ OR ‘market entr*’ OR approval* OR (‘drug approval’/exp) OR authorisation* OR authorization* OR reimbursement* OR (‘reimbursement’/exp) OR ‘health technology assessment’ OR ‘health technology assessments’ OR HTA OR HTAs OR (‘biomedical technology assessment’/exp) OR payer* OR shortage* OR (‘drug shortage’/exp) OR (‘resource shortage’) OR (‘employment’/exp) OR (‘cost’/exp) OR (‘cost control’/exp) OR (‘drug cost’/exp) OR (‘health care cost’/exp) OR costs OR benefit* OR disadvantage* OR advantage* OR (‘innovation’/exp) OR (‘organization’/exp) OR (‘organisation’/exp) OR (‘organizational’/exp) OR (‘organisational’/exp) OR (‘investment’/exp) OR (‘research’/exp) OR (‘drug development’/exp) OR (‘drug cost’/exp) OR (‘access’/exp) OR (‘employment’/exp)) OR (theor* OR framework* OR (‘conceptual framework’/exp) OR (‘economic model’/exp) OR empir* OR case stud* OR case report* OR (‘case report’/exp) OR experim* OR (‘experiment’/exp) OR (‘experimental design’/exp) OR (‘field experiment’/exp) OR experience* OR (‘experiences’/exp) OR observ* OR explorat* OR (‘empirical research’/exp) OR (‘observational study’/exp) OR (‘observational method’/exp) OR (‘case report’/exp)) OR ((‘context’/exp) OR context* OR (‘mechanism’/exp) OR mechanism* OR condition* OR (‘condition’/exp) OR factor* OR influence* OR (‘economic aspect’/exp) OR (‘country economic status’/exp) OR (‘economic parameters’/exp) OR (‘economic status’/exp) OR (‘economic development’/exp) OR (‘health insurance’/exp) OR infrastructure OR (‘economic inequality’/exp) OR ‘know-how’ OR ‘know how’ OR ‘technical capability’ OR (‘capability’/exp) OR capacit* OR (‘capacity’/exp) OR countr* OR budget* OR health* OR ‘market size’ OR ‘market volume’ OR segmentation OR (‘segmentation’/exp) OR sanction* OR medicin* OR drugs OR drug OR (‘drug’/exp) OR (‘drug industry’/exp) OR (‘drug manufacture’/exp) OR (‘drug research’/exp) OR (‘health care organization’/exp) OR pharmaceutic* OR (‘pharmaceutics’/exp) OR (‘medicinal product’/exp) OR ‘goods and services’ OR (‘budget’/exp)) OR (pandem* OR COVID OR corona OR COVID19 OR COVID-19 OR coronavirus OR CoV OR SARS-CoV-2 virus OR ‘extreme urgenc*’ OR ‘national emergency’ OR ‘national emergencies’ OR ‘global emergency’ OR ‘global emergencies’ OR ‘excessive price’ OR ‘excessive pricing’ OR ‘excessive prices’ OR ‘extreme price’ OR ‘extreme prices’ OR rare OR orphan OR ATMP OR advanced therapeutic medicinal product OR gene OR cell-based OR ‘cell based’ OR ‘cell therap*’ OR oncolog* OR biologic* OR (‘pandemic’/exp) OR (‘pandemic influenza’/exp) OR (‘Coronavirinae’/exp) OR (‘Severe acute respiratory syndrome coronavirus 2’/exp) OR (‘emergency’/exp) OR (‘rare disease’/exp) OR (‘orphan disease’/exp) OR (‘orphan’/exp) OR (‘gene therapy’/exp) OR (‘cell based gene therapy’/exp) OR (‘cell therapy’/exp) OR (‘biological product’/exp) OR ‘biopharmaceutic agent*’) OR (royalt* OR remunerate* OR (‘remuneration’/exp) OR (‘prospective payment’) OR pay OR payment* OR paying OR recompens* OR compens* OR restitution* OR (‘restitution’/exp) OR reward* OR (‘reward’/exp) OR (‘monetary reward’/exp) OR (‘delay discounting’/exp) OR payoff* OR (‘payoff matrix’/exp) OR settlement* OR (‘settlement’/exp) OR arrangement* OR agreement* OR (‘agreement’/exp) OR contract* OR (‘contract’/exp) OR (‘financial management’/exp) OR fee OR fees OR (‘fee’/exp) OR earning* OR damage* OR detriment* OR profit* OR (‘profit’/exp) OR incentive* OR (‘incentive’/exp) OR (‘economic incentive’/exp) OR (‘disincentive’/exp) OR (‘tax incentive’/exp) OR (‘monetary reward’/exp) OR (‘perverse incentive’/exp) OR exclusivit* OR (‘equity’/exp) OR (‘compensation’/exp) OR (‘reward’/exp)))

Appendix 1.2.3. EBSCO Business Source Complete

Date	27/09/2021 - 436 results
Strategy	(((compulsory licen*) OR ("march in rights") OR (SU compulsory licensing))) AND (S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8) S1 TX ("government* use" OR voluntary OR procur* OR tender* OR purchas* OR "tiered pricing" OR "price tiering" OR "segment* pricing" OR "price control*" OR (SU government regulation) OR (SU government legislation) OR (SU voluntary) OR (SU procurement) OR (SU procurement strategy) OR (SU procurement control) OR (SU procurement process) OR (SU procurement and supply chain management) OR (SU procurement negotiations) OR (SU tender) OR (SU tendering) OR (SU purchasing) OR (SU purchase) OR (SU purchasing and supply chain management) OR (SU purchasing and chain management) OR (SU price differentiation) OR (SU price control) OR (SU price control act)) S2 TX (economic* OR "industrial organization*" OR externalit* OR "hold-up problem*" OR "hold up problem*" OR "competition law" OR "competition polic*" OR (SU economic) OR (SU economics) OR (SU economy) OR (SU industrial organization) OR (SU industrial organizational) OR (SU industrial organization model) OR (SU externalities) OR (SU externalities economics) OR (SU hold up) OR (SU competition law) OR (SU competition policy)) S3 TX (impact* OR effect* OR consequence* OR implement* OR outcome* OR result* OR repercussion* OR fallout* OR (SU impact) OR (SU effects) OR (SU consequences) OR (SU implementation) OR (SU implementing) OR (SU implement) OR (SU outcomes) OR (SU outcomes or benefits or effects or impact or effectiveness) OR (SU results) OR (SU repercussions) OR (SU repercussions or effects or impacts or consequences) OR (SU fall out)) S4 TX (innovation* OR investment* OR compet* OR 'R&D' OR discovery OR development OR research OR medicin* price* OR "drug price*" OR "drug price setting" OR "drug price-setting" OR expenditure* OR "market access" OR "market entr*" OR approval* OR authorisation* OR authorization* OR reimbursement* OR "health technology assessment" OR "health technology assessments" OR HTA OR HTAs OR payer* OR shortage* OR employment OR cost OR costs OR benefit* OR disadvantage* OR advantage* OR (SU innovation) OR (SU investment) OR (SU competition) OR (SU competitiveness) OR (SU r&d or research and development) OR (SU discovery) OR (SU discovery phase) OR (SU development) OR (SU research) OR (SU medicine prices) OR (SU drug prices) OR (SU drug price regulation) OR (SU expenditure) OR (SU market access) OR (SU market entry) OR (SU market entrance) OR (SU approval) OR (SU authorization) OR (SU reimbursement) OR (SU health technology assessment) OR (SU HTA) OR (SU HTA studies) OR (SU shortage) OR (SU HTA studies) OR (SU employment) OR (SU cost) OR (SU costs or cost or expense) OR (SU benefits or advantages or positive effects or importance or impact) S5 TX (theor* OR framework* OR empir* OR case stud* OR case report* OR experim* OR experience* OR observ* OR explorat* OR (SU framework or model or theory) OR (SU empirical study) OR (SU empirical research) OR (SU empirical) OR (SU empirical evidence) OR (SU empirical article) OR (SU case study) OR (SU case study research) OR (SU case study or case studies) OR (SU case study or case report) OR (SU experiment) OR (SU experimental study) OR (SU experimental research) OR (SU experimental research design) OR (SU experimentation) OR (SU experience) OR (SU observation) OR (SU observational study) OR (SU observational learning) OR (SU

	observational) OR (SU observational research) OR (SU exploration) OR (SU exploratory research) OR (SU exploratory) OR (SU exploratory study) OR (SU exploratory research design) OR (SU exploratory data analysis))
	S6
	TX (context* OR mechanism* OR condition* OR factor* OR influence* OR infrastructure OR 'know-how' OR "know how" OR "technical capability" OR capacit* OR countr* OR budget* OR health* OR "market size" OR "market volume" OR segmentation OR sanction* OR medicin* OR drugs OR drug OR pharmaceutic* OR "goods and services" OR (SU context) OR (SU contextual) OR (SU contextual factors) OR (SU mechanism) OR (SU conditions) OR (SU factors or causes or influences or reasons or determinants) OR (SU infrastructure) OR (SU know-how) OR (SU technical capacity) OR (SU capacity) OR (SU countries) OR (SU budget) OR (SU health) OR (SU healthcare) OR (SU health care) OR (SU market size or market share or industry size or industry or market growth or industry growth or outlook) OR (SU segmentation) OR (SU segment) OR (SU segmentation strategies) OR (SU sanctions) OR (SU medicine or medical or health or healthcare) OR (SU pharmaceutics) OR (SU goods and services))
	S7
	TX (pandem* OR COVID OR corona OR COVID19 OR COVID-19 OR coronavirus OR CoV OR SARS-CoV-2 virus OR "extreme urgenc*" OR "national emergenc*" OR "global emergenc*" OR "excessive pric*" OR "extreme* pric*" OR "rare" OR "orphan" OR "ATMP" OR "advanced therapeutic medicinal product" OR "gene" OR "cell-based" OR "cell based" OR "cell therap*" OR "oncolog*" OR "biologic*" OR (SU pandemic or epidemic or outbreak or covid-19 or coronavirus) OR (SU covid-19 or coronavirus or 2019-ncov or sars-cov-2 or cov-19) OR (SU urgency) OR (SU national emergency) OR (SU rare diseases or rare disease or rare disorder or rare defect or orphan disease) OR (SU advanced medical technology) OR (SU gene therapy) OR (SU genes) OR (SU cell-based) OR (SU cell therapy) OR (SU cell therapy market) OR (SU oncology) OR (SU oncology therapy) OR (SU biological) OR (SU biologic therapy) OR (SU biological therapy) OR (SU biosimilars) OR (SU biosimilar))
	S8
	TX (royalt* OR remunerate* OR pay OR payment* OR paying OR recompens* OR compens* OR restitution* OR reward* OR payoff* OR settlement* OR arrangement* OR agreement* OR contract* OR fee OR fees OR earning* OR damage* OR detriment* OR profit* OR incentive* OR exclusivit* OR (SU royalty) OR (SU renumeration) OR (SU pay) OR (SU payment) OR (SU paying) OR (SU compensation) OR (SU compensation system) OR (SU restitution) OR (SU reward) OR (SU reward system) OR (SU rewards and incentives) OR (SU rewards and motivation) OR (SU payoffs) OR (SU settlement) OR (SU arrangement) OR (SU agreement or contract) OR (SU fees) OR (SU earning) OR (SU earnings) OR (SU damage or impact or harm or effect) OR (SU detriment) OR (SU detrimental effect) OR (SU profit) OR (SU profits or performance or sales or benefits) OR (SU exclusivity))

Appendix 1.2.4. RePEc

Date	08/10/2021 – 166 results
Strategy	((“compulsory licensing”|“compulsory license”|“compulsory licence”)|(“march in rights”|“march in right”))+((“government use”|voluntary|procurement|procurement|tender|purchasing|purchase|“tiered pricing”|“price tiering”|“segment pricing”|“price control”|“group purchasing”)|(economic|“industrial organization”|externality|externalities|“hold-up problem”|“hold up problem”|“competition law”|“competition policy”|“competition policies”|economics)|(impact|effect|consequence|implementation|outcome|result|repercussion|fallout)|(innovation|investment|compet|“R&D”|discovery|development|research|“medicine price”|“drug price”|“drug price setting”|“drug price-setting”|expenditure|“market access”|“market entry”|“market entries”|approval|authorisation|authorization|reimbursement|“health technology assessment”|“health technology assessments”|HTA|HTAs|payer|shortage|employment|cost|benefit|disadvantage|advantage|investment|“research activity”|“drug discovery”|“direct expenditure”|“access to health care”|“approval process”|employment)|(theor|framework|empir|“case study”|“case studies”|“case report”|experiment|experience|observation|observing|explorat|“empirical research”)|(context|mechanism|condition|fact|influence|infrastructure|“know-how”|“know how”|“technical capability”|capacity|country|countries|budget|health|“market size”|“market volume”|segmentation|sanction|medicine|drug|pharmaceutic|“goods and services”|“technical expertise”|budget)|(pandemic|COVID|corona|COVID19|COVID-19|coronavirus|CoV|“SARS-CoV-2 virus”|“extreme urgency”|“extreme urgencies”|“national emergency”|“national emergencies”|“global emergency”|“global emergencies”|“excessive price”|“extreme price”|rare|orphan|ATMP|“advanced therapeutic medicinal product”|gene|cell-based|“cell based”|“cell therapy”|“cell therapies”|oncology|biologic|coronaviridae|emergency|emergencies|“rare disease”|“orphan disease”|“gene therapy”|“gene therapies”|“cell therapies”|“cell therapy”|biopharmaceutics)|(royalt|remunerate|pay|payment|paying|recompens|compens|restitution|reward|payoff|settlement|arrangement|agreement|contract|fee|fees|earning|damage|detriment|profit|incentive|exclusivity))

Appendix 1.3. Search strategy for grey literature

Date	30/09/2021 – 55 results
Data sources	Websites of relevant organisations • i.e. World Trade Organisation, World Intellectual Property Organisation, World Health Organisation, World Bank, Organisation for Economic Cooperation and Development, South Centre, European Federation of Pharmaceutical Industries and Associations Reports from consultancy agencies and advisory bodies • i.e. ABDTOPConsult, Office of Health Economics, Simon Kucher & Partners Reports from compulsory licensing commissions • Dutch compulsory licensing commission • Canadian commission of inquiry on the pharmaceutical industry Research syntheses by the Graduate Institute Geneva Global Health Centre Google Scholar • e.g. books, doctoral or Master theses, university research papers, monographs
Strategy	Combinations of ‘economics’, ‘impact’, ‘compulsory licensing’ and ‘pharmaceuticals’ No restrictions on geography or date of publication Material written in English, Dutch, French or German

COMPULSORY LICENSING FOR EXPENSIVE MEDICINES

OVERALL CONCLUSIONS

Worldwide, there are serious concerns about the availability and affordability of medicines. These concerns are likely to increase in the future given the increasing personalization of medicines, the complementarity of diagnostics and treatments, and the complexity of new medicines, such as biologics, which often come with high prices.

Compulsory licensing implies that a government allows someone else to produce a patented product or process without the consent of the patent owner or plans to use the patent-protected invention itself. It has been suggested as a potential tool to drive down the price of certain medicines. The possibility for governments to allow competition on the market (or at least the possibility of using it during price negotiations) would prevent patent holders from enforcing their patent rights to sell essential medical products at unjustified and excessively high prices.

There is a non-exhaustive list of legal grounds for granting CLs available in the Paris Convention and the TRIPs Agreement, such as national emergency or extreme urgency, public non-commercial use, anti-competitive practices, dependency of patents, public health, abuse and failure to work. Some of these grounds could be used as a legal basis if one may want to use CLs to address excessive pricing. Yet, quite some discretion is left to the Member States to define the grounds justifying the grant of a CL, the material criteria and the procedure. Some countries explicitly mention excessive pricing as a ground for granting a CL or interpret it as example of a public health reason for granting a CL.

Most CLs have so far been granted by developing countries and in emerging economies. There are only a **few examples of CLs** granted in **high-income countries**. However, these examples were not necessarily related to high prices, but rather to the availability of the medicines. Moreover, some were issued by competition authorities rather than through the patent law compulsory licensing route.

Against this background, this report assessed the legal and practical feasibility and the possible economic impact on the medicines market of CLs for medicines sold at very high prices.

One of the main conclusions of this report is that the use of CLs for very expensive medicines must take into account the **broader picture** of the regulation of medicines and the institutional and governance framework for protecting medicines against market competition. CLs find their legal basis in patent law. However, patents are not the only mechanism for protecting medicines against market competition. Other forms of protection, such as data- and market exclusivity law are also relevant. At the moment, the EU framework, does not provide for any explicit waivers of such exclusivities linked to CL regimes that apply within the EU territory. This lack of exceptions to regulatory data- and market exclusivities may lead to tensions between the regulatory system harmonized at the European level, which provides the basis for regulatory data- and market exclusivities, and the effective use of CLs with regard to patents, which still falls under the competences of the national legal systems.

Another observation is that one of the main purposes for granting patents, data- and market exclusivity is to encourage and reward innovation. For a small country like Belgium, with a strong representation of national and international pharmaceutical and biotechnology companies, intervening in the protection mechanisms for medicines is *theoretically* expected to have **negative local consequences in terms of investment in research and development, (high-tech) production capacity, employment, knowledge and competence building, competitive position, international trade relations**, etc. However, given the limited availability of comparable empirical data, it is extremely difficult to make reliable predictions about the *actual* consequences of CL in Belgium for very expensive medicines. The fact that Belgium is a small country can have different, sometimes opposing effects, making it difficult to predict on a theoretical basis what the actual consequences will be. Being a small country with a limited market, a CL issued by Belgium might on the one hand not have a significant impact for the company because it can recoup its investments from sales in other high-income countries. On the other hand, given that Belgium is in the international reference pricing basket of other countries, the (possible) lower price of the products produced under a CL in Belgium might have international price implications.

Another theoretical argument found in literature is that companies could reduce their clinical trial activities in countries that issue CLs. Belgium is considered to be an attractive country for conducting clinical trials, given the expertise available and the high concentration of (academic) hospitals. The balance between these benefits and the relocation to other countries with maybe less attractive conditions for performing clinical trials from the perspective of the companies is yet unclear.

In general, the impact of compulsory licensing will probably depend on how often and in which context it will be applied. In line with international treaty obligations and in order to ensure a sustainable and resilient health system, the grant of CLs should not be "mainstreamed" and should remain the 'exception' rather than the 'rule'. An appropriate and proportional use of CL requires for a **case-specific careful balancing of interests** where multiple factors play a role. Currently there are no guidelines for this balancing.

A first important step concerns the question *when* a very expensive medicine would potentially be eligible for compulsory licensing and whether there is a threshold above which medicines are considered to be '**excessively priced'**. Several relevant competition cases exist that deal with excessive pricing and can be taken into account in determining how to identify what should be considered as "excessive" and "unfair". However, there is no uniform method to define what is an excessive or unfair price and the fact that these cases relate to off-patent drugs mandates some caution in the comparison. For innovative medicines, several economic approaches have been proposed to define an acceptable price, such as value-based pricing (based on pre-defined cost-effectiveness thresholds or willingness to pay) and cost-plus pricing. However, these methods entail a lot of practical and methodological constraints (e.g. determination of the threshold, availability of cost data, …).

Apart from the already mentioned possible barriers to CL, the possible impact on the investment and innovation climate and the long term accessibility of medicines, the granting of compulsory licensing might also give rise to **practical and procedural problems** that need to be taken into consideration. The production of patented medicines requires specific know-how and access to the necessary raw materials, which is not always evident. Licensees might also have difficulties in obtaining a marketing authorization in the short term or might have to invest in additional (expensive) clinical studies.

Furthermore, the TRIPs Agreement requires that an **adequate remuneration** is paid to the patent holder in case a CL is granted. There is currently no uniform method to assess what is an adequate remuneration. A lack of access to cost data of the originator company is one of the complicating factors. However, the most important hurdle is that, in contrast to CL applied in low- or middle income countries, in high income countries it will be very hard to negotiate a remuneration level found to be acceptable to the biopharmaceutical innovator whilst providing a positive innovation climate and global patient welfare rationale.

It should also be considered whether the CL will effectively lead to a price reduction, considering the possible costs for clinical trials, data collection, reasonable remuneration, setting up the production line for the generic production, etc.

Finally, there might be a barrier in terms of the minimum profitable scale of generics production capacity to produce the medicine for a small market like Belgium. Art. 31(f) TRIPs restricts CLs "predominantly for the supply of the domestic market" and thus does not allow production for export to countries that do not have their own production capacity. However, a permanent waiver was created to Article 31(f) since many developing countries have insufficient or no manufacturing facilities hampering the feasibility of CLs for those countries. Many high-income countries, including the EU and its Member States, decided to opt out of using the waiver as an importer for their own medicines supply and are hence, as long as the opt-out stays in place, ineligible to import medicines manufactured in another country under CLs within this system. Hence, this creates a barrier for generic firms in Belgium to export medicines under CL to other high income countries.

The **Belgian legislation** already contains several legal bases for granting a CL in specific circumstances. Although some of them might be relevant in the context of excessive prices, this hypothesis is currently not explicitly foreseen. There is (at the time of the writing of the report) a legislative proposal foreseeing a revision of the current ground for CL for public health

reasons to include the possibility of imposing CL for very expensive medicines. Several modifications and/or clarifications relating to the material rules, the procedure and the relevant governance mechanisms have been suggested in this study.

If CLs are to become a suitable instrument in price negotiations, with the necessary legal certainty for all the parties involved, the following elements (that address the European as well as the Belgian level) may help to better accommodate the compulsory licensing mechanism, in combination with other mechanisms:

1. Even though practice teaches us that CLs are (or will be) used as an instrument in price or licensing negotiations, the procedure for the actual use of such licenses in Belgium must still be fine-tuned. Otherwise, CLs will lose their credibility as an effective negotiation instrument.

   Various legal grounds potentially come into consideration to justify CLs for expensive medicines. Public, non-commercial use is used by other member countries of the World Trade Organisation to enable so-called 'government use' or Crown use in the UK, whereby the government allows a public authority or a commercial contractor to produce a patented invention for the benefit of the general public. In many cases, this appears to be the simplest way of meeting a public need, as the government can decide this “ex officio”, without the need for a request from a third party and without the need for prior negotiations with the patent holder. On the other hand, prior negotiations with the patent holder may ensure that the CL is seen as a more proportionate measure, imposed only if all previous options failed. In various countries, particularly in the United States, CLs have been granted as a remedy against anti-competitive practices and to assure product availability as well.

2. It is desirable to explore opportunities for EU Member States to collaborate and coordinate initiatives for imposing CLs. This seems even more logical to do within the context of the unitary patent, where a unitary patent title will provide uniform protection across all participating Member States, but where CLs will still be granted at the national level.

3. Possible adaptations to the current European legal framework on regulatory exclusivities (i.e. data- and market exclusivities) should be considered. In that scope the possibilities to create a waiver of regulatory exclusivities at the EU level in cases where a CL is granted should be explored. This also includes the careful consideration and study of alternative regimes to counter the competitive advantage with regard to medical data. Such schemes should both incentivize the disclosure of relevant data through compensation mechanisms or other regulatory trade-offs, but also provide for the compulsory disclosure and usability of data under exceptional circumstances, subject to reasonable compensation for the investments made and data generation.

   In addition, it is desirable for national medicines regulatory authorities and the EMA to strengthen their requirements for data transparency when a dossier for marketing authorization is submitted. Data that is necessary to demonstrate the safety and efficacy of new compounds does not necessarily require the disclosure of tacit knowledge on how to effectively manufacture more complex biologics. Yet, it could be argued that more information would need to be disclosed to demonstrate the safest manufacturing of such products. However, according to the Clinical Trials Regulation confidentiality is respected where it is essential to protect commercially confidential information, unless there is an overriding public interest. It remains to be seen, what “overriding public interest”, exactly means and if it can be effectively enforced.

4. Cooperation and exchange of expertise should be improved between the administrations concerned and the respective Federal Public Services (e.g. Ministries of Social Affairs and Public Health, the Ministry of Economy and Employment and the Belgian Competition Authority and the National Institute for Health and Disability Insurance).

5. It is advisable to pursue a robust, transparent and coherent policy on the pricing and reimbursement of medicines. Initiatives in this area can

be taken at the European level, among others by exchanging information about price negotiations and agreements, and by better coordination and harmonisation of health policy among Member States.

An inspiring example is BeNeLuxA, in which Belgium, the Netherlands, Luxembourg, Austria and Ireland carry out joint horizon scans of important pharmaceutical innovations, carry out joint health technology assessments (HTA) and conduct joint price negotiations. Such collaborations help to streamline procedures between Member States of the European Union and to strengthen the position of health authorities in price negotiations with the pharmaceutical industry. This can be particularly important when dealing with very expensive medicines.

6. In national law, measures can be taken to optimize the use of patent exemption for pharmacists. In the Netherlands, the health authorities have issued regulatory guidance's for (hospital) pharmacies preparing medicines, including ATMPs, publicly supporting the preparation of lifesaving expensive drugs by pharmacies. In this way, their availability and affordability are guaranteed.

   However, due to practical and legal constraints, the production of drugs in pharmacies at lower prices is only possible for certain drugs (e.g. those that are not too complicated to prepare), in specific circumstances (non-industrial production) and depends on the availability of raw materials.

7. Inventions and results of research by universities and public research institutions are often licensed to pharmaceutical companies for drug development. Today, universities and research institutes have developed proactive patenting and licensing strategies that enable them to negotiate, license and earn licensing revenue.

   In several countries, principles and instruments have been developed to encourage these public institutions, as well as public and private sponsors of research such as NGOs or Foundations, to impose 'socially responsible licensing conditions'. This may include ensuring that the pricing of the end products does not jeopardize accessibility and affordability.

8. Both governments and the pharmaceutical industry are aware that collaborative models for patent licensing, such as patent pools and clearinghouses, can function as an interesting alternative to exclusive production and to single bilateral or cross-licensing, at least in the context of developing economies catching up with Western manufacturing standards.

   These models can be particularly useful in situations where many related inventions have been patented by many different organizations and where access to these inventions is essential for the development and marketing of a (new) product. To gain access to all those patent rights, one has to enter into a multitude of licensing negotiations, which often lead to an accumulation of royalties. Further study regarding the role that patent pools and clearinghouses could play in excessive price cases is recommended.

   In order to address a specific public health problem, one could also take initiatives at the international level, for example through public-private partnerships, to negotiate with patent holders about joint public health-oriented licenses. This could be a more sustainable solution than compulsory licensing.