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IMPACT ASSESSMENT

Accompanying the document

Proposal for a Regulation of the European Parliament and of the Council amending Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products

{COM(2018) 317 final} - {SEC(2018) 246 final} - {SWD(2018) 241 final} - {SWD(2018) 242 final}

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Glossary

Term/Acronym	*Meaning/Definition*
API	Active pharmaceutical ingredient (the part of any medicine that produces its effects)
Biosimilar medicines or biosimilars (also known as 'follow-on biologics' or 'subsequent entry biologics')	A biosimilar is a biological medicine highly similar to another already approved biological medicine (the 'reference medicine'). Unlike the small molecules of classical medicines, which are 'chemically' synthesised, the much more complex biosimilars are extracted or synthesised from biological sources such as blood or tissues, and for this reason cannot be fully identical to their reference products. EMA evaluates biosimilars in the EU
Bolar exception	The Bolar exception, which allows small-scale manufacturing of generic/biosimilars medicines to take place during the patent/SPC protection period of the reference medicine in order to conduct the testing required to obtain regulatory approval for the generic/biosimilar
Blockbuster	A medicine with annual global sales of over USD 1 billion
Day-1	First day following expiry of intellectual property (IP) protection for a given medicine. For practical reasons (such as national-level pricing and reimbursement negotiations), generics/biosimilars rarely enter on the market on the very first day following SPC expiry. Therefore throughout this document '*day-1*' entry shall be understood as referring to entry on the first practically possible day, or more generally to a 'rapid' or 'timely' entry
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
Follow-on product	Generics and biosimilars are also called 'follow-on' products
Generic medicines ('generics')	A generic medicinal product is a copy of an original non-biologic 'reference medicine' whose IPR and market protection has lapsed or expired. The generic medicine is usually manufactured by a different company. Generics have the same qualitative and quantitative composition in active substances and the same pharmaceutical form as reference medicinal products
Manufacturer of generics and biosimilars	This term includes manufacturers of generics and/or biosimilars as well as manufacturers of APIs corresponding to those generics/biosimilars
Originators or innovators	They are typically the SPC holders, but are increasingly becoming leaders in the production and commercialisation of biosimilars
SPC	A supplementary protection certificate is a sui generis IP right that extends by up to 5 years the effect of a patent in Member States (with an extra 6 months added if a paediatric investigation plan is conducted). SPCs apply to human medicinal (or plant protection) products subject to regulatory authorisation
TRIPS	Agreement of the World Trade Organization (WTO) on Trade-Related Aspects of Intellectual Property Rights

1. INTRODUCTION: POLITICAL AND LEGAL CONTEXT

1.1. Political context

The *Single Market Strategy*[1] announced a targeted recalibration of certain aspects of patent and Supplementary Protection Certificate (SPC) protection, aiming to tackle the following problems:

(1) Loss of export markets (in unprotected third countries), and of timely *day-1* entry onto Member State markets, for EU-based manufacturers of generics and biosimilars, due to the unintended effects of the current EU SPC regime; in this regard, it was suggested to introduce in the EU SPC legislation an 'SPC manufacturing waiver' allowing manufacturing of generics and biosimilars, within the EU, during the SPC term.

(2) Fragmentation resulting from the uneven implementation of the current SPC regime in the Member States that could be solved in connection with the upcoming unitary patent, and the possible creation thereafter of a unitary SPC title.

(3) Fragmented implementation of the Bolar research exemption[2].

The European Parliament resolution on the Single Market Strategy[3] endorsed the Commission's intentions and notably '*urge[d] the Commission to introduce and implement before 2019 an SPC manufacturing waiver*', so as to boost the competitiveness of the generics and biosimilars sector, '*while not undermining the market exclusivity granted under the SPC regime in protected markets*'.

In June 2016, the Council of the European Union called upon the Commission to engage in a wider review of IP incentives in the pharmaceutical sector[4]. In particular, the Council invited the Commission to conduct, before 2019, an evidence-based analysis of the impact of EU pharmaceutical incentives on innovation, availability and accessibility of medicinal products, including on pricing strategies. Among those incentives, the Council considered that particular attention should be given to SPCs, the 'Bolar' patent exemption, data and market protection, market exclusivity for orphan medicinal products, and incentives and rewards for paediatrics[5].

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1 Document COM(2015)550. See also the subsequent inception impact assessment on patents and SPCs.

2 The exception is defined by Article 10(6) of Directive 2001/83 on the Community code relating to medicinal products for human use, stating that '*Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products*'. A similar provision can be found in Article 13(6) of Directive 2001/82/EC on the Community code relating to medicinal products for veterinary use.

3 2015/2354(INI).

4 Council Conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States (17.6.2016).

5 Medicinal products enjoy data and market protection, or market exclusivity for orphan medicines, following their authorisation, which run in parallel to patent and SPC protection, and may in some cases last longer than the SPC protection (the impact of these two types of protection on innovation, availability and accessibility of medicinal products is being analysed by the Copenhagen Economics study).

As regards the review of the SPC Regulation and following a series of studies (see Annex 1 and section 4), an inception impact assessment[6] was published in February 2017 announcing possible legislative and non-legislative proposals. In October 2017, a 12-week online public consultation was launched; its results are summarised in Annex 2.

As regards the wider pharmaceutical review, the Commission contracted an economic study[7]. The Commission also intends to conduct an evaluation of the orphan and paediatric legislation, with further analysis in 2018-2019[8].

1.2. Scope of the impact assessment

This impact assessment focuses on two specific problems, (a) the **loss of export markets due to delayed entry** and (b) delayed entry onto EU markets, that **decrease the competitiveness of EU-based manufacturers of generics and biosimilars**. It considers a targeted initiative in this area. Other aspects related to the review of the SPC regime, and a wider pharmaceutical incentives review, will be dealt with via separate initiatives at a later stage. The reasons for this approach are the following:

(1) Even though the public consultation showed wide support for the introduction of a **unitary SPC**, it would be premature at this stage to table a proposal for the creation of a unitary SPC, as the unitary patent package is not yet in force.

Secondly, whilst the public consultation and ongoing analysis show a **need for more clarity as regards the way the SPC Regulation is applied in practice**, it would be preferable to await the outcome of certain pending cases before the Court of Justice of the European Union (CJEU) before proceeding to offer practical guidance.

Thirdly, as regards the **Bolar exemption** (which is enshrined in the pharmaceutical acquis), the public consultation and ongoing studies point to the need for more clarity, which could be offered through guidance.

(2) There is an **urgent need to tackle the specific problems faced by EU-based generics and biosimilars manufacturers**. As discussed below, the markets for generics and biosimilars are highly competitive and steadily growing. Under the current SPC rules however, EU-based manufacturers of generics and biosimilars are put at a competitive disadvantage vis-à-vis manufacturers capable of producing generics and biosimilars outside the EU. As of 2020, a significant number of medicinal products will go off-patent and off-SPC[9], opening a significant market for generics – and biosimilars in particular (expected to amount to EUR 95bn) – to competition. For example, in 2015, the originator firm Pfizer spent USD 17bn to purchase Hospira (a leading developer of biosimilars) in view of the USD 100bn patent cliff faced by biologics up to 2025 (a USD 20bn biosimilars market is expected by 2020)[10]. This upcoming 'patent cliff' will come in a context of SPC protection now mainstreamed across the Union, thus forcing companies who are

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6 http://ec.europa.eu/smart-regulation/roadmaps/docs/2017_grow_051_supplementary_protection_certificates_en.pdf

7 Copenhagen Economics study.

8 See inception impact assessment.

9 See Annex 14 for details. See also: *World Preview 2017, Outlook to 2022*, EvaluatePharma, 2017.

10 https://www.sec.gov/Archives/edgar/data/78003/000007800315000038/x999315.htm

willing to invest in the new opportunities to start – or relocate – their manufacturing outside the EU.

The EU was a pioneer in the development of regulatory procedures to approve biosimilars: the EMA authorised the first biosimilar in 2006 (to Sanofi), while the FDA did so only in 2015. However, there are clear signs that Europe is now losing its competitive edge as a hub for manufacturing of generics and biosimilars, with trade partners now quickly catching up[11]. For example, South Korea invested 35% of its national medical R&D budget in biosimilars development in 2012 (see Deloitte's Winning with biosimilars-Opportunities in global markets[12]), and Canada, while accepting to introduce SPC protection as a result of the negotiations with the Union on the Comprehensive Economic and Trade Agreement (CETA), nevertheless insisted on including an SPC manufacturing waiver in the Agreement, so as to allow its own firms to reap the benefits of the new generics and biosimilar markets.

Therefore, and as testified both by the respondents to the public consultation and in various studies, there is an urgent need for the EU to restore the competitiveness of EU-based manufacturers of generics and biosimilars. Doing nothing or postponing an initiative would further weaken European industry and unravel the EU's pioneering-effect competitive advantage in the biosimilar sector in particular.

(3) The **competitiveness issues addressed in this impact assessment can be addressed in a stand-alone manner**. In fact, the issues under discussion here, and the measures taken to address them, are not related to the wider debate on the optimal scope and duration of IP protection in the pharmaceutical sector in the EU. It should, moreover, be noted that the public consultation and study results have not pointed to the need for a broader re-opening of the SPC regime.

1.3. The EU Supplementary Protection Certificate regime

An SPC can extend by up to five years the protection conferred by the basic patent, but only with respect to the medicine(s) covered by the related marketing authorisation(s) to place the protected reference medicine(s) on the market[13]. An SPC is therefore considered a *sui generis* intellectual property right. SPC protection was first introduced in the EU in 1992 and is currently governed by Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products[14].

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[11] The Asia-Pacific region has more biosimilars in development, led by China (269) and India (257), than anywhere else in the world (The USA counts with 187 under development). See annex 7 and Deloitte Report 2018 Global life sciences outlook Innovating life sciences in the fourth industrial revolution: Embrace, build, grow. Available at: https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-ls-outlook-2018.pdf

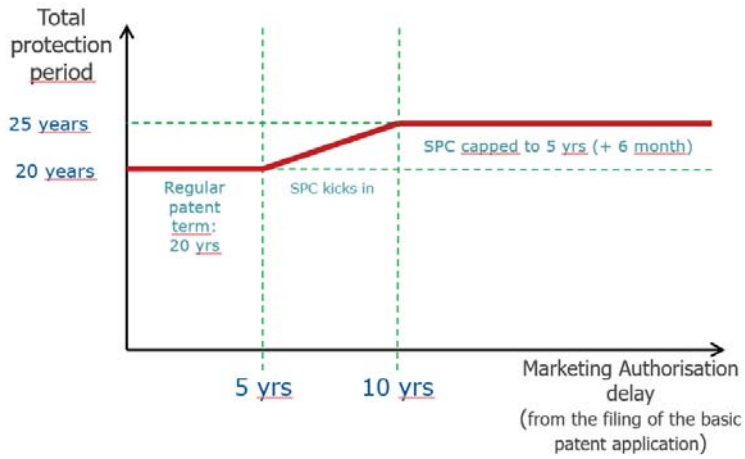
[12] https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-biosimilars-whitepaper-final.pdf

[13] Therefore, the SPC is not formally an extension of the patent. The subject matter of protection of the SPC needs to be seen in the context of the protection conferred by the reference patent (the latter is generally broader), and the marketing authorisation granted (which is purpose-bound, and thus more limited).

[14] It should be recalled that two kinds of SPCs are available in the EU: the SPC for medicinal products, governed by Regulation (EC) No 469/2009, and the SPC for plant protection products, governed by Regulation (EC) No 1610/96. Only the former is addressed by the current initiative, since the specific

SPC protection aims to offsetting the loss of effective patent protection due to the length of necessary testing, clinical trials and marketing authorisation procedures, thereby providing the pharmaceutical industry with appropriate incentives to innovate.

An SPC takes effect at the end of the term of the basic patent, and can be granted for a period equal to the period which elapsed between the date on which the application for a basic patent was filed and the date of the grant of the first authorisation to place the product on the market in the EU, reduced by five years. This means that not all patented and authorised medicines benefit from 5 years of SPC protection. Some may not be eligible for SPC protection at all (if the marketing authorisation was granted relatively quickly[15]); some may enjoy SPC protection having the full duration[16]; while others enjoy SPC protection but on the basis of a shorter duration. According to the *Copenhagen Economics* study[17], the average duration of SPCs granted in the EU amounts to 3.5 years.



The benefits of an SPC for its holder[18] are significant. Since an SPC '*confer*[s] *the same rights as conferred by the basic patent*'[19], the monopoly resulting from the basic (reference) patent is extended and enables its holder to prevent competitors from practicing the invention (manufacturing the medicine, offering it for sale, storing[20] it, etc.) in those Member States in which an SPC has been granted[21].

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problems described below in connection with medicinal products are not necessarily faced in connection with plant protection products, whose legal framework and market dynamics are different (just to take one example, no patent exemption similar to the 'Bolar' one is available for plant protection products in most of the Member States as confirmed by submissions to the Commission's public consultation).

15 No later than 5 years after the filing of the patent application (Art. 13(1) of Regulation 469/2009).

16 In certain specific cases, as set out in Regulation (EC) No 1901/2006 on medicinal products for paediatric use, the term can be extended by a further six months if a Paediatric Investigation Plan has been submitted to the EMA.

17 See Annex I, overview of studies conducted.

18 The SPC holder usually also holds the reference patent, although other situations are possible – for instance that the patentee licenses the patent and that the licensee invests in the clinical trials and obtains the marketing authorisation and the SPC.

19 Article 5 of Regulation 469/2009. Although the subject matter of protection is more limited (Article 4).

20 Stockpiling waivers for patent rights (not for SPCs, which are out of the scope of TRIPS and are not global-harmonised rights) have been subject to dispute in the context of the TRIPS Agreement. In 1999, a Dispute Settlement Body (DS114) of the WTO was established to rule on the European Communities and their Member States' complaint against Canada arguing, among other things, that the stock-piling provision stipulated in the Canadian Patent Act curtailed the rights conferred on a patent owner provided in Article

Annex 8 includes a detailed table summarising the main impacts of the current EU SPC regime for medicines, as governed by Regulation (EC) No 469/2009, on various stakeholders during the SPC protection period.

Reliance on SPC protection is significant and increasing. The number of SPC applications filed in Member States has tripled from about 500 applications in 1993 (in then EU-12) to 1,518 in 2013 (in EU-28). A recent study (Kyle) shows that the share of new medicine introductions having an SPC in at least one Member State increased from 75% in the early 1990s to 86% today[22]. Biologics account for about 16% of medicinal products subject to an SPC[23].

In addition to more medicines benefitting from SPC protection, SPCs are also protected in an increasing number of Member States. States that acceded to the EU from 1986 onwards were given transition periods during which they were not yet required to put in place SPC protection systems. The lapse of these transition periods has led to the gradual roll-out of SPC protection system across the whole EU. The effects of this roll-out are now being felt in particular in those Member States that joined the Union as and from 2004.

1.4. Strong evolution of pharmaceutical markets in the EU and globally

Since the introduction and codification of the SPC regime in 1992 and 2009 respectively, the European and global markets for pharmaceuticals have undergone very profound changes:

(i) Global demand for medicines is increasing, with a significant switch towards generics and biosimilars

The global pharmaceutical market has dramatically changed in the past 25 years. The fast growing economies of Asia, Central and South America – the so-called 'pharmerging' regions – combined with ageing populations in the traditional industrialised regions, have driven **massive global demand for medicines** over these decades. This is confirmed by industry data, which shows that total global spending on medicines increased from EUR 950 billion in 2012 to EUR 1.1 trillion in 2017. The USA represents 40% of this global market, while China (20%) has now displaced the EU into third place (with less than 15%). Biologics will represent 25% of the pharmaceutical market value by 2022 (Deloitte, 2017[24]).

Meanwhile, this growing global demand for pharmaceuticals is being accompanied by a **shift towards ever-greater market share by generics and biosimilars**, which could represent 80% of medicines by volume by 2020 and about 28% of global sales (Deloitte,

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28.1 of TRIPS, and were not within the limited exceptions provided by Article 30 TRIPS. The Panel ruled that stockpiling is indeed not justified under Article 30 for patent rights. The decision of the Panel was not appealed.

[21] According to the Mejer study, SPC protection for a single medicinal product is filed, on average, in 20 Member States today.

[22] According to Kyle, there were the change in drug development (e.g. introduction of secondary clinical endpoints) has increased the relevance of SPCs over time.

[23] DG GROW calculations based on AdP database.

[24] https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-biosimilars-whitepaper-final.pdf

2018), with a future compound annual growth rate estimated at 6.9% (partly due to efforts by governments to contain overall healthcare costs). According to Medicines for Europe, 56% of medicines by volume currently supplied in the EU are generics or biosimilars[25]. That being said, penetration rates vary considerably from one Member State to another[26].

(ii) Pharmaceutical R&D and manufacturing in the EU is significant but patterns are changing

The pharmaceutical sector in the EU is significant. According to Eurostat, there are about 4 000 enterprises active in this sector and together they provide about 570 000 jobs (figures from 2015). R&D expenditure in the EU amounted to EUR 27bn in 2015. Calculations by EFPIA show the following (these figures include Switzerland):

INDUSTRY (EFPIA total)	2000	2010	2015	2016
Production	127,504	199,400	238,437	250,000 (e)
Exports (1) (2)	90,935	276,357	365,303	375,000 (e)
Imports	68,841	204,824	269,012	275,000 (e)
Trade balance	22,094	71,533	96,291	100,000 (e)
R&D expenditure	17,849	27,920	33,557	35,000 (e)
Employment (units)	554,186	670,088	739,499	745,000 (e)
R&D employment (units)	88,397	117,035	113,713	115,000 (e)
Total pharmaceutical market value at ex-factory prices	89,449	153,685	193,742	202,000 (e)
Payment for pharmaceuticals by statutory health insurance systems (ambulatory care only)	76,909	129,464	131,685	134,000 (e)

The leading Member States in pharmaceutical R&D investment are Germany, UK and France. Belgium, Denmark and Sweden are intensive in R&D and manufacturing. Germany and Italy are the leading manufacturers of pharmaceuticals in absolute terms; however, while the trade balance in Germany is very high, Italy has a negative trade balance. The leading Member States in employment in this sector (in absolute terms) are Germany and France. Ireland, Denmark, Belgium and Sweden are highly intensive in manufacturing and have large trade balance. Member States that acceded to the EU as of

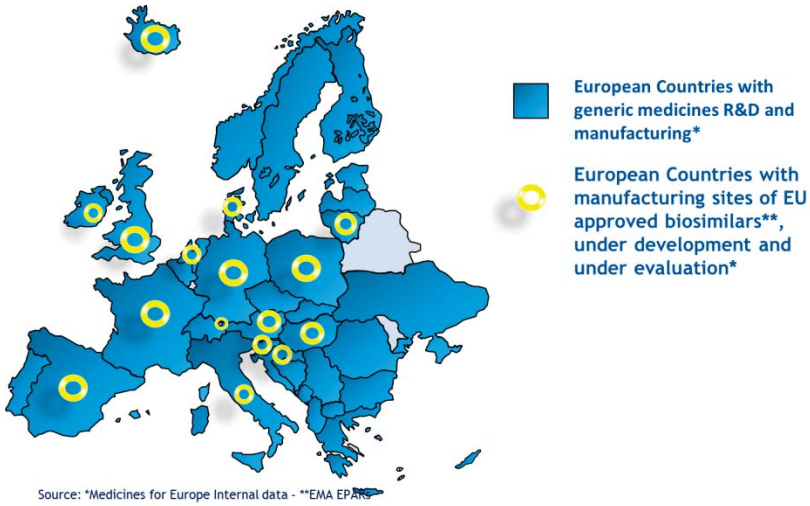
[25] According to IMS Health, there have been a number of successful launches of non-biologics blockbusters medicines in the EU (e.g. fingolimod, rivaroxaban, palperidone, and abiraterone) that will be the subject of generics development programmes and market launches over the longer term. In the biosimilars sector, IMS Health also signals that the dominance of biological therapies in the top 10 products in Europe anticipates the future importance of the biosimilar industry.

[26] Greece and Italy only have 18% penetration by volume, while the UK and Germany have over 80% penetration by volume representing over 35% in terms of value. (Source: OECD Health Statistics 2016).

2004 (in particular Poland and Hungary) account for over 50 000 jobs combined, notably in the generics sector[27]. However, investment in R&D is low in these Member States.

The pharmaceuticals manufacturing sector in the EU is composed of a relatively small number of large capital-intensive enterprises, although small and medium-sized enterprises (SMEs) are active in manufacturing as well, in particular as regards generics (details in annex 16)[28]. 60% of European production is generated by global firms who are active in several Member States[29]. Manufacturing includes innovative drugs, biological/biosimilars, as well as high-end APIs[30] and value-added generic medicines.

Whilst the largest share of EU manufacturing is controlled by patent- and SPC-holding companies, the generics and biosimilar sector in the EU comprises 350 manufacturing sites, accounts for over 160 000 jobs and exports to over 100 countries. According to IMS Health, the company that provides information, services and technology for the healthcare industry, the generics and biosimilar sector accounts in volume for 56 % of prescribed medicines in 2016 and accounted for 22% of the total sales of medicines in 2014. As illustrated in the map provided by Medicines for Europe, its companies are established in most Member States as indicated in the map below (originator firms also have biosimilars plants in other Member States, but these are not indicated):



According to the Eudra Good Manufacturing Practice (GMP) database which is maintained and operated by the EMA, 234 sites in 19 Member States are authorised to produce biologics and biosimilars (see annex 11 for details).

Biosimilar production requires costly and complex development and manufacturing processes[31], but is also highly lucrative. Given that approval of biosimilars started in the EU much earlier than elsewhere (already from 2006), and given Europe's excellent ecosystem (including universities) and infrastructure (including clinical and contract

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[27] See annex 11 for detailed Member State statistics on industry structure, R&D, trade, FDI and EMA-compliance manufacturing sites.

[28] According to Eurostat, since 2010, the number of enterprises in the EU-28 for which pharmaceuticals manufacturing is their principal activity has remained stable and amounts to around 4 000.

[29] That is, with the controlling company located outside the reporting country.

[30] *Chemicals Producers Association* (CPA) report (2015), Competition in the world APIs market.

[31] See annex 4.

research organisations), the EU quickly became the world leader for the development and manufacturing of biosimilars (with 31% of global FDI in manufacturing and R&D for biosimilars currently taking place in the EU)[32].

Today, the classical boundaries between originators and generics/biosimilars manufacturers are more blurred. Some originators have branches devoted to generics (e.g. Novartis/Sandoz, Pfizer and Merck KGaA are the top sellers of unbranded products in the EU[33]) and some traditional generic manufacturers are developing innovative or high value- added generics and biosimilars (e.g. Mylan, Dr. Reddy's or Teva[34]). This does not, however, necessarily translate into jobs in the EU, as originators tend to increasingly manufacture biosimilars and generics outside the Union, and notably in Canada, the USA and Asia[35] (e.g. Samsung Bioepis manufactures in Asia and registers biosimilars at the EMA and FDA, that are then commercialised by the originator firms Merck and Biogen[36]; Pfizer bought Hospira, a leading manufacturer of biosimilars with manufacturing capacity in Asia and North America; and Celltrion manufactures biosimilars in Asia for Pfizer[37]).

It should be noted that in the field of pharmaceutical innovation, start-ups and SMEs play an increasingly important role, in particular as regards the initial steps of innovation. In fact, pharmaceutical companies are increasingly outsourcing their R&D. Today, significant innovation comes from specialised SMEs focused on the initial steps of R&D and development, with less than 25% of the new medicines being developed by originators (Deloitte, 2018). According to a report by Accenture (2016)[38], over the past decade, 60% of innovator small molecules and 82% of innovator biologics have their roots outside big pharmaceutical companies (see for more details, Annex 16 on SME Test).

(iii) Global developments of pharmaceutical R&D and manufacturing

25 years ago, pharmaceutical R&D and manufacturing was essentially situated in the USA, the EU and Japan[39]; today pharmaceutical R&D and manufacturing[40] is a global phenomenon. The EU has traditionally been the biggest exporter of pharmaceuticals, representing over 25% of the Union's total high-tech exports. In recent years however,

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32 Commission services calculations based on FT fDi database.

33 Cf. Table 5 in Kyle (2017). The ranking is based on the number of product launches (of a unique chemical combination) per firm observed in 2016 in a set of Member States, not on revenues or market share.

34 http://www.tevapharm.com/research_development/rd_focus/pipeline/

35 Manufacturing biotechnology sites in China, Singapore and India are already complying with *Good Manufacturing Practice* which is a standard required to produce medicines for the EU market. See Annex 11 for details.

36 www.samsungbioepis.com/en/pipeline/

37 https://dcatvci.org/5058-biosimilars-opportunities-and-challenges-in-the-us-and-eu

38 https://www.accenture.com/t20150527T203922__w__/us-en/_acnmedia/Accenture/Conversion-Assets/Microsites/Documents/Accenture-The-Future-of-Pharmaceutical-Innovation-Tackling-the-RD-Productivity-Gap-Online.pdf

39 Gambardella, A., Orsenigo L., & Pammolli, F. (2000), *Global competitiveness in pharmaceuticals: a European perspective*, available at https://mpra.ub.uni-muenchen.de/15965/1/MPRA_paper_15965.pdf

40 See table in page 42 at: https://www.ifpma.org/wp-content/uploads/2017/02/IFPMA-Facts-And-Figures-2017.pdf

India, Singapore and Israel have also managed to position themselves as major pharmaceutical exporters (IFPMA 2017), while China is now the world leader for the production of APIs (by volume), according to the World Health Organisation.

Regarding biosimilars development, according to Deloitte's 2018 Global Life Sciences Outlook:

> 'Led by China, the Asia-Pacific region has more biosimilars in development than anywhere else in the world. China has the potential to become the frontier market for biosimilar drugs (269 biosimilars under development). The growth of biosimilars could push the industry into an innovative phase'.

Indeed, all four BRIC countries (Brazil, Russia, India and China) have updated their regulatory rules and are becoming increasingly attractive for investments in biosimilars[41] (see Annex 7 for more detailed information). Global competition is therefore fierce, requiring the EU to take the steps needed to remain competitive.

2. PROBLEM DEFINITION

A problem tree is included at the end of this section.

2.1. Decreasing competitiveness of EU-based generics/biosimilars manufacturers

In the current international context, and given the evolution and dynamics of the pharmaceutical market, the EU SPC protection, established back in 1992, is unintentionally acting to the disadvantage of EU-based[42] manufacturers of generics and biosimilars vis-à-vis non-EU-based manufacturers, and this detrimentally affects the whole EU pharmaceutical ecosystem. Responses to the public consultation confirm that EU-based manufacturers of generics and/or biosimilars are losing competitiveness with respect to non-EU based ones.

As identified in the Single Market Strategy, it is urgent (see section 1.2 and 2.1.3) to tackle the difficulties faced by such manufacturers regarding export during the SPC term and entry onto the EU market immediately after SPC expiry.

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[41] *IMS Health* identified in 2011 South Korea, India and Brazil as key macroeconomic drivers of growth, attracting foreign capital by creating manufacturing and R&D centres of excellence for biosimilars. According to the *Financial Times* fDi database, India and China are among six top countries in terms of the number of FDI announcements in biotechnology (life science) R&D and manufacturing. According to the EudraGMP database, sites in Brazil, India and China are already complying with EU standards for the production of medicinal products. See Annex 7 for details.

[42] Evidently, no problem arises, for a given medicine, in respect of those Member States where no SPC has been granted, and where manufacturing may freely take place after patent expiry. However, as explained below, this situation has a minor impact, as the geographical coverage of SPC protection across the EU is usually very large.

2.1.1. Two specific problems

Manufacturers[43] of generics and/or biosimilars (based in Member States where an SPC has been granted for the reference medicine), face two problems:

– **Problem 1**: *during the period of protection covered by the certificate of the reference medicine in the EU*, they cannot manufacture for any purpose, including export outside the EU to countries where SPC protection for the reference medicine has expired or never existed, while manufacturers based in those third countries can do so[44];

– **Problem 2**: *immediately upon the expiry of the certificate*: they are not ready to enter the EU market on *day-1*[45], since the EU SPC system does not allow manufacturing in the EU until then. By contrast, manufacturers based in third countries where SPC protection for the reference medicine has expired earlier or never existed[46] can be ready from *day-1* to enter, via exports, the EU market, and thus gain a considerable competitive advantage.

These problems put EU-based manufacturers at a competitive disadvantage vis-à-vis manufacturers located outside the EU in both global market and in the (*day-1*) EU market. This is aggravated by the dynamics of generics/biosimilars markets whereby, after expiry of patent/SPC protection of the reference medicine, only the first generics/biosimilars to enter the market capture a significant market share and are financially viable (see section 2.2.2 below).

In the public consultation on SPCs, these two problems were confirmed in submissions by the group of generics/biosimilars, as well as by the group of patients/doctors/insurers', as follows:

Table 2.1.1.

	Generics/biosimilars' opinion				**Patients/doctors/insurers' opinion**			
	Yes (The problem exists)	No	Don't know	No answer	Yes (The problem exists)	No	Don't know	No answer
Problem 1	56	1	2	4	10	1	4	-
Problem 2	53	3	3	4	6	3	6	-

[43] Whether they have their headquarters in the EU or in a third country (this includes generics/biosimilars divisions of innovative pharma companies).

[44] At least if they are based in a country having no SPC protection (e.g. China, India, Brazil, Mexico, Russia), or having SPC *with a manufacturing waiver for export purposes* (e.g. Canada– which is very relevant in relation with the highly lucrative US market), or countries such as Israel with shorter SPC protection than the EU.

[45] Although SPCs are granted nationally, Article 13 of Regulation 469/2009 is designed to ensure that all SPCs granted by Member States for the same medicine expiry simultaneously (in a few cases there may be temporary distortion).

[46] While TRIPS provides for minimum standards of patent protection in WTO countries, it does not cover SPCs.

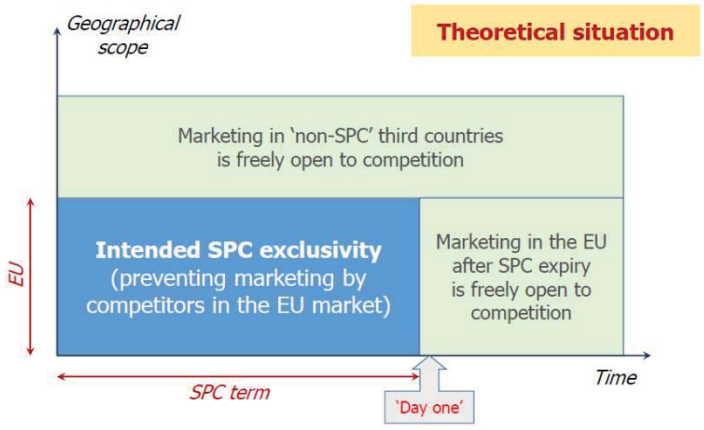
2.1.2. Unintended side-effects of the EU SPC framework

Taking a step back, the Bolar exemption (governed by Directive 2001/83/EC and Directive 2001/82/EC which in practice can be considered a manufacturing waiver for testing and clinical trials[47] purposes) was intended to ensure that a generic could enter the market as soon as possible after the expiry of patent/SPC protection. Without this exemption, necessary testing and clinical trials prior to the authorisation of a generic or biosimilar medicine could only start after such expiry, which practically speaking, would extend the patent/SPC protection period of the reference medicine by several months, if not years in some cases, beyond its legal duration (considering the time needed to develop a generic or biosimilar and get it approved). The Bolar exemption has eliminated this untended side-effect of the strong patent/SPC protection, based on the basic rationale that free competition should be allowed as soon as protection expires.

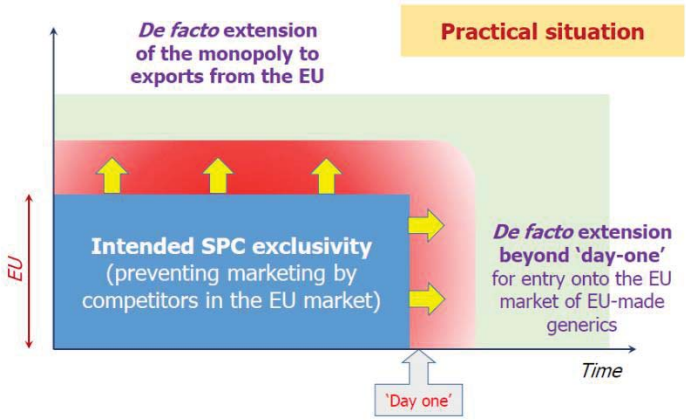
Regarding the SPC manufacturing waiver, firms are facing a situation similar to the pre-Bolar one. While the legitimate purpose of an SPC is to prevent the manufacturing for the purpose of marketing of competing products on the EU market when it is in effect, it has two unintended consequences that were not foreseen, namely preventing generics/biosimilars (1) from being manufactured in the EU and exported to third countries (where no legal protection applies) during the EU SPC term, and (2) from being manufactured in the EU (and then stored) early enough to be placed on the EU market immediately from *day-1*.

The absence of an SPC manufacturing waiver, in practical terms, results in unduly extending SPC protection beyond its legal term. This is detrimental to the *day-1* entry of generics/biosimilars onto the EU market (as they can be supplied from *day-1* by firms based in 'non-SPC' third countries), but also, much more so, to the competitiveness of EU-based generics/biosimilars manufacturers, which are not able to compete with those based in 'non-SPC' third countries, neither in terms of export during the SPC term, nor of *day-1* entry onto the EU market.

The following charts underline the difference between the theoretical (intended) and practical (i.e. unintended and *de facto*) consequences of the scope of the exclusivity conferred by SPCs.



[47] Development of biosimilars involves some clinical trials.



2.1.3. Magnitude of the problem and urgency to act

The problems described above preclude major export opportunities for EU-based manufacturers of generics and biosimilars (about EUR 1bn yearly for a sample representing 32% of relevant medicines (see detailed quantification in section 6.3, and tables 7.1 and 7.2)). They also imply a loss of 'lead time' for EU-based manufacturers wanting to enter into the EU market after expiry of SPC protection, thus making these manufacturers forego significant opportunities in a fast-growing global pharmaceutical market, which is undergoing a significant shift toward generics and biosimilars.

As indicated in section 1.2, as of 2020, a growing number of medicinal products will go off-patent/off-SPC[48], opening a significant market for generics – and biosimilars in particular (expected to amount to EUR 95bn) – to competition. Indeed, the global market for generic medicines is expected to increase by 50% over the 5 year period up to 2021, reaching EUR 500bn. In this context, the biologics market is booming, with annual sales of over EUR 150bn (biologics currently top the list of blockbusters), and originators increasingly entering the market of biosimilars. The Pugatch study (2017)[49] estimates that every year a global market of between USD 2.7bn and USD 5.4bn is opened to generics and biosimilars competition.

EU-based manufacturers of generics and biosimilars are therefore at risk of foregoing significant sales opportunities, both within EU and in global markets. This will act to the detriment of existing companies, but will also deprive new companies from the possibility of starting- and scaling up in high-growth markets. Companies will be faced with a stark choice: either to manufacture in Europe, where they are confronted with a legal barrier; or to manufacture abroad.

There is an **urgent need to tackle the specific problems faced by EU-based generics and biosimilars manufacturers.** Markets for generics and biosimilars are becoming highly competitive, and these markets are steadily growing driven by a major patent/SPC cliff of blockbusters, especially in the biologics sector, and by increasing global demand for medicines (see further section 1.2).

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[48] See Annex 14 for details. See also: World Preview 2017, Outlook to 2022, EvaluatePharma, 2017.

[49] http://www.pugatch-consilium.com/?p=2518

This has been understood by EU's trade partners that recently have been investing in pharmaceutical manufacturing and biosimilars development[50].

Doing nothing, or postponing an initiative would, firstly, further weaken the EU pharmaceutical industry (by not allowing it to seize the new emerging opportunities), and secondly, unravel the EU's pioneering-effect competitive advantage in the biosimilar sector in particular.

2.2. Two problem drivers

The two identified problems share the following drivers:

- Many of the EU's trading partners grant weaker or no SPC protection, which is in stark contrast to the EU's own SPC protection, thus leading to asymmetry in SPC protection globally;
- The market for generics and biosimilars is highly competitive with a strong '*first mover*' effect (i.e. a clear advantage for the first mover) both in the export and EU markets.

2.2.1. Asymmetry in SPC protection globally

While the TRIPS agreement obliges all EU trade partners to provide at least 20-year patent protection, it does not impose SPC protection – which is a *sui generis* right. Many trade partners of the EU do not provide for SPC or SPC-like protection at all (such as the BRIC states)[51], some offer SPC protection with a manufacturing waiver for export purposes (e.g. Canada), while others offer SPC or SPC-like protection that is in general shorter than the EU SPC protection (e.g. USA and Israel[52]).

The following table shows that, in most cases, SPC protection is the longest in the EU.

Country	**Molecules with known SPC expiry date**	**Molecules with SPC expiry date earlier than in the EU**	**Average difference in SPC expiry dates between EU and third country** (years)
US	109	93	2.06
Korea	44	40	2.86
China	41	41	3.31
India	22	22	3.07
Canada	40	40	3.53

Note: See Annex 9 for details.

[50] The Asia-Pacific region has more biosimilar in development (led by China (269) and India (257)) than the rest of the world (the USA has 187 under development): See annex 7 and Deloitte Report 2018 Global life sciences outlook Innovating life sciences in the fourth industrial revolution: Embrace, build, grow. Available at: https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-ls-outlook-2018.pdf

[51] As of 2016, 56 out of the 164 states who are members of the WTO have a form of SPC-like protection for medicinal products. Conversely, this means that 108 of these state have no such protection.

[52] Based on the data available on the differences in the expiry dates between EU and the USA: 1) the overview provided by Medicines for Europe shows that in 80% of cases, protection expires later in the EU than in the USA, 2) the Deloitte study reports that SPC protection of only 4 out of the 11 most important biologics expires earlier in the EU, 3) QuintilesIMS selected a sample of 25 molecules and concludes that in many instances, the SPC in a Member State expires earlier than in the USA. However, it includes Poland and Slovenia, where SPC has been introduced only recently.

Even if the EU were able to convince third countries to accept SPC- or SPC-like protection via its FTAs, CETA is likely to have a precedent effect in future FTA negotiations negotiated. Third countries accepting to introduce, or increase, SPC protection might well, at the same time, ask for a manufacturing waiver.

On this basis, it can be observed that:

— there is a reasonably level playing field between most countries of the world insofar as *patent* protection is concerned (with a duration of 20 years), as provided for under TRIPS;

— there is a lack of a level playing field between the EU and other countries regarding *SPC* (or SPC-like) protection, which is simply not available in many third countries; more specifically, there is a lack of a level playing field between EU-based manufacturers of generics/biosimilars and those based in most third countries (56 submissions from generics/biosimilars to the public consultation claim that the longer the difference in the duration of protection, the less attractive the EU is for their manufacturing activities).

Therefore, generics and biosimilars manufacturers established in third countries with no (or shorter) SPC or SPC-like protection are able to start manufacturing earlier than their EU-based competitors (this is a driver to the first problem). This timing advance in manufacturing also puts them in a much better position for *day-1* entry onto the EU market (the driver of the second problem).

Thus, the strong SPC protection in the EU introduced in the early 1990s is now creating unintended consequences not foreseen by the legislator at that time. In the early 1990s, developing countries did not constitute major competitors regarding the development of generics (whose market share was in any event limited). In addition, biosimilars did not even exist at that time. As a consequence, the two main problems described above had a low impact (causing little distortion). They were therefore not addressed in the *travaux préparatoires* of the 1992 Regulation (COM(90)101 final). However, today, modern infrastructure for the manufacturing of generics and biosimilars can be found in many developing countries that have no SPC protection (and notably in the BRIC states).

2.2.2. The 'first mover' advantage

These problems faced by EU-based generics and biosimilars manufacturers are aggravated by the dynamics of the generics/biosimilars markets where frequently only the first products to enter markets in a timely way after protection expires capture a significant market share and are financially viable. In the EU, generic firms entering one year after the first generic entrant only capture 11% of the first entrant's market share[53]. Even though the decline in prices for biosimilars is not as steep as in the case of generics, there is a race in this market to launch first[54], since later entrants have difficulty in gaining market share without a further reduction in prices. For biosimilars, studies show that in 2016, the first biosimilars to reach the market captured over 70% market share

[53] CRA study (2017). A number of studies support the existence of a first mover advantage effect for generic products. See Sharjarizadeh *et al* (2015), Yu and Gupta (2008), Hollis *et al* (1991).

[54] The degree of first mover advantage depends, in part, on the switching costs between reference product and the generic or biosimilar. Switching costs for biosimilars tend to be higher than for generics, including switching studies, longer-treatment periods, physician-acceptance and other entry barriers. This suggests that the effects of a 'first-mover' advantage might be stronger for biosimilars.

(biosimilar volume)[55]. Second and third biosimilar entrants captured respectively 30-40% and 5-22% market share.

In order to capture those potential sales, companies must supply the EU market either from their own plants or by subcontracting to third parties based in countries where protection of the reference medicine has already expired.

2.3. Consequences: relocation and decreasing attractiveness of the EU as a pharmaceutical hub

The problems above result in a lack of a level playing field between EU and non-EU based generic and biosimilar producers, when it comes to competing in both global markets and *day-1* entry in the EU. As it will be shown below, this affects not only EU-based manufacturers of generics and biosimilars, but also EU-based originators, and even EU patients (e.g. in terms of diversified supply). Thus, the whole EU pharmaceutical ecosystem is affected.

This situation is particularly detrimental for small and medium-sized EU pharmaceutical companies (see Annex 16 on SME Test), since they rarely possess manufacturing facilities in 'non-SPC' third countries. The creation and growth of EU-based start-ups is also affected, as they require a proper ecosystem on top of a regulatory environment free of unintended legal barriers. This situation gives way to a number of negative consequences that will be exacerbated over time.

The main consequence of the above-mentioned problems is increased relocation and/or outsourcing of the manufacturing of generics/biosimilars outside the EU, and loss of business opportunities inside the Union more generally, as companies will have a tendency to circumvent the current legal barriers they face, and will increasingly manufacture in third countries with weaker or no SPC protection, so as to be able to compete in global markets or be ready for *day-1* entry onto the EU market.

Three examples of relocation:

'Levofloxacin' (an antibiotic that reached the sales-status of blockbuster before the SPC expiry) went out of SPC protection in 2011 in Member States. Previously, a generic manufacturer decided to set up production in Poland because SPC protection was not available in that country. From 2010 to 2016 (i.e. following SPC expiry in the USA and later in most EU Member States) the compounded market value creation (sales according to IQVIA) was more than EUR 120m. The generic manufacturer claims that the production would have been moved outside of the EU if the SPC had been applicable in the recently-joined Member States at that time.

An EU-based generic manufacturer reported that it decided to set up the production of 'remifentanil' in Serbia, so as not to face the legal barriers to manufacturing in the EU. This product was SPC-protected in all Member States at the time. The value creation of the generic medicine is over EUR 10m from 2011 to 2016 (according to IQVIA).

A developer of generics and biosimilars, headquartered in Spain, has reported the successful launch of a monoclonal antibody (a complex biosimilar) in several countries in the American continent, though the firm has had to expand production to Argentina due to EU SPC protection.

Source: provided by generic manufacturers.

[55] *The Impact of Biosimilar Competition in Europe* (2017). The report analyses the impact on volume on two biosimilar therapy classes, Anti-TNF and EPO.

Delocalisation/outsourcing of pharmaceutical production will come with **additional consequences**, as follows:

- **Detrimental impact on manufacturing capacity, employment and skills** in the EU generics and biosimilars sector:
  - *Loss of jobs* in the EU pharmaceutical industry, in particular the generics and biosimilars sector, which accounts for 160 000 jobs in the EU, according to Medicines for Europe.
  - *Loss of know-how* and *a brain drain* of highly-skilled jobs, especially in the biosimilars sector, where R&D is increasingly shifting to other countries, notably in Asia.
  - *Relocation of R&D*, in particular for biosimilars[56]: the biosimilars sector is R&D intensive, and R&D for biosimilars tends to be located where manufacturing takes place. If manufacturing of biosimilars is rendered less attractive in Europe, then there is a risk that R&D for biosimilars will also leave the Union, causing Europe to lose its related expertise and competitive advantage. In the generics sector, co-location of R&D and manufacturing is less frequent, and the risk of delocalisation of R&D is thus lower.
  - *Loss of manufacturing capacity*: once production is delocalised, it might well never return to the EU. This risk affects EU-based SPC-holders (that also use the manufacturing capacity of generic manufacturers) as well as generics and biosimilars manufacturers. According to *Medicines for Europe*, the minimum cost of relocating the production of a single biological product is EUR 10m and it takes a minimum of 1.5-2 years. If the relocation requires additional regulatory approvals to ensure that the safety, quality and efficacy of the product are not affected, costs easily multiply. Switching API suppliers has a high cost due to the requirement of new stability batches and new analytical studies on impurities, among others. It is estimated that for the more complex APIs, the cost associated to a change of API supplier could be around EUR 4m. Therefore, once an API supplier is chosen, the decision tends to be irreversible.

- **Detrimental impact on the EU pharmaceutical industry as a whole**, including the innovative pharmaceutical industry in the longer term:
  - Delocalisation of manufacturing capacity of medicines outside the EU might negatively affect originators investments and manufacturing in the Union, as originators often outsource production and are investing in biosimilars. As already mentioned, originators are heavily investing in developing and commercialising biosimilars in the EU and other markets to compete with the highly-lucrative innovative biologics (patent/SPC protected) of other originators. EMA databases (details in annex 5) show that 15 out of 33 biosimilars with current valid authorisations in the EU issued to major originator firms (e.g. Amgen, Boehringer, Eli Lilly, Merck and Sanofi) or their biosimilar divisions (e.g. Pfizer-Hospira, Novartis-Sandoz and Novartis-Hexal). Samsung Bioepis

[56] Alcacer, J. and Delgado M. (2016). *Spatial organization of firms and location choices through the value chain*. Management Science, 62(11), 3213-3234. Analysing locations of new establishments of biopharmaceutical firms in the USA from 1993 to 2005, authors show that collocation of activities varies in the value chain. Although present in all activities, it is larger for R&D and manufacturing than for sales.

and Celltrion, which have 6 biosimilars authorisations at EMA, often manufacture and license to originators[57]. Approximately 30% of commercial biologics (reference products) are manufactured by contract manufacturing organisations[58], some of which are located in Asia (e.g. Samsung Bioepis).

- Loss of administrative regulatory-related skills in the EU: it is preferable that regulators be located near an advanced R&D and production ecosystem. If it is delocalised, there will be lessened impact of EU rules on the global regulatory environment, or other trade partners could even set the future regulatory rules for global markets. This would impact adversely on EU-based originators as well.

[57] https://www.dcatvci.org/5058-biosimilars-opportunities-and-challenges-in-the-us-and-eu

[58] http://www.pharmtech.com/biosimilars-supporting-contract-manufacturers-growth

- **Detrimental impact on EU patients and national public health budgets/systems**:
  - ***Less diversity of (quality) generics and biosimilars to EU patients, and reduced security of supply,*** if the production is concentrated in particular geographical regions outside the EU.
  - An increasing dependence on imports of generics has been a trend in the EU. As reported by Member States to the Commission public consultation, the share of EU-manufactured generics decreased from 60% in 2010 to 55% in 2013 in the EU. A Commission Staff Working Document from 2014[59] revealed that while in the 1980s more than 80% of APIs destined for the EU market were of European origin, the proportion had decreased to 20% in 2008. The increased dependency on non-EU sources[60] has already led to concerns with regard to maintaining security and quality of supply in the EU[61].
  - These concerns have materialised in recent years also in the form of some episodes of shortages, in the EU, of medicines mostly supplied from outside the EU following accidents or unexpected events[62]. The website of the EMA[63] provides a catalogue of shortages of supply of medicines in the EU. It should be noted that some shortages are due to disruptions to production which takes place exclusively outside the EU.
  - An increasing risk of imported counterfeit and falsified medicines has also been detected by EU customs authorities, which in 2016 seized almost 400 000 pharmaceutical articles.
  - A significant majority of citizens in the public consultation -- 32 out of 43 submissions -- indicated that they care about the origin of production of the medicines they consume (only 3 respondents suggested that they do not care). Some of the submissions express supply and quality concerns.
  - The relocation of clinical trials may also be detrimental to certain groups of patients, as participants in such tests may benefit from experimental medicines.
  - In the medium term, competition in the EU will be reduced, especially for medicines that are not so profitable (Kyle 2017), but still have important therapeutic value. Reduced competition affects access to medicines for EU patients and health expenditure for EU public health budgets. As often happens, reduced competition may lead to price increases.

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59 SWD(2014)216.

60 China is the world's leading producer and exporter of active pharmaceutical ingredients (APIs) by volume, accounting for 20% of total global API output, and having displaced India. (Source: http://www.who.int/phi/publications/2081China020517.pdf) In the past, a strong delocalisation of API manufacturing to Asia led to a significant dependency on commodity-APIs from Asia. According to the CRA report, currently Asia accounts for 63% of the world's API production. European API production, mainly in Spain and Italy, accounts for 21% of the world market.

61 https://www.reuters.com/article/us-pharmaceuticals-europe-india/eu-recommends-suspending-hundreds-of-drugs-tested-by-indian-firm-idUSKBN16W0A4

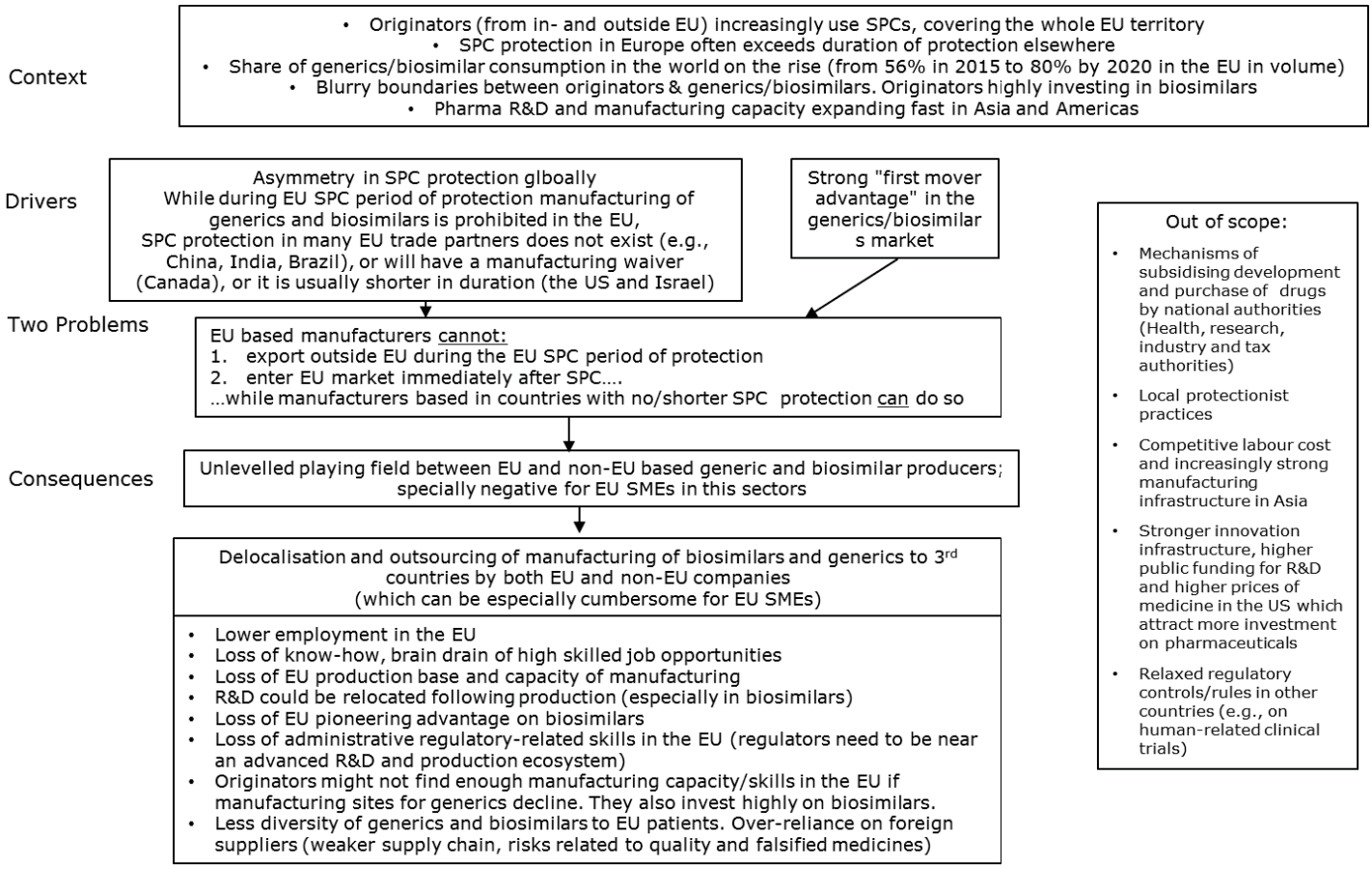
62 The Tianjinin explosion in 2015 in China damaged storehouses and production lines of medicines that led to shortages of supplies in the EU.

63 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000376.jsp&mid=WC0b01ac05807477a6

- Patients in a few Member States were not able to access to certain treatments until a biosimilar was available. Therefore, limiting the *day-1* entry capacity for EU biosimilars in those Member States could make a difference for some EU patients.

It is thus apparent that the current situation vis-à-vis delocalisation and outsourcing is not only detrimental for EU-based manufacturers of generics and biosimilars, but also for other categories of stakeholders.

Problem tree: context – drivers – problems - consequences



3. WHY SHOULD THE EU ACT?

3.1. Legal basis

Regulation (EC) No 469/2009 concerning the SPC for medicinal products is based on Article 114 of the Treaty. An EU legislative initiative would prevent the heterogeneous development of national rules and practices which directly affect the functioning of the internal market. Thus, EU action to tackle the asymmetry in SPC protection and the 'first mover' effect should be grounded on this legal base.

While the envisaged action does have an effect on the trade relations between the EU and third countries, its centre of gravity is the competitiveness of manufacturers of medicines within the internal market.

3.2. Necessity for action at EU level

At national level, agreements between generics/biosimilar manufacturers and originators have been concluded (see section 6.2), however without properly addressing the objective to create a level playing field for generics/biosimilar manufacturers within the whole of the EU territory.

Firstly, it should be recalled that these agreements are of a voluntary nature. While in individual cases they may have led to positive results (e.g. allowing individual companies to advance manufacturing), originators are not bound by them. Generally speaking, and as reflected in submissions to the public consultation, these agreements are not considered to have been successful and these actions are therefore not sufficient to address the challenges and objectives described in the problem definition.

Secondly, assuming they have encouraged *day-1* entry of generics and biosimilar, such agreements are limited to the jurisdiction of one Member State and do not cover the full territory of the Union. Even if individual Member States introduced binding rules on manufacturing, its territorial effect would always be limited.

By contrast, action at EU level would avoid the development of possibly diverging national legislation; avoiding such diverging national approaches has been a main objective of the SPC Regulation. EU action would also enable the legislator to tackle - from an internal market perspective - the issue of the competitive advantage enjoyed by manufacturers based outside the EU over their competitors within the EU, a competitive advantage unintentionally created by the SPC Regulation itself.

As a consequence, intervention at EU level is considered necessary.

3.3. Added value of EU action

EU-level action would bring significant added-value compared to national-level action to the extent that it would preserve the integrity of the internal market, by providing for a uniform, transparent and fair approach.

Indeed, while soft-law approaches based on voluntary agreements between originators and generics/biosimilars manufacturers are already possible today (and used in certain Member States), as explained above, an increasingly heterogeneous and non-transparent situation across the EU would result if their use were generalised.

4. OBJECTIVES: WHAT IS TO BE ACHIEVED?

An 'objectives tree' is included at the end of this section.

4.1. General objectives

The general objective of the policy action is to **create a level playing field** for the manufacturing of generics and biosimilars in the EU vis-à-vis manufacturing in third countries, for the purposes of export to third-country markets, and for timely entry into the EU-market 'on day 1'. This would defend and increase the global **competitiveness** of the EU pharmaceutical industry (including, but not limited to, manufacturers of generics/biosimilars) and on jobs in the EU.

As stressed by Parliament, this objective should be achieved without undermining the market exclusivity granted under the SPC regime in protected markets.

4.2. Specific objectives

The specific objectives sought with this initiative are the following:

(1) Ensure that SPC protection in the EU does not prevent EU-based manufacturers of generics and biosimilars from entering unprotected third country markets during the EU SPC protection period.

The criteria for monitoring and evaluating this objective will be, among other things, the evolution of future exports of EU generics and biosimilars (including APIs), the share of EU exports of these products, and the market share of EU generics/biosimilar in third country markets.

(2) Ensure that SPC protection in the EU does not prevent EU-based manufacturers of generics and biosimilars from entering the EU market on day 1.

For some products, this objective can be partly achieved through fulfilling specific objective (1). This is because building manufacturing capacity in a Member State for export purposes during the SPC term would, for certain products, allow for a quicker scale up of production to enter the EU market on day1.

The criteria for monitoring and evaluating of this objective will be the future evolution of the EU market share of EU-manufactured generics and biosimilars.

Through fulfilling objectives (1) and (2), the following beneficial consequences would result:

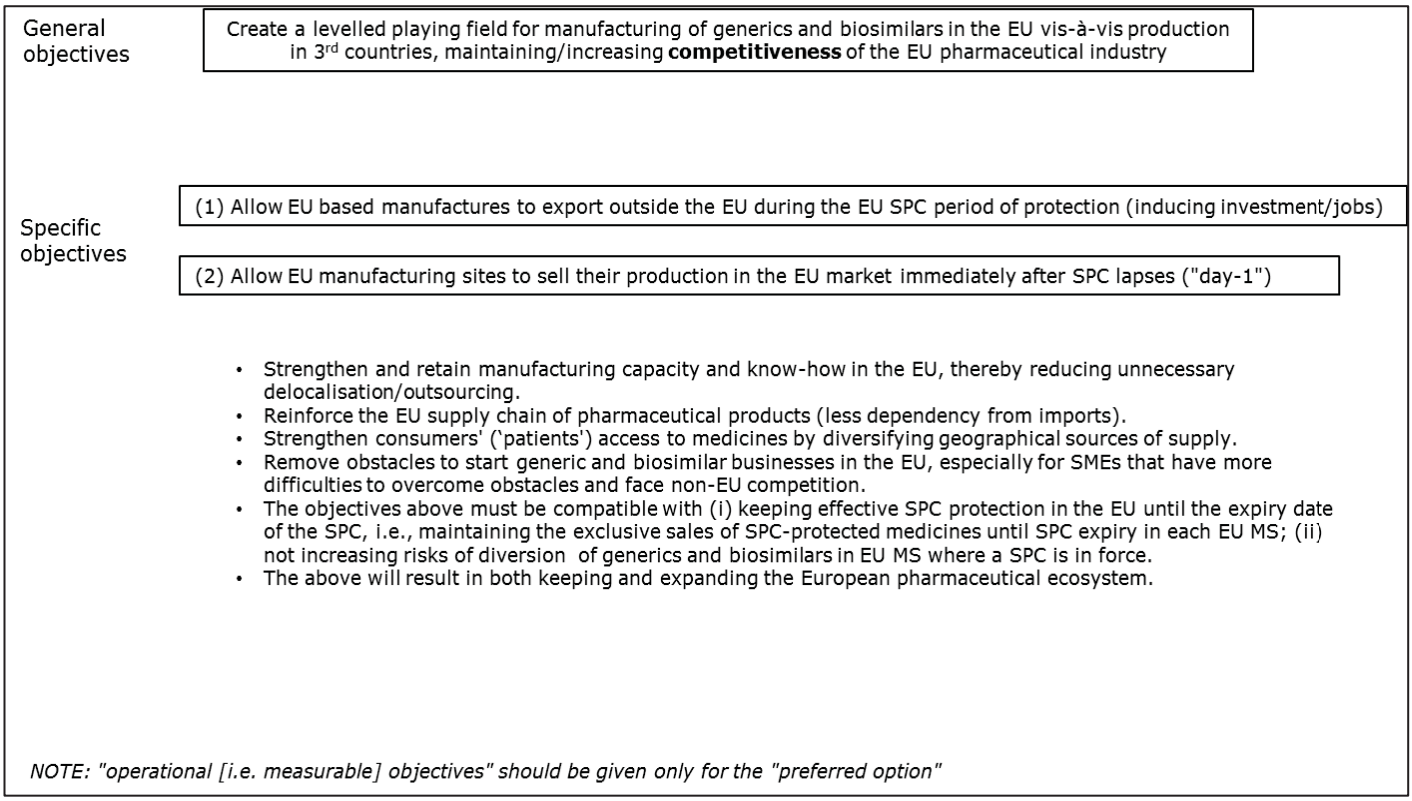
- strengthening and retaining manufacturing capacity and know-how in the EU, thereby reducing unnecessary delocalisation/outsourcing;
- reinforcing the EU supply chain of pharmaceutical products (less dependency on imports);
- strengthening EU patients' access to medicines by diversifying geographical sources of supply;
- reinforcing the sustainability of the EU health systems, including from the perspective of the national public health budgets;
- removing obstacles to starting generic and biosimilar businesses in the EU, especially for SMEs that have more difficulties in overcoming obstacles and facing up to non-EU competition[64].

The above objectives must be compatible with: (i) keeping effective SPC protection in the EU until the expiry date of the SPC, i.e. maintaining the exclusive sales of SPC-protected medicines until SPC expiry in each Member State; and (ii) not increasing risks of diversion of generics and biosimilars in Member States where an SPC is in effect.

Additional monitoring criteria for both objectives would be the evolution of the future number of manufacturing sites in the EU, and jobs in the different segments of the EU-based pharmaceutical industry.

[64] Other obstacles can also exist, such as lack of funding and social/labour market conditions.

Objectives of the initiative – Objectives tree



5. WHAT ARE THE AVAILABLE POLICY OPTIONS?

5.1. What is the baseline from which the options are assessed?

The baseline scenario related to this initiative is 'no policy change' (*status quo*/option 0). With no policy action, the identified problems would not be fixed. As described in section 2.3, this would generate a number of negative consequences for manufacturers of generics or biosimilars (loss of competitiveness), for patients and health systems, and for the EU pharmaceutical sector as a whole.

In this scenario, some Member States could still apply unilateral approaches at national level, e.g. via voluntary agreements between stakeholders (as explained under section 5.3.1, 5.3.2 and 6.2). However, such approaches are not likely to be effective and risk undermining the single market.

5.2. Options discarded at an early stage

The following options have been discarded at an early stage:

5.2.1. Trying to persuade third countries to adopt SPC protection in line with that of the EU (i.e., reducing the existing global SPC protection asymmetry)

The Commission has already persuaded, via FTA negotiations, a few third countries to introduce SPC-type protection. However, major trading partners have refused to accept SPC provisions in FTAs, or have accepted lower levels of SPC protection, such as Canada. CETA obliges Canada to introduce at least a 2-year SPC protection that will benefit the exports of European pharmaceuticals to Canada which amount to about EUR

4bn annually[65], but CETA also allows Canada-based generics and biosimilars, during those 2-years of SPC protection, to manufacture for export purposes.

The situation of the base-line scenario could be improved by giving higher priority to the introduction of SPC protection in third countries in on-going and future FTA negotiations. However, giving higher priority to the introduction of SPC protection in FTA negotiations is not a realistic option to effectively meet the objectives, since some trade partners might not accept, in the short to medium term, to introduce SPC protection. In addition, such negotiations take time and, as regards the outcome, the EU is – by definition – dependent on the other partner.

5.2.2. Expanding the scope of the EU 'Bolar patent/SPC exemption' to allow for advance manufacturing for export purposes

The Bolar patent exemption, defined by Articles 10(6) of Directive 2001/83 on the Community code relating to medicinal products for human use and Articles 13(6) of Directive 2001/82 on the Community code relating to medicinal products for veterinary use, allows small-scale manufacturing of generics/biosimilars to take place during the patent/SPC protection period of the reference medicine, in order to conduct the testing required to obtain regulatory approval. The aim of this exception is to speed up the regulatory approval of generic/biosimilar medicines, and their entry into the market once the patent/SPC of the reference medicine has expired. In theory, one option could hypothetically be to expand the scope of the Bolar exemption to include manufacturing for export and/or stockpiling for EU *day-1* entry (see the Roland-Berger study).

However, submissions received in the context of the public consultation did not identify this as an option. In addition, given that the Bolar exemption applies to both SPCs and patents, expanding the Bolar exemption to allow for export manufacturing and stockpiling during the patent term could conflict with Article 28 of TRIPS.

5.2.3. New ad-hoc licensing measures

A specific type of license could be defined, which would be applied for by a generic/biosimilar company and granted by a competent authority, or alternatively negotiated with an SPC-holder under the supervision of a competent public authority[66], free of charge or against payment of a license fee[67]. This option would bring transparency for the SPC-holders that could identify and monitor the beneficiaries of such a license.

However, from the perspective of generic companies, the administrative procedures would involve costs and time delays, making it uncertain whether applying for a license would be economically sound. Moreover, SPC holders could tactically delay the grant of a license (e.g. via multiple appeals) making investment for generics very uncertain, or asking for unreasonably high royalties.

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[65] EFPIA welcomed the European Parliament's green light to CETA: https://www.efpia.eu/news-events/the-efpia-view/statements-press-releases/20170215-efpia-welcomes-the-european-parliament-s-green-light-to-ceta/

[66] In 1993, Italy adopted a similar measure for the SPCs granted in Italy under the Italian law preceding the introduction of the EU SPC system.

[67] See *Max Planck Institute* study on SPCs for the European Commission.

5.2.4. Cutting down the duration of the SPC

Cutting down SPC maximum duration (for instance, to the 2 years provided for in CETA) would reduce the EU SPC protection asymmetry with respect to most third countries.

However, this option has several major drawbacks:

- It would significantly affect the current period of exclusivity (of up to 5.5 years in total) enjoyed by SPC holders with respect to placing their products on the EU market (it should be stressed that none of the retained options of this impact assessment affect this core exclusivity of SPC holders). Such a drastic option would go directly against the fundamental objective of SPCs, which is to compensate for the loss of effective patent protection due to development and authorisation procedures.
- It would not solve the issue of timely *day-1* entry onto the EU market, unless the EU SPC protection were completed removed in the EU, i.e. to align the EU with 'non-SPC' third countries with manufacturing capacity, such as India.

Such an approach would roll back and overturn more than 25 years of EU intellectual property policy. It received almost no support from stakeholders in the public consultation (only 1% of the respondents to the public consultation supported this option, and in a different context to the problem definition articulated in this impact assessment).

5.3. Description of the policy options

Aside from the status quo (option 0), a number of policy options are considered below to ensure that SPC protection in Member States does not prevent EU-based manufacturers of generics and biosimilars from competing on an equal IPR footing with manufacturers based in third countries. Apart from the status quo, two broad approaches can be envisaged:

(1) Soft law approaches based on voluntary industry-led initiatives to allow EU-based manufacturers of generics and biosimilars, during the SPC term of the reference medicine, to manufacture for export and/or stockpile purposes (Option 1).

(2) Amending the EU SPC legislation so as to allow EU-based manufacturers of generics and biosimilars, during the SPC term of the reference medicine, to manufacture for export and/or stockpile purposes (Options 2 to 4).

The table below displays these two approaches that are considered (in addition to the status quo option) to tackle each of the two problems:

Approaches related to the 1st problem (Objective 1: export during the EU SPC term)	**Approaches related to the 2nd problem** (Objective 2: *day-1* entry in the EU)
Status quo	Status quo
Soft-law approach allowing advance manufacturing for export purposes	Soft-law approach allowing advance manufacturing for stockpiling purposes
Export waiver legislation (possibly with anti-diversion measures such as specific labelling)	Waiver legislation (possibly with anti-diversion measures), which could be an export waiver (to some extent) or a stockpiling waiver

In total, nine (3 x 3) possible combinations of approaches are possible to tackle the two problems. Six of these combinations would entail different types of approaches to tackle

each of the two problems (e.g. the EU SPC regime could be amended so as to allow export during the SPC term, while a soft-law approach would be promoted in order to allow stockpiling so as to facilitate *day-1* entry) leading to complex implementation, requiring users to become familiar and develop different operational strategies to achieve the two objectives. Among those six combinations, those combining the status quo with another approach might not tackle one of the problems.

For these reasons, the options analysis below does not address specifically all nine possible combinations, while it nevertheless distinguishes between a waiver for export-only purposes and a waiver for *day-1* entry purposes (whose combination constitutes a further option).

On this basis, the following options can specifically considered regarding the two specific objectives:

<table>
<tr><th></th><th>Objective 1: export during the EU SPC term</th><th>Objective 2: day-1 entry in the EU</th></tr>
<tr><td>Option 0</td><td colspan="2">Status quo</td></tr>
<tr><td>Option 1</td><td colspan="2">Soft-law approach allowing advance manufacturing for both export & stockpiling purposes</td></tr>
<tr><td>Option 2</td><td>Export waiver legislation[68]</td><td>(No action or soft law approach)</td></tr>
<tr><td>Option 3</td><td>(No action or soft law approach)</td><td>Stockpiling waiver legislation</td></tr>
<tr><td>Option 4</td><td colspan="2">Legislation on both export and stockpiling waivers</td></tr>
</table>

5.3.1. Option 0: status quo

Not taking any policy action has already been described (cf. the baseline described above).

The EU would continue to negotiate FTAs with an IPR chapter that includes SPC provisions, but as explained above, this trade approach is not effective to tackle the problems identified (FTA negotiations take years and a number of trade partners successfully resist adopting EU-like SPC protection).

In this baseline scenario, a few Member States have already considered, or introduced, soft-law measures at national level (e.g. the LEEM-CEPS framework agreement in France – cf. below) aiming to allow advance manufacturing of generics during the patent/SPC term of the reference medicine for timely *day-1* entry. As mentioned below, such a national non-regulatory approach, while it may be satisfactory in individual cases, is not desirable from the point of view of the single market, especially regarding uniformity, fair treatment and transparency. These national approaches have not led to successful results so far.

[68] An export waiver might, to a certain extent, also improve EU *day-1* entry (2nd problem/objective) if the manufacturing capacity already established for export can be quickly scaled up on *day-1* to meet demand in the EU.

5.3.2. Option 1: voluntary industry-led agreements/'soft-law' approaches

Without requiring any legislative changes, the Commission in collaboration with Member States could try to facilitate further voluntary agreements between generics/biosimilars manufacturers and originators consisting of allowing advance manufacturing of generics during the SPC term of the reference medicine. Such voluntary agreements could cover manufacturing export purposes to unprotected third countries and (this option 1)/or for stockpiling purposes for timely *day-1* entry onto the EU market.

5.3.3. Option 2: introducing a manufacturing waiver for export purposes in Regulation 469/2009

This option envisages an amendment to Regulation 469/2009 to create an exemption to the SPC right[69] that prevents manufacturing of SPC-protected products by non-authorised third parties. This waiver for export purposes would allow developers of generic and biosimilar products to manufacture these products in a Member State during the term of the SPC protection, with a view only to exporting them to third countries with shorter or no SPC protection.

This waiver (for export-only) would also exempt a reasonable temporary storage that would happen between production and effective export of batches. Such temporary storage/stockpiling could not be used for *day-1* entry onto the EU market (i.e. the entire production under the waiver of this option 2 being exclusively for export markets).

However, manufacturers producing in the EU under this (export-only) waiver could be better prepared for timely entry into the EU market by scaling up their established production on *day-1*. Therefore, indirectly this option 2 also tackles to some extent the objective 2 (timely *day-1* entry). Its effectiveness in this latter regard would depend on the capability of firms to rapidly scale up production to meet demand.

5.3.4. Option 2-bis: implementing Option 2 with anti-diversion measures

Anti-diversion measures could consist of any of the following: a special labelling requirement, a notification requirement[70], a right to conduct inspections by the SPC holder, or the introduction of a reversal of the burden of proof in case of litigation. This could reduce the risk that that some of the products manufactured in a Member State under the waiver could end up on the market of that or another (SPC-protected) Member State. Section 6.4. further discusses several anti-diversion measures and their impact.

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[69] By an amendment to Article 5 (limitation to the effects conferred by the SPC) or Article 4 (exception to the scope of protection of the SPC).

[70] From *Max Planck Institute*'s draft final report: A notification-based solution was developed in CJEU case law concerning repackaging of branded goods in the context of parallel imports. When the original package (in which branded goods were first released on the EU market) is replaced by a different one on which the protected mark is affixed or otherwise remains visible, the giving of prior notice to the trade mark holder is one of the conditions that must be fulfilled in order for such measures to be admissible under Art. 15 of Directive (EU) 2436/2015 on Trade Marks. If no such notice is given to the proprietor, the parallel importer infringes the trade mark right 'on the occasion of any subsequent importation of that product, as long as he has not given the proprietor such notice'.

The design of specific anti-diversion measures would need both to take into consideration the level of additional burden for SMEs (See Annex 16 on SME Test) and to address confidentiality concerns.

5.3.5. Option 3: introducing a manufacturing waiver for stockpiling purposes in Regulation 469/2009

Similar to option 2, under this option, Regulation 469/2009 would be amended to create an exemption to the SPC right that prevents manufacturing of SPC-protected medicines by non-authorised third parties. This waiver for stockpiling purposes would allow developers of generic and biosimilar products to manufacture and stockpile these products in the EU during the term of SPC protection, with a view to being fully ready for timely *day-1* entry in Member States.

5.3.6. Option 3-bis: similarly to option 2-bis above, option 3 could be implemented with anti-diversion measures

5.3.7. Option 4: introducing a manufacturing waiver for export and stockpiling purposes under Regulation 469/2009

The SPC waiver proposed under this option would combine the features of the waivers of options 2 and 3. It would tackle both identified problems. Thus, this SPC manufacturing waiver for export and stockpiling would allow developers of generic and biosimilar products to manufacture these products in a Member State during the term of the SPC protection with a view not only to exporting them to third countries with shorter or no SPC protection (as in option 2), but also to storing them to be able to enter the EU market as and from *day-1* (as in option 3).

5.3.8. Option 4-bis: similar to options 2-bis and 3-bis, option 4 could be implemented with anti-diversion measures

5.4. Timing scenarios for applicability of options 2 to 4bis

In addition to the key options presented above which relate to the substance (i.e. the actual effects) of a waiver, and irrespective of which of them is preferred, a number of choices can be made regarding the 'time-bound applicability' of the waiver. It should be recalled that each SPC goes through four successive stages: (1) *not yet applied* for; (2) *applied for*; (3) *granted* (but not yet in effect, since the basic patent is still in force), and (4) *in effect* (i.e. after the basic patent has expired).

In this context, a waiver could be made applicable as follows (from the broadest to the narrowest capture in terms of SPCs covered):

- scenario 1: to all SPCs, even those which *are already in effect* when the waiver is introduced;
- scenario 2: only to granted SPCs which *will enter into effect* only after the waiver is introduced;
- scenario 3: only to SPCs which *will be granted* after the waiver is introduced (i.e. only to SPC applications);
- scenario 4: only to SPCs which *will be applied for* after the waiver is introduced (i.e. only to future SPC applications).

The respective impact of these scenarios – which anyway will be of a transient nature only – is analysed in section 6.8 below.

Annex 10 provides further information about the expected numbers of SPCs that would be affected by each of these scenarios.

6. WHAT ARE THE IMPACTS OF THE POLICY OPTIONS?

Further to the analysis below on the impact of the identified options, the tables in section 7 below provide a detailed description of the impact of the options described above. (See also Annex 16 on SME Test.)

6.1. Impact of option 0

The evolution of the problems related to the **baseline scenario** (no policy action) is analysed in section 2.3 above: delocalisation of manufacturing of generics and biosimilars and related consequences such as loss of employment in the EU, loss of pharmaceutical-related know-how, and relocation of R&D activities following delocalisation of manufacturing. A quantification of lost opportunities can be found in section 6.3 below.

Whilst option 0 is likely to seriously affect the competitiveness of the EU pharmaceutical industry (in particular but not limited to the generics and biosimilar sectors), it will also entail negative consequences for the (health) public purse and for patients, in terms of security and quality of supply and access to medicines.

6.2. Impact of option 1: voluntary industry-led agreements

The impact of voluntary, industry-led initiatives, even if stimulated at EU level, is likely to be limited. Indeed, being voluntary, such agreements may be refused by the SPC holder of the reference medicine, may only be adhered to by a few manufacturers of generics/biosimilars, or be subject to dissuasive conditions (e.g. high financial compensation requested by the SPC-holder).

Experience shows that comparable initiatives launched in some Member States have not been very effective. The LEEM-CEPS framework agreement, introduced in 2009 in France[71], is an example at national level of this soft-law approach. It is focused on speeding up *day-1* entry of locally manufactured generics and biosimilars, in exchange for compensation to the SPC holder. The LEEM-CEPS initiative has provided results for only four medicines since 2009.

While this option might be helpful in individual cases, it may not be optimal from the perspective of the single market as a whole, as regards uniformity, fair treatment or transparency.

If however it were pursued, the Commission could accompany such an approach with guidelines clarifying best practice, with the view to reducing the impact of the above-mentioned potential drawbacks. It should be noted that neither the public consultation nor

[71] See Art. 35.a.iii of the 'LEEM-CEPS' framework agreement – http://solidarites-sante.gouv.fr/IMG/pdf/accord_cadre_version_definitive_20151231.pdf

the various studies feeding into this impact assessment favoured a voluntary approach to tackle the first identified problem.

6.3. Impact of option 2: SPC manufacturing waiver for export-only purpose

6.3.1. Findings of studies

The impact of this option has been analysed and discussed by an independent study contracted by the Commission (CRA study) and other studies sponsored by the pharmaceutical industry (2 by generics companies and 4 by the originators industry). Annex 12 provides a description and estimations of each of the studies sponsored by industry.

Whilst there are divergences in opinion and in study results as regards the magnitude of the impact of the introduction of an export waiver in the EU, all studies confirm that the net impacts of such a waiver on the EU's pharmaceutical trade balance (net sales) and on job creation in the EU would be positive.

The CRA and OHE (for EFPIA) studies estimate the additional exports for EU-based manufacturers of generics and biosimilars, the potential negative impact on the exports of EU SPC-holders in unprotected markets and the impact on jobs in the EU. The CRA study, based on a sample of 117 non-biologics molecules and 17 biologics molecules (representing about 32% of all molecules expiring in the EU over the considered period, per each of the two categories of molecules), for which the SPC term expires later in the EU compared to 8 third countries[72], estimates that an SPC manufacturing for export-only purposes could result in additional export sales by EU-based production of those generics of EUR 7.6bn and for EU-based production of those biosimilars of between EUR 463m and EUR 2.97bn over 10 years[73].

CRA estimates, for that sample, a potential negative impact of this waiver on EU SPC holders' sales of between EUR 139m to EUR 278m for unprotected non-biologics market and between EUR 868m and EUR 1.7bn for unprotected biologics markets over a 10 year period.

Therefore, the net additional trade balance for the EU pharmaceutical industry represented by the sample of CRA would be between EUR 6bn to EUR 10bn over 10 years.

The OHE study reviews some of the assumptions undertaken in the CRA study and recalculates its outcomes, estimating additional sales for EU-based manufacturers ranging between EUR 1.2bn and EUR 3.9bn for the sample over 10 years. OHE estimates potential negative loses of exports for EU SPC holders ranging between EUR 298m and EUR 573m (the EU pharmaceutical industry exported EUR 220bn in 2016 according to the EFPIA datacentre). Therefore, according to OHE, the additional net trade balance for the EU pharmaceutical industry represented by the CRA sample of molecules over a decade could be between EUR 696m and EUR 3.6bn.

In terms of job creation, CRA estimates that the additional net exports could be translated into an additional 20 000 to 25 000 direct jobs in the generics and biosimilars sector

[72] Australia, Brazil, Canada, China, Japan, Russia, Turkey and the USA.

[73] These results are only based on a sample of 32% of the molecules. The real impact of the waiver could be of much higher magnitude when considering all the market.

(assuming constant productivity in the sector). OHE estimates that the reduction of exports by the SPC-holders would negatively impact on originator jobs. OHE also reduced the estimations of CRA of generic/biosimilar job-growth to between 2 837 to 9 430 new jobs (if SPC-holders lose 10% of their sales). However, the OHE calculations fail to take account of the jobs that could be created/retained/transferred across divisions by originators, who are currently investing massively in biosimilars (see annexes 5 and 7).

These numbers above should be considered as the lower range since, as mentioned above, the effects here are estimated on a sample of 117 non-biological and 17 biological molecules, representing around one-third of the relevant market.

The Pugatch study focuses exclusively on the potential impact of the waiver on originators based in the EU-28 and Switzerland. It estimates that between 0.6% and 1.04% of the global sales of the originators sector could be *open to competition* (i.e. as opposed to actual losses), if the EU introduces an SPC manufacturing waiver. The Pugatch study does not take into account that EU exports by originators can also include biosimilars manufactured by originators.

Pugatch estimates that those percentages could represent between USD 1.34bn and USD 2.27bn of the global sales by European originators annually. However, Pugatch does not estimate which part of those shares opened to competition could be retained by European originators (or taken by their own exports of EU-manufactured biosimilars and generics), and which part will be taken by non-EU originators, EU-generics/biosimilars and non-EU generics/biosimilars.

In terms of jobs, Pugatch estimates that the share of the exports that could be open to competition represents 4 600 to 7 750 employees in the originators sector. It does not estimate how many of those jobs could ultimately be lost, or transferred to the generics/biosimilars branches of other originators benefiting by the waiver. Therefore, the labour figures of Pugatch cannot be compared with the ones of CRA and OHE.

6.3.2. Feedback from public consultation

According to the inputs provided to the public consultation, **generic and biosimilar companies** (63 on-line submissions) support the introduction of an SPC manufacturing waiver. 56 out of 63 submissions are of the opinion that SPCs disadvantage EU-based generics/biosimilars manufacturers compared with those based in countries with no SPC when exporting their products outside the Union (1 respondent denies this problem, and 2 do not know), and indicate that they would invest more in EU manufacturing and would expect a high increase in their exports (6 submissions expect some competition with the exports of EU SPC holders).

Originators' submissions to the consultation reflect their broad opposition to the introduction of an EU SPC waiver: 54 out of 71 originators do not consider that EU-based generics/biosimilars manufacturers face the above problems.

More specifically, as regards the **views of originators**, they consider that:

- *It would send a negative policy signal to originator pharmaceutical companies and to trade partners as regards the EU commitment to IP*.

  However, it should be recalled that the EU has rolled out SPC protection to third countries via FTAs in favour of originators (according to EFPIA, EU exports to

Canada of pharmaceutical products worth EUR 4bn yearly will significantly benefit from the new SPC protection introduced in Canada through CETA).

- *The waiver would erode some of SPC holders' export sales (45 out of the 71 submissions of originators to the public consultation expressed this concern).*

  However, as analysed above, the magnitude of that erosion is limited and compensated by the economic gains expected by the waiver. In addition, EU SPC-holders will in the medium term face increasing competition as more and more countries invest in development and manufacturing of generics and biosimilars (annex 7).

- *A waiver would conflict with the Union's international obligations, notably FTAs concluded by the EU.*

  A waiver would complement the Union's trade policy approach overall. A waiver would also be consistent with existing international trade agreements, such as the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) between members of the World Trade Organisation (WTO), as well as those free trade agreements (FTAs) that the EU has concluded with third countries and which foresee protection of the nature of supplementary protection, such as CETA, which provides for a manufacturing waiver for export purposes.

- *The waiver would disincentive investments in R&D in the EU[74] and may therefore result in some relocation of R&D outside the EU.*

  Despite the waiver, the global IPR protection and enforcement framework in the EU would remain the strongest worldwide.

  Given that an export waiver would have a very limited effect on sales of SPC holders (no effect in protected markets) and does not affect to other major pharmaceutical-specific EU incentives for innovation, there would not be a meaningful negative knock-on effect on R&D incentives for originator products as a result (as the economic gains expected from R&D would be broadly the same).

- *The waiver would create a risk of illicit diversion of generics/biosimilars (made in the EU under the waiver) onto the EU market during the term of SPCs; this risk would be higher since the waiver would allow manufacturing in the EU during the SPC term* (see also section 6.4.1).

  A risk of foreign products being illicitly placed on the EU market is already present today. It is kept at bay by the EU's pharmaceutical legislation and its legislation regarding the enforcement of intellectual property rights. In addition, the waiver could be implemented with specific anti-diversion measures, which could actually help reduce the risk of diversion onto the EU market (see section 6.4).

  It should also be noted that there is no evidence of illicit diversion resulting from the existence of the 'Bolar exemption' in the EU, which itself if a form of manufacturing waiver for clinical trials purposes (and is available during the term of both patents and SPCs).

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[74] The waiver would reduce protection, to recoup originator investments in R&D in the EU (57 out of the 71 submissions of originators expressed this concern).

- *The exports gained by EU generics/biosimilars manufacturers would compete principally with SPC holders' products made in the EU (i.e. due to the EU 'goodwill branded effect'), and only in a negligible way with products made in countries such as China, Brazil or India, in view of the local barriers to imports.*

  Contracting manufacturing organisations working under EU or US good manufacturing practice (GMP) are stablished globally. Biosimilars are taking up quickly not only in developed countries but globally. Asian plants are also manufacturing for originators, including for those originators' biosimilars divisions (see section 2.3 and annex 7). In relation to supposed local barriers in 3rd countries, the EU trade policy aims to remove those barriers (industry information provided to the Commission indicates that EU-based manufacturers have been able to export to those markets upon expiry of the EU SPC[75]).

Regarding the feedback of SMEs in the sector of manufacturing of generics and biosimilars, and SMEs devoted to innovative medicines (See Annex 16 – SME Test for further details):

Among the 63 respondents defining themselves as mostly manufacturers of generics/biosimilars, 12 respondents identified themselves as an SME and 1 as a start-up. The vast majority of **SMEs manufacturing generics and biosimilars** supports the introduction of a waiver in the EU, and considers that the longer duration of SPCs in the Union compared to non-EU countries makes manufacturing in the Union less interesting for them.

Regarding **pharmaceutical innovative SME**, among the 71 respondents defining themselves as mostly originators, 2 respondents identified themselves as an SME involved in medicines biotechnology and one as a start-up in the field of biopesticides. In addition, several European pharmaceutical associations such as EUCOPE, EBE, and EuropaBio conveyed the views of their start-ups and SME members in their submissions and accompanying letters sent to the Commission during the public consultation. A few national innovative pharmaceutical associations focused on start-ups and SMEs-members (Belgium and Germany) also provided their views.

These associations representing innovative SMEs have expressed concerns that the introduction of a manufacturing waiver would dilute SPC protection and therefore dilute the financial rewards they would receive for their inventions, as well as their possibility to get and secure funding for their innovative R&D (in particular because any process of legislative change might stir up uncertainty and dampen the willingness of financial institutions to invest). They also highlight that EU-manufactured generics are likely to compete for market shares in unprotected markets with the original brands and thus decreasing the actual or projected market share of these SMEs products.

As indicted above, these concerns may however be overstated, as the economic impact on originators of the introduction of a manufacturing waiver would be minimal (SPC holders maintain full SPC-related market exclusivity in the Union). Despite the waiver, the global IPR protection and enforcement framework in the EU would remain the strongest worldwide.

[75] The Italian association Aschimfarma has indicated that its members exported products to the value of EUR 150m to Brazil, China, Russia and Mexico in 2016-17.

Three **associations representing patients and doctors** favoured an SPC manufacturing waiver on the grounds that it would promote early competition in the market, and thus more affordable medicines. Some replies from public authorities claim that there is an increasing dependency on imports of medicines and APIs. Increased dependency on non-EU sources has already led to stakeholder concerns with regard to maintaining security and quality of supply in the Union (as discussed in section 2.3).

Shifting part of the production established under this export waiver on EU *day-1* into the EU (in cases where it is possible to quickly scale up the production to meet the demand), could improve the timely entry of generics and biosimilars into the EU market.

It should be recalled however that EU-based manufacturers of generics and biosimilars could also achieve additional sales from exports to Member States where SPC protection has not been obtained. However, such a situation could in practice be easily prevented by SPC holders by extending SPC protection to all Member States. At some point in the future, the possible introduction of an EU unitary SPC title would also be relevant in this context.

Many stakeholders consider that an amendment of the SPC Regulation to introduce an export-only waiver would not imply any implementation costs for the EU budget, Member State authorities or manufacturers of generics and biosimilars.

6.4. Impact of option 2-bis: SPC manufacturing waiver for export purpose with anti-diversion measures

6.4.1. The risk of diversion

One of the reasons raised by SPC holders to oppose the introduction of an SPC manufacturing waiver is the potential risk of illicit diversion onto the EU market, or onto foreign markets still protected, of generics and biosimilars manufactured in the EU under the waiver (58 of 71 originator respondents to the public consultation expressed this concern). Today, any generic or biosimilar product found on the territory of a Member State where an SPC is in effect is considered, by default, to infringe the SPC. With a waiver, this would not necessarily be the case anymore, which these stakeholders consider might make the identification of infringing products more difficult.

Other respondents to the public consultation (coming notably from the generics/biosimilars industry) consider this risk to be low, given that:

- The supply of medicines is highly regulated by the EU acquis on falsified medicines (Directive 2011/62/EU), which includes:
    - Obligatory safety features – a unique identifier and an anti-tampering device - on the outer packaging of medicines;
    - A common, EU-wide logo to identify legal online pharmacies;
    - Tough rules on the import of active pharmaceutical ingredients;
    - Strong record-keeping requirements for wholesale distributors.
- The EU Bolar patent exception also created a type of manufacturing waiver in 2004 for regulatory approval purposes for generics and biosimilars (not for export or stockpiling purposes), and no particular illicit diversion of products has been reported in this context.

– Already today, generics and biosimilars could potentially try to enter '*at risk'* (i.e. in breach of existing IP protection in the EU) the EU market via imports from unprotected third countries.

6.4.2. Possible anti-diversion measures

While opinions regarding the risks of diversion differ, anti-diversion measures could be envisaged in order to minimise any additional risk of diversion and provide additional transparency. This would work to the benefit of originator companies, by reducing the risk of exposure to IP infringements compared to the situation today.

Over 70% of SPC-holding companies who responded to the Max Planck Institute's survey favoured four different types of anti-diversion measures in the event that a manufacturing waiver were to be introduced in the EU:

(a) Compulsory special labelling for the products produced under the waiver

This would require generics/biosimilars manufacturers to affix clear indications or labelling on the product packaging manufactured under a waiver, for export purposes (and/or stockpiling purposes under policy options 3 and 4)

That special labelling should not conflict with existing labelling requirements for medicines in export markets. For example, in the case of medicines for the EU market, Article 54 of Directive 2001/83/EC sets out the labelling requirements for medicines.

This labelling option was also favoured by SPC-holders and generic/biosimilars manufacturers (over 70% for both categories), should a waiver be introduced.

However, while such labelling can be expected to be effective in respect of products to be exported under an export waiver (option 2), it appears to be less necessary in respect of products to be stockpiled for EU *day-1* entry (options 3 and 4 below) given the already strict traceability requirements imposed by the Directive 2011/62/EU on falsified medicines.

Regarding the costs associated with special labelling, the sector is already subject to traceability measures in the EU under that Directive. As a proxy for estimation of the cost of labelling, the evaluation of Regulation 953/2003 to avoid trade diversion into the EU of certain key medicines[76] found that a pharmaceutical company incurred costs of circa EUR 200 000 between 2003-15 for adding a logo on its packs. However, that cost included significant fees derived from the obligation of getting regulatory authorities to amend/extend marketing authorisations for the medicines due to a change of packaging (which might not be necessary to implement this option).

(b) Ex-ante information

This would require generics/biosimilars manufacturers to notify SPC holders, or a public body (e.g. by Member State bodies), of their intention to rely on the waiver

[76] https://ec.europa.eu/transparency/regdoc/rep/10102/2016/EN/10102-2016-125-EN-F1-1.PDF

– possibly with a specification of the quantities and destinations – before starting manufacturing[77].

This option would create a slight additional administrative burden for generics/biosimilars manufacturers, and might create confidentiality issues if overly detailed information was required from such manufacturers.

A notification – combined with the timely publication of the related information – would be beneficial for SPC holders, as it would increase transparency and legal certainty, and facilitate identification by them of possible instances of illicit diversion, as they would have information regarding a manufacturer's intention to use a waiver in respect of a product. An advantage of such notification requirements for generics/biosimilars manufacturers is that the public body to which notifications were sent could publish the notifications, or alternatively give them, under request, to a court (or an equivalent body) in the event of litigation, so as to demonstrate the manufacturer's good faith.

In addition, a further safeguard would be the legal obligation on the manufacturer, pursuant to existing IPR enforcement legislation, to ensure that products are not released on the domestic market prior to expiry of the SPC.

(c) Ex-post notification

This would require generics/biosimilars manufacturers to inform SPC holders, or a public body, that they have manufactured products under the waiver, for export purposes (and/or stockpiling purposes for options 3 and 4) – possibly with a specification of the quantities and destinations. SPC holders could effectively use the information to prepare customs 'applications for action' aiming to prevent re-imports.

The assessment is similar to preceding point b, with slightly increased (ex-post) transparency for originators and an increased administrative burden for generics/biosimilars manufacturers.

(d) Shifting the burden of proof for infringement from SPC holders to generic manufacturers

This would require generics/biosimilars manufacturers, when they are found to have manufactured, in a territory where an SPC is in effect, a product covered by an SPC, to prove that the product is intended for export, failing which the product would not enjoy the waiver.

Any legislation introducing an SPC manufacturing waiver, if accompanied with anti-diversion and transparency measures, would take due account of the cost of such measures (e.g. operative cost, administrative burden), which could potentially have a dissuasive effect regarding the actual use of the waiver. The cost of anti-diversion measures would be negligible for major manufacturers, but it could have a more significant impact on SMEs.

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[77] The draft final report of *Max Planck Institute* study states that the SPC holder would, in that basis, be in a better position to monitor the market for possibly infringing products. A corresponding solution was developed in CJEU case law concerning repackaging of branded goods in the context of parallel imports (C- 102/77 (para. 14); C-427/93 (para. 78); C-348/04 (para. 64)).

6.4.3. *Retained anti-diversion measure for option 2-bis*

In view of the above analysis, the preferred anti-diversion measure for this option 2-bis (an SPC manufacturing waiver for export-only purposes with anti-diversion measures) would be a legal obligation to label products produced under the waiver, and a requirement for any manufacturer of generics or biosimilars intending to make use of the waiver to notify this intention to a Member State public authority, which would publish that information.

This labelling would allow effective and easy identification of generics/biosimilars to be exported under the waiver, and to check whether they are genuinely in the process of being exported. This labelling should be removable once the products have been exported outside the EU, in order not to conflict with any labelling requirement in the countries of destination, nor interfere with possible repackaging.

The notification requirement would improve transparency for SPC holders. A manufacturer to public authority notification would reduce the risk of collusion between the SPC-holder and potential manufacturers vis-à-vis the option of a manufacturer-to-SPC-holder notification.

This approach appears to be cost-effective and proportionate, and is favoured by SPC holders as well as manufacturers of generics/biosimilars.

An amendment of the SPC Regulation to introduce an export-only waiver with anti-diversion measures would not imply any implementation costs for the EU budget and very limited costs for Member State authorities, in relation to receiving the notifications of the intention of firms to use the waiver, publishing the information, and providing it, under request, to a court in the event of litigation. As discussed above, the measures should take into account the potential cost of implementation on manufacturers of generics and biosimilars, especially for SMEs.

6.5. Impact of Option 3: SPC manufacturing waiver for stockpiling purposes

The impact of this option has been analysed and addressed by the studies contracted by the Commission. It should be noted that stakeholder studies have focused mostly on an export-only waiver.

Generics and biosimilars manufacturers consider that a stockpiling waiver would greatly contribute to level the playing field between the manufacture of generics and biosimilars in the EU versus manufacturers based in third countries with regard to timely EU *day-1* entry. According to the inputs provided to the public consultation, 53 out of 63 respondents representing generics and biosimilars companies (3 respondents deny this problem, and 3 do not know) consider that SPCs disadvantage EU-based generics and biosimilars manufacturers compared with those based in countries with no SPC when placing their products on the market in the EU immediately after the SPC expires. 41 submissions by generics and biosimilars companies indicate that they have obtained marketing authorisation(s) in the EU before the expiry of the SPC of the reference medicine (under the Bolar exemption). Many of them would be also interested in complementing their 'early' marketing authorisations with the possibility of manufacturing for stockpiling purposes (i.e. during the SPC term of the reference medicine) in view of timely entry of their products onto the EU market, or some other mechanism that would have an equivalent effect.

This stockpiling waiver would also support EU generics/biosimilars manufacturers that are only interested in selling within the EU. In this regard, 3,372 pharmaceutical SMEs manufacture in the EU, 1,765 of those SMEs export, and 1,362 of them export outside the EU.

As discussed under option 2, originators' submissions to the consultation oppose the introduction of any type of SPC waiver.

The CRA study estimates that an SPC waiver for stockpiling purposes would result in savings on pharmaceutical expenditure from this earlier competition and therefore lead to a speedier reduction of prices in Member States upon expiry of the SPC. CRA conducted a simulation of the impact on pharmaceutical expenditures on the basis of observed delays in generic and biosimilar entry during a sample period (Q1 2008 to Q3 2014) if such delays were reduced by up to 6 months. Their analysis indicates that if generic entry were brought forward by 6 months, savings on pharmaceutical expenditure would amount to EUR 1.1bn over a three-year period for the sample examined, due to the faster decline in prices, corresponding to a 4% saving. Regarding the biologics market, savings would amount to EUR 15m over a three-year period for a limited sample of 17 molecules examined, which corresponds to a 1% saving (it should be noted that as biosimilar penetration increases over time, the beneficial effects on pharmaceutical expenditure would also increase).

However, from the perspective of pharmaceutical expenditure, it could be argued that, in the medium to long term, timely entry of generics and biosimilars in the EU would tend to happen anyway from non-EU based producers under the baseline scenario (i.e. without any waiver). Therefore, in the long term, and disregarding concerns related to the strength and diversification of the supply chain, the stockpiling feature may not necessarily have such a significant impact on savings to the health systems of those Member States with a sizable national market.

Patients, as indicated above, would enjoy additional sources of supply of medicines with this stockpiling waiver. As explained under option 2, a few patient and health practitioner groups, as well as public health institutions, favoured the SPC manufacturing waiver on the grounds that it would facilitate access to more affordable medicines.

As mentioned above, such a waiver could potentially reduce the risk of relocation, not only of manufacturing, but also of R&D (in the biologics/biosimilars sector).

Since a stockpiling-only waiver would likely improve the timely entry of EU-manufactured generics and biosimilars, it could tackle – similar to an export waiver – the concerns expressed by some public authorities and citizens about over-reliance of imported medicines analysed in option 2 above.

An amendment of the SPC Regulation to introduce this stockpiling-only waiver would not imply any implementation costs for the EU budget and Member State authorities.

6.6. Impact of Option 3-bis: SPC manufacturing waiver stockpiling purposes with anti-diversion measures

The labelling measures proposed for option 2-bis above (waiver for export-only purposes with anti-diversion measures) might be unnecessary for this option 3-bis (stockpiling for entry in the EU market) in view of the strict traceability requirements imposed by Directive 2011/62/EU on falsified medicines.

Among the anti-diversion measures discussed in subsection 6.4.2, the preferred one for this option 3-bis would be a legal obligation for the manufacturer to notify a public body (e.g. a public authority of the Member State of establishment of the production facility) of the launch of production for stockpiling purposes. That public body would publish the content of the notification, or store it and provide it, under request, to a court in the event of litigation. This would be a simple notification, not generating significant burden or cost on the applicant or the public body.

An additional safeguard for a manufacturing waiver for stockpiling purposes could consist of confining the effect of the waiver to the final months of the term of the SPC of the reference medicine.

The introduction of a stockpiling-only waiver with the preferred anti-diversion measure above would imply a negligible cost in additional administrative capacity in for the public body charged with receiving, publishing and dispatching (by a court order) the notification.

6.7. Impact of Options 4 and 4-bis: SPC manufacturing waiver for export and stockpiling purposes (with anti-diversion measures)

An SPC manufacturing waiver for both export and stockpiling purposes would address both identified problems (manufacturing for export purposes and for timely entry into EU *day-1* markets). The implications of these options 4 (and 4-bis) stem from the combination of effects described for options 2, 2 bis, 3 and 3 bis above.

Options 2 to 4 would be especially beneficial for EU SMEs manufacturing generics or developing biosimilars, because they do not necessarily have access to the necessary funding or skills to outsource or delocalise production outside the EU.

Anti-diversion measures in options 2-bis, 3-bis and 4-bis should take account of potentially dissuasive costs for SMEs (additional operational costs (e.g. labelling), the need to contract specialised attorneys (e.g. for potentially complex notification procedures, and court proceedings).

The preferred anti-diversion measure for this option 4-bis would be a combination of the preferred measures for options 2-bis (external labelling and notification for production for export purposes) and 3-bis (notification for production intended for stockpiling).

6.8. Impact of the options for the timing of the introduction of the manufacturing waiver

Scenario 1 (namely immediate application to all SPCs, including those which are *already in effect* when the waiver is introduced): the manufacturing waiver could arguably be viewed as a clarification of the initial objective of SPC protection (which, as explained above, was never intended to prevent exports outside the EU nor *day-1* entry onto the EU market after SPC expiry). This could justify its immediate entry into force, as happened with the EU Bolar patent exemption in 2004. However, this approach is not preferred, as it might negatively affect the acquired (property) rights and legitimate expectations of SPC holders. In addition, it is not considered useful since, in respect of SPCs already having taken effect, it would be late at that stage for generics/biosimilars manufacturers to make investment decisions (especially for export purposes).

These objections are also, to a certain extent, valid for **scenario 2** (namely application only to granted SPCs which will enter into effect after the waiver is introduced), and therefore this scenario is not preferred either.

Scenario 3 (namely application only to SPCs which *will be granted* after the waiver is introduced) would strike an appropriate trade-off, by making the waiver applicable to specific SPCs within a reasonable timeframe without affecting SPCs already granted, or granted and having taken effect. Under this scenario, while only a limited number of SPCs would benefit from the waiver in the first years, the introduction of a waiver in EU SPC legislation would already send a clear political signal, and affect investment decisions by manufacturers of generics/biosimilars (and reduce pressure to relocate outside the Union) well before the waiver starts to become actually applicable to a significant number of – and eventually all – SPCs. This scenario would apply to pending SPC applications, but a short transition period could provide an appropriate solution here.

Scenario 4 (namely application only to SPCs *which will be applied for* after the waiver is introduced) would result in the waiver only becoming applicable to a substantial percentage of all SPCs only after many years. This solution would not address the problems at hand in the short to medium term, and is thus not preferred, considering the urgency to act.

7. HOW DO THE OPTIONS COMPARE?

Table 7.1 provides information comparing the policy options in the light of the criteria of effectiveness (how each option achieves the specific objectives) and efficiency (cost-benefits analysis).

Table 7.2 compares the impacts of the policy options on stakeholders. (See also Annex 16 for the SME test.)

For the proportionality assessment and coherence of the preferred option (option 4-bis) see section 8 below.

None of the options considered can be implemented by Member States individually in a satisfactory matter. The problems identified are of an EU dimension. Member States taking unilateral action would lead to a distortion of the single market for pharmaceuticals, one of the core objectives of the exiting SPC Regulation.

Table 7.1: Comparison of policy options against effectiveness and efficiency criteria

(Note: 'G/B' = generics/biosimilars)

	Effectiveness		**Efficiency**
	Objective 1: Allow G/B export during the SPC term	**Objective 2:** Allow timely EU market entry *from day-1*	
Option 0	(0)		--
Option 1: voluntary industry-led agreements	**(≈)** Such agreements would not necessarily be available for all G/B manufacturers, as each agreement would require case-by-case negotiation. Risk of delays in starting exports (SPC holder can file appeals or delay negotiations). This uncertainty would likely prevent G/B manufacturers from making upfront investment decisions (in the EU) based on the hypothetical possibility that such agreements might be made in some cases several years later.		**Net effect (≈)** **Benefits (≈):** No major changes expected in investment in the EU. Delocalisation and losses of jobs in the EU G/B sector will continue. **Cost (≈/-):** It might need the support/involvement of national administrations (e.g. mediation, appeals to be handled by courts). Originators might require the payment of royalties by G/Bs

Option 2: SPC manufacturing waiver for <u>export</u> purposes	**(++)** EU-based G/Bs could export without any prior authorisation (no risk of delays as in option 1 above)	**(+)** For some products, the EU G/B manufacturing capacity established for export could be quickly switched for *day-1* entry in the EU.	**Net effect (+)** • CRA study (see revised by OHE): Increase of the EU pharmaceutical trade balance by EUR 6 -10bn over 10 years for a sample of molecules representing 32% of the relevant market; > 20 000 additional jobs for that sample. **Benefits (+)**: More exports, and – to a certain extent – improved EU *day-1* entry. More investment in the EU (jobs in manufacturing, and in biosimilars R&D). Implementation does not require public funding. • CRA study (see revised by OHE): Increase of EU exports of generics/biosimilars by EUR 8-10.6bn over 10 years for a sample of molecules of molecules representing 32% of the relevant market; > 20 000 additional jobs for that sample. • CRA study: in term of improving EU *day-1* entry, it is estimated that bringing forward by 6 months the entry of the generics/biosimilars sample implies EUR 1.1bn savings to the pharmaceutical health budget over 3 year. **Cost (≈)**: Illicit generics/biosimilars diversion (counterfeiting risk) would not significantly increase. Erosion of jobs in innovators limited compared with the new opportunities in generics/biosimilar sector. • CRA study: decrease of EU SPC holders' exports of EUR 0.14 - 0.28bn over 10 years for a sample or 117 non-biologics, and 0.8 - 1.7bn losses for 17 biologics; • OHE estimates EUR 0.3 to 0.6bn losses in the non-biologics segment (Note: the EU pharmaceutical industry exported EUR 220bn in 2016 with steady growth (EFPIA datacentre)).
Option 3: SPC manufacturing waiver for <u>stockpiling</u> purposes	(0)	**(++)** *Day-1* entry onto the EU market would be ensured or accelerated	**Net effect (+)** CRA study estimates benefits in terms of savings for EU public health budgets expenditure in pharmaceuticals of up to 8% for the analysed sample (Bringing forward by 6 months the entry of the generics/biosimilars sample implies EUR 1.1bn savings over 3 years). **Benefits (+):** More investment in the EU (jobs in manufacturing, and in biosimilars R&D). Additional savings for health authorities due to more efficient EU *day-1* entry. Implementation does not require public funding. CRA study estimates benefits in terms of savings for EU public health budgets expenditure in pharmaceuticals of up to 8%. **Cost (≈):** Risk of illicit diversion onto SPC-protected markets could increase. Erosion of jobs in innovators limited compared with the new opportunities in the G/B sector.

Option 4: SPC manufacturing waiver for <u>export</u> and <u>stockpiling</u> purposes	(++) A waiver for export and stockpiling purposes would fully solve both problems.	**Net effect (++)** • As in option 2 and option 3 **Benefits (++):** More investment in the EU (jobs, as above). Additional savings for health authorities due to more efficient EU *day-1* entry. Implementation does not require public funding. • As in option 2 + option 3 **Cost (≈):** Risk of illicit diversion onto the EU could increase. Erosion of jobs in innovators limited compared with opportunities in the G/B sector. • As in option 2 above
Options *2 bis, 3 bis* and *4 bis*: SPC manufacturing waiver (for export and/or stockpiling purposes) with <u>anti-diversion measures</u>	Same efficiency as corresponding option 2 (**(++)/(+)**), option 3 (**(0)/(++)**) and option 4 (**(++)/(++)**), provided that the anti-diversion measures are not overly costly or burdensome.	**Net effect (++)** • As in option 2, 3 or 4. **Benefits (++):** As in options 2 to 4 if the anti-diversion measures are not too costly or burdensome (especially for SMEs). • As in option 2, 3 or 4. **Cost (≈):** The risk of illicit diversion would be virtually absent (i.e. unchanged). Negligible increase of administrative costs for the parties (including public administrations) related to the anti-diversion measures. • As in option 2, with negligible additional costs for generics/biosimilars manufacturers (and public authorities) to implement anti-diversion measures.

Table 7.2: Comparison of the impacts of policy options on stakeholders

Notes: (1) 'G/Bs' = generics/biosimilars manufacturers; (2) Originators also develop biosimilars.

Stakeholders → Policy options ↓	**EU-based G/BMs** (attention to SMEs)	**SPC holders**	**EU patients and Member States health budget**	**EU citizens as employees**	**EU regulatory experts/agencies**
Option 0 / **Baseline**	0	0	0	0	0
Option 1: voluntary industry-led agreements	**(0/≈)** They will continue to have strong incentives to delocalise/outsource production (if not R&D, especially for biosimilars) to third countries that resist the introduction of EU-type SPC. Possible payments to originators (royalties)	**(0/≈)** Minor changes Slightly increased competition from EU G/Bs in some cases, but only when an agreement is agreed, and possibly compensated by royalties. They could get possible royalties.	**(0/≈)** Minor changes See positive effects as in the options 2 to 4 below, but only limited to a few cases and in a few Member States (when and where agreements are reached).	**(0/≈)** No significant improvements in job opportunities in the EU G/Bs industry	**(0)** Not much effect in limiting the risk of losing the predominant role and influence of the EU rules on the global regulatory environment, especially for biosimilars
Option 2: Introduce an SPC manufacturing wavier for <u>export</u> purposes only	**(++)** A legal barrier to investment in generics/biosimilars production in the EU would be lifted (also positively affecting biosimilars R&D). Contrary to option 1 above, they would not face uncertainty by linking upfront investments on hypothetical future voluntary agreements. **Estimated benefits** (i.e. additional exports) for a sample (32% of the relevant market): EUR 7.6bn in generics, EUR 1.2 to 2.1bn in biosimilars (CRA study); or EUR 2-3bn (OHE-EFPIA).	**(≈/0)** Their SPC-protected sales would not be affected. They are massively entering in the business of biosimilars and they can also benefit from production in the EU. With the export waiver, in the short term they would face earlier additional competition from EU-based G/Bs in off-patent export markets. With the stockpiling waiver, in the short term they would face earlier additional competition from EU-based G/Bs in off-SPC EU market. However, in the medium/long term they will anyway face competition from non-EU-based biosimilars. By limiting the risk of delocalisation of generics, originators will find more opportunities of manufacturing production in the EU. **For an export waiver, estimated lost sales by SPC holders** (for a sample of 32% of the relevant market)[78]: • EUR 139 - 278m for non-biologics and EUR 868m – 1,7bn for biologics (CRA study); • EUR 191 - 573m (OHE-EFPIA) for non-biologics. If the waiver is accompanied by anti-	**(+)** They would enjoy some improvement in better timely access to generics/biosimilars of high EU-made quality, and therefore a more diversified source of supply.	**(+)** More investments and jobs opportunities in the generics/biosimilars sector in the EU. This would overcome any potential losses, in the short term, in the innovators sector (in the medium/long term innovators will face competition from biosimilars exported from third countries). Originators will also create jobs for their biosimilars activities in the EU and can benefit from this option.	**(≈)** It would limit the risk of losing the predominant role and influence of the EU rules on the global regulatory environment, especially for biosimilars.
Option 3: Introduce an SPC manufacturing wavier for <u>stockpiling</u> purposes only	**(++)** As in option 2 above. The stockpiling option would be an additional incentive for generics/biosimilars investment in the EU.		**(++)** The stockpiling feature would bring additional time gains for timely access in the EU *day-1*, and a more diversified source of supply.		

[78] The Pugatch study estimates that between 0.61% and 1.04% of global sales of originators would be opened to competition, as opposed to sales actually lost.

Stakeholders → Policy options ↓	EU-based G/BMs (attention to SMEs)	SPC holders	EU patients and Member States health budget	EU citizens as employees	EU regulatory experts/agencies
		diversion measures, this would decrease the current exposure of originators to IP-infringements (and therefore lead to clear benefits also for this industry).			
Option 4: Introduce an SPC manufacturing wavier for export and stockpiling purposes	The impacts of options 2 and 3 would be cumulative				
	Estimated benefits (additional sales in the EU market in addition the additional export sales estimated in option 2): Exceeding the above figures which relate to an export-only waiver.		**Estimated savings** on public health budgets expenditure on pharmaceuticals of up to 8 % (CRA study).	Estimated impact on **employment by EU-based G/B firms**: For the sample considered CRA estimate an increase of 20 000 – 25 000 direct jobs. OHE-EFPIA estimates a net increase of pharmaceutical jobs of 2,837 to 9,430 (assuming 10% loss of sales for originators).	

8. PREFERRED OPTION

8.1. Preferred option

The preferred option of this impact assessment is option 2-bis, namely amending Regulation (EC) No 469/2009 to introduce an SPC manufacturing waiver for export purposes, accompanied by anti-diversion measures. This option is considered to be the most balanced and proportionate approach, which also takes account of the views and concerns of both generic/biosimilar firms and originator firms, in a field that is particularly sensitive.

This would fully address the first identified problem (loss of export markets) and would address, to a certain extent, the second identified problem (lack of timely EU *day-1* entry).

The preferred anti-diversion measures would be:

- compulsory labelling; and
- compulsory notification to a public body of the intention to manufacture products pursuant to the waiver.

With an SPC manufacturing waiver for export purposes, the accompanying anti-diversion requirements would constitute an effective means to allow for easy identification of any generics/biosimilars illicitly diverted onto the EU market during the SPC term (instead of being exported). This would work to the clear advantage of the entire EU pharmaceutical industry, including originators. I t would clearly be in the interest of the manufacturer to label and notify its intention of relying on the waiver. It goes without saying however that if the manufacturer were tempted to illicitly divert part of the production onto the EU

market during the SPC term, the products could then be deemed, by default, as IP-infringing. Labelling and notification requirements constitute a guarantee for SPC holders and were suggested by stakeholders during the consultation conducted by Max Planck Institute for the Commission in the context of the contracted study on the legal aspects of the EU SPC.

The preferred option 2-bis appears the most proportionate to achieve, in a satisfactory manner, the objectives pursued by this initiative taking into consideration the interests and concerns of all parties, for the following reasons:

(1) It is a realistic measure, and more effective than option 1 (i.e. industry-led agreements) that can be unilaterally refused by SPC holders, or for which each individual implementation can be subject to appeals or overly lengthy negotiations;

(2) It is a simple and non-costly measure for stakeholders and Member State authorities to implement;

(3) It could deliver potential early effects for investments and growth in the sector;

(4) Its effectiveness to achieve both objectives, and its efficiency, will be easy to monitor (see next sub-section);

(5) The anti-diversion measures will also add transparency to the pharmaceutical system in the EU;

(6) It does not have any impact on overall SPC protection within the EU (i.e. SPC holders would continue to enjoy their market exclusivity in the EU until *day-1*), and any risk associated with illicit diversion onto the EU market is minimised with anti-diversion measures;

(7) The administrative costs for the Commission to adopt the legislative proposal and for future monitoring and evaluation purposes would not require any new budgetary commitment.

Insofar as the objective of promoting the swift entry of EU-made generics and biosimilars onto the EU market immediately after SPC expiry (i.e. on *day-1*), this objective would be achieved, to a certain extent, for manufacturers having set up manufacturing capacity for export purposes (recalling that 1 362 EU-based pharmaceutical SMEs already export outside the Union, see Annex 16), as they might be able, after SPC expiry, to use the same manufacturing capacity (or scale it up) with a view to swiftly supplying the EU market.

Coherence of each option with other EU policies objectives

Regarding the coherence of each option with other EU policies objectives, it is compatible with **health** policies (including taking due account of regulatory labelling requirements). The preferred option would also be consistent with EU pharmaceutical legislation. All obligations flowing from that body of law also apply to manufacturers that would take advantage of the derogation introduced by the waiver. In particular, this proposal would not affect the existing EU rules and safeguards laid down in Directive 2011/62/EU amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, with regard to the prevention of the entry into the legal supply chain of falsified medicinal products, and as laid down in EU legislation on civil and customs enforcement of intellectual property rights (namely Directive 2004/48/EC and Regulation (EU) No 608/2013). Furthermore, this initiative does not provide for any derogation from, and is applied without prejudice to, the applicability of

all relevant Union pharmaceutical legislation on the manufacture of generics and biosimilars, including Directive 2001/83/EC on the Community code relating to medicinal products for human use, as amended, and Commission Delegated Regulation (EU) No 2016/161 on the rules for the safety features, which lay down stringent standards regarding the identification and monitoring of certain medicines placed on the market in the Union in order to guarantee the reliability of the supply chain and to safeguard public health.

An SPC manufacturing waiver would not contradict EU **trade** policy, because it is not a protectionist measure for EU companies:

- The aim is to *level the playing field* regarding the manufacturing of generics and biosimilars in the EU (whether the manufacturer is an EU or non-EU company) vis-à-vis third countries-based manufacturing. It is about improving the competitiveness of the EU as a hub for the pharmaceutical industry.
- The waiver co-exists with ongoing efforts from the EU to continue to export its SPC model of protection to third countries via FTAs.

This proposal complements the Union's trade policy approach overall and is consistent with existing international trade agreements, such as the *Agreement on Trade-Related Aspects of Intellectual Property Rights* (TRIPS) between members of the World Trade Organisation (WTO), as well as those free trade agreements that the EU has concluded with third countries and which foresee protection of the nature of the EU supplementary protection certificate.

Table 8: Summary of the costs and benefit of this preferred option

Stakeholders	Costs	Benefits	Likelihood of the benefits
EU based manufacturers of generics and biosimilars	**(≈)**	(++)	Very high. They can invest in the EU with full certainty that their EU production can enter on *day-1* global and EU markets
3rd-country based manufacturers of generics and biosimilars	**(0)**	**(0)**	They will face additional competition from EU manufacturing. However, the global demand for medicines is high and they will continue to have a strong demand
SPC-holders	**(≈)**	**(≈)**	**(≈)** In the short run (while the biosimilar capacity is built in third countries) they can see additional competition on off-patent/SPC markets due to the EU generics/biosimilars exports. Their EU sales during the EU SPC term would not be affected SPC-holders also manufacture biosimilars and can benefit from the waiver in some cases, and from a stronger industrial base in the EU Anti-diversion measures will offer additional protection against IP infringements SPC-holders are currently facing
EU patients and health budgets	(0)	(+)	They can benefit from a more robust supply of medicines, and a more geographical diversification of the supply
EU employees	(0)	(+/++)	High for developers and manufacturers of biosimilars and generics. Negligible, especially in the medium and long term, for jobs in the SPC-holders sector. SPC protection in the EU is not affected, SPC holders will face competition abroad either from EU-based or third-country based

			manufacturers, and SPC-holders can also create jobs for their biosimilars manufacturing activities in the EU
EU regulatory expertise	**(≈)**	**(≈/+)**	Limit the risk of losing the predominant role of the EU rules on global regulatory environment
EU R&D	(0)	(+)	Positive impact on biosimilars R&D, which requires investments of several hundred million euro per biosimilar

8.2. REFIT (simplification and improved efficiency)

REFIT considerations are not warranted, as this initiative is not a revision of Regulation 469/2009, but a targeted amendment to tackle the problems identified.

A broader evaluation of Regulation 469/2009 may be considered in the context of the on-going analysis of pharmaceutical incentives requested by the Council in June 2016.

The preferred option is strictly limited to the introduction of an SPC manufacturing waiver, without affecting the other features of the EU SPC regime such as the subject matter of protection and duration, especially since certain CJEU cases related to SPCs are still pending.

9. HOW WILL ACTUAL IMPACTS BE MONITORED AND EVALUATED?

After the entry into force of the preferred option, the Commission will monitor its implementation with a view to assessing its effectiveness.

Given that the manufacturing exemption will apply to the SPC entering into effect, the first evaluation should take place about five years from the entry into force of the exemption. In the first two to three years after the entry into force, the G/B companies can be expected to adjust their investment decisions taking into account the exemption. During this time, no changes in production or exporting activities are expected.

The initiative could be considered as successful if it influenced companies' investment/location decision to produce molecules covered by the manufacturing exemption in the EU without harming the R&D activities of companies developing new medicines. This could be measured by means of a survey among pharmaceutical companies active in the EU.

The table below shows the list of monitoring indicators. As a starting point, the period five years prior to the entry into force of the exemption should be considered. These indicators could be calculated for the EU and compared to other developed economies (e.g. the USA, Canada) taking into account the potential impact of reforms of pharmaceutical patent laws or pharmaceutical entry regulations.

Operational objectives	Monitoring indicators
More manufacturing of generics and biosimilars in the EU	- Trends in the number of EU G/B manufacturing sites - Profile of EU G/B manufacturing sites - information on employment, turnover, R&D as reported in company level databases

More exports of EU-manufactured generics and biosimilars	- Trends in annual exports of EU-based G/B - Analysis of entry of EU branded/manufactured products in export markets for molecules covered by manufacturing exemption in the EU - Analysis of sales dynamics and competition (number and origin of entrants) in export markets for the molecules covered by manufacturing exemption
Timely *day-1* entry in the EU for EU-manufactured generics and biosimilars	- Trends in the number of marketing authorisations of generic and biosimilar products granted to the companies with manufacturing sites in the EU and timing of entry in Member States. This indicator should take into account the size of the company and in case of SME it dependence on the large company - Location of manufacturing for *day-1* entry: trends in manufacturing sites for the molecules covered by manufacturing exemption in the EU and outside

The available data sources include, but are not limited to: Eurostat, OECD, data provided on EMA website, Eudra GMP, databases on pharmaceutical pricing (e.g. IMS Health) or company level databases (e.g. Bureau van Dijk). These sources should allow constructing all the above indicators without the need for any additional reporting by companies.

As regards the benchmark for the monitoring indicators, an increase or no (negative) change to the levels prior to the entry into force could be considered as a success. A counterfactual analysis is required to fully capture the impacts of the proposal.

ANNEX 1: PROCEDURAL INFORMATION

- ***Lead DG, Decide Planning/CWP references***

DG for Internal Market, Industry, Entrepreneurship and SMEs (DG GROW)

- ***Organisation and timing***

The deadline for adoption of a proposal by the Commission is May 2018.

Interservice meetings took place on 31.03.2017, 7.07.2017, 6.12.2017, 6.2.2018, 28.2.2018 and 27.4.2018.

- ***Consultation of the RSB***

An upstream meeting with the RSB took place on 12.1.2018.

This impact assessment was sent to the RSB on 12.2.2018.

A meeting with the RSB took place on 7.3.2018. On 9.3.2018 the RSB delivered a positive opinion with some reservations. The table below clarifies how these reservations have been reflected in the final version of this impact assessment.

RSB comments	***DG GROW's replies***
Main considerations (1) The report does not sufficiently reflect the views and concerns of relevant stakeholder groups, including SPC holders and SMEs.	The views of SPC holders are better reflected (in particular in section 6.3.2), and an SME Test has been included as new Annex 16. Appropriate cross-references to, and content from, new Annex 16 are included through the text of the impact assessment. The content of annex 2 (stakeholders views) has been expended (including specifically description of the SMEs participating in the Commission consultation and their views).
(2) The report does not elaborate all relevant options and their key dimensions, in particular regarding the timing of the waivers.	The description of the options and the analysis of their impact have been expanded; in particular the timing issues are now commented in section sections 5.4 and 6.8) in addition to Annex 10. The notification requirements (safeguards) are better explained in section 6.4.2.
Further considerations and adjustment requirements (1) The different parts of the report (problem description, objectives, impacts) should more systematically reflect the concerns of all stakeholder groups, including the SPC holders. In this regard, it could be useful to revise the	A new paragraph on general objectives has been inserted into section 4.1. The views of SPC holders, including innovative SMEs, are better reflected (in particular in section 6.3.2).

objectives in order to better reflect the importance of the continued protection of patent rights.	The content of annex 2 (stakeholders views) has been expended.
(2) The analysis should better reflect the strengths and weaknesses of the key studies. In addition, it should clarify the robustness of the cost and benefit estimates.	Annex 12 provides a summary of the eight studies evaluating the impact of the manufacturing waiver. The main strengths and weaknesses of each study are discussed in detail, and a table recapping a comparison of all studies has been added.
(3) The set of options should be more complete and detailed. The main report should include the options for the timing of the introduction of the manufacturing waiver. This is currently analysed in an annex. The report further needs to consider differentiating the options on the duration of the stockpiling waiver in comparison with the duration of the export waiver. It should also consider the accompanying use of a soft-law approach for some options.	The timing considerations have been summarised in the main text (see sections 5.4 and 6.8) in addition to Annex 10. Section 6.4.2 on possible anti-diversion measures has been strengthened. Clearer explanations have been provided (section 6.5) regarding the stockpiling, including the possibility (and rationale) of limiting the stockpiling waiver to the last months of the term of the SPC. The use of soft law has also been considered.
(4) The report should better explain the potential impacts of the manufacturing (notably of the stockpiling) waiver with regard to the EU's trade policy and to the compatibility with WTO-TRIPS provisions.	International issues (including TRIPS and FTAs) have been addressed in a more detailed way (cf. Sections 6.3.2 and 8.1).
(5) The impact assessment should include a more comprehensive analysis of costs and benefits of the proposed options for SMEs. It should also better reflect SME views on the different options and their potential impacts.	Impacts on SMEs have been analysed in a more detailed way in the main text as well as in Annex 16, which provides a specific 'SME test'.
(6) The report should include a proportionate evaluation of the specific effects of the SPC legislation, covering both the origins of the SPC legislation as well as the intended and unintended consequences of it. It should also explain the timing of the more comprehensive evaluation of the Intellectual Property Rights framework for medicinal products. In addition, it should clarify the REFIT dimension of the initiative, i.e. examine potential for simplification and burden reduction.	This initiative is not about reviewing the SPC system in general. Such a review is still ongoing, and is related to a wider review of pharmaceutical incentives asked for by the Council.

- ***Evidence, sources and quality***

DG GROW has conducted and contracted several studies related to SPCs in the context of the *Single Market Strategy* (the first 3 studies were published together with the SPC online public consultation):

- A study contracted to Charles River Associates (CRA) on '*Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*'[79] (CRA study – 2016);
- An in-house DG GROW analysis of the SPC framework in the EU: '*25 years of SPC protection for medicinal products in Europe: Insights and challenges*'[80] (Mejer study – 2017);
- A study on the economic aspects of the SPC: '*Economic Analysis of Supplementary Protection Certificates in Europe*' (Kyle study - 2017)[81];
- A study on the legal aspects of the SPC awarded to the *Max Planck Institute* (MPI);
- A study analysing the combined effect of pharmaceutical incentives in Europe, realised by Copenhagen Economics.

In addition, the following eight studies evaluating the impact of manufacturing waiver were sponsored by generic/biosimilar stakeholder and SPC-holders:

- Vicente, V., & Simões, S. (2014). *Manufacturing and export provisions: Impact on the competitiveness of European pharmaceutical manufacturers and on the creation of jobs in Europe*. Journal of Generic Medicines (BluePharma)
- Roland Berger (2015), *Extension of the Bolar exemption regarding production for export and launch preparation*. (Pro Generica)
- Nomisma (2015), *The generic drugs system in Italy. Scenarios for sustainable growth*. (Assogenerici)
- Sussell, J. A., Tebeka, M. G., Jena, A. B., & Vanderpuye-Orgle, J. (2017), *Reconsidering the economic impact of the EU manufacturing and export provisions*. Journal of Generic Medicines (AbbVie)
- Logendra and Troein (2017), *Assessing the impact of proposals for a Supplementary Protection Certificate (SPC) Manufacturing Exemption in the EU*. Quintiles IMS (EFPIA)
- Pugatch Consillium (2017), *Unintended Consequences* (AbbVie, La Roche & US Chamber of Commerce)
- Office of Health Economics (2018), *Review of CRA's Report* (EFPIA)

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[79] https://publications.europa.eu/en/publication-detail/-/publication/6e4ce9f8-aa41-11e7-837e-01aa75ed71a1/language-en

[80] https://ec.europa.eu/docsroom/documents/26001/attachments/1/translations/en/renditions/native

[81] https://ec.europa.eu/docsroom/documents/25621/attachments/1/translations/en/renditions/native

– European Economics (2018), *Impacts of Reducing Patent and Extended Protections against Manufacturing for Stockpiling and Export* (EuropaBio).

Annex 12 critically discusses main strengths and weaknesses of the studies evaluating impact of manufacturing waiver.

ANNEX 2: STAKEHOLDERS' VIEWS

consultationJanuary[82]A total of 231 replies were provided to the on-line consultation: 43 replies from the general public, 71 from originators industry/associations, 63 from generics and biosimilars industry/associations, 15 from health authorities/doctors/patients groups (mostly from national organisations dealing with health insurance/reimbursement/health technology assessment, from a doctors' organisation, and 2 from patients' associations), 34 from patent offices/practitioners, and 5 from industry/trade authorities.

The statistics corresponding to respondents identified as SMEs or start-ups are the following:

- Among the 63 respondents defining themselves as mostly manufacturers of generics/biosimilars, 12 respondents identified themselves as an SME and one as a start-up;
- Among the 71 respondents defining themselves as mostly originators, 2 respondents identified themselves as an SME involved in medicines biotechnology and one as a start-up in the field of bio-pesticides.

In addition, several pharmaceutical associations (Medicines for Europe, EUCOPE, and EuropaBio) also represent pharmaceutical start-ups and SMEs and conveyed SME views both by responding to the public consultation and/or by sending position papers to the Commission services. The input of these position papers is taken into account in this summary of replies.

- **Views expressed by generics/biosimilars manufacturers**

Most generics/biosimilars ('G/B') manufacturers support the introduction of a manufacturing waiver, considering that:

— SPCs disadvantage EU-based G/B manufacturers compared with those based in countries with no SPC when exporting G/Bs outside the Union. This problem is confirmed by 56 out of 63 G/B respondents (1 respondent denies this problem, and 2 do not know).

— SPCs disadvantage EU-based G/B manufacturers compared with those based in countries with no SPC when placing G/Bs on the market in the EU immediately after the SPC expires; this problem is confirmed by 53 out of 63 G/B respondents (3 respondents deny this problem, and 3 do not know).

— The EU SPC, in its current form, increases reliance on imports of medicines and active pharmaceutical ingredients from outside the EU;

[82] https://ec.europa.eu/info/consultations/public-consultation-supplementary-protection-certificates-spcs-and-patent-research-exemptions_en

— The entry into force of the EU SPC regulations in a Member State triggers the delocalisation to another country or licensing of manufacturing to a country with no or less stringent SPC type protection;

— Already today, it is not always possible to source active pharmaceutical ingredients ('APIs') from the EU;

— The introduction of an SPC manufacturing waiver in the EU would increase their sales in countries outside the EU when protection abroad expires; would lead them to increase their manufacturing in the EU; would not increase the risk of infringement of SPCs in the EU; and would not significantly reduce originators' sales in countries outside the EU when protection abroad expires.

The vast majority of **SMEs** manufacturing generics and biosimilars also share these views, and in general consider that the longer duration of SPCs in the Union compared to non-EU countries makes manufacturing in the Union less interesting for them.

- **Views expressed by originators**

Originators' submissions to the consultation reflect their broad – though not overwhelming – opposition to the introduction of an EU SPC manufacturing waiver: 54 out of 71 originators do not consider that EU-based manufacturers face export or EU *day-1* entry-related problems vis-à-vis their competitors based in non-EU countries (with shorter or no SPC protection).

A strong majority of the originators consider that the current EU SPC framework does not put EU based generics/biosimilars manufacturers at a disadvantage compared with foreign-based manufacturers, neither when exporting generics/biosimilars outside the EU nor when it comes to placing generics/biosimilars on the EU market when SPC protection in the EU expires.

Most originators oppose the introduction of an SPC manufacturing waiver in the EU, considering that it would:

— increase the risk of infringement of SPCs in the EU;

— reduce protection to recoup their investments in R&D in the EU;

— reduce their sales in countries outside the EU when protection abroad expires;

— erode IPR protection, sending a negative message to those innovating and investing in the EU, or intending to do so;

— increase competition from EU-based generics/biosimilars on the EU market;

— provide EU-based generics/biosimilars manufacturers with limited benefits only – arguing that European generics companies are often the first to market in the EU, and that SPC(-like) protection is also available in firms'main export markets (the USA, Japan, etc.).

Regarding **pharmaceutical innovative SME**, among the 71 respondents defining themselves as mostly originators, 2 respondents identified themselves as an SME involved in medicines biotechnology and one as a start-up in the field of biopesticides. In addition, several European pharmaceutical associations such as EUCOPE, EBE, and EuropaBio conveyed the views of their start-ups and SME members in their submissions and accompanying letters sent to the Commission during the public consultation. A few national innovative pharmaceutical associations focused on start-ups and SMEs-members

also provided their views. These associations representing innovative SMEs have expressed concerns that the introduction of a manufacturing waiver would dilute SPC protection and therefore dilute the financial rewards they would receive for their inventions, as well as their possibility to get and secure funding for their innovative R&D. They also highlight that EU-manufactured generics are likely to compete for market shares in unprotected markets with the original brands and thus decreasing the actual or projected market share of these SMEs products.

- **Views expressed by other stakeholders**

A large majority of the 43 citizens who answered the consultation state that they care about the origin of productions of the medicines they consume, while only 3 said they do not care.

10 out of 15 respondents in the group of patients/doctors/insurers agree that the EU SPC system puts EU-based manufacturers of generics and biosimilars at a disadvantage vis-à-vis competitors based in third countries when it comes to export. Only 1 respondent considers that this is not a problem. 6 respondents of this category see also an issue regarding timely EU *day-1* entry for EU-based manufacturers of generics and biosimilars. 3 respondents do not consider that this is a problem.

Outside the framework of the public consultation, strong political support was expressed for the introduction of a manufacturing waiver by Parliament in a number of Resolutions; in particular, its May 2016 Resolution on the *Single Market Strategy* '*urge[d] the Commission to introduce and implement before 2019 an SPC manufacturing waiver*', so as to boost the competitiveness of the generics and biosimilar sector, '*while not undermining the market exclusivity granted under the SPC regime in protected markets*'.

ANNEX 3: WHO IS AFFECTED AND HOW?

- **Practical implications of the initiative**

As mentioned above, the main impacts of the introduction of an SPC manufacturing waiver would be:

— **EU-based manufacturers of generics/biosimilars** would benefit from a more level playing field in respect of third-country manufacturers, as they would be able to (1) manufacture generics/biosimilars in the EU during the SPC term for exporting them to ('non-SPC') third countries, and/or – depending on whether the waiver would be for export and/or for stockpiling purposes – (2) manufacture and stockpile generics/biosimilars in the EU just before the end of the SPC term for being able to supply the EU market immediately after SPC expiry (from *day-1*). It should not be forgotten that the increasing number of originator firms possessing generics and biosimilar divisions or subsidiaries in the EU would also benefit from the waiver.

To implement anti-diversion measures, the generics/biosimilars manufacturers would have to foresee certain obligations, such as labelling and notification.

— The pressure to relocate the manufacturing of generics/biosimilars outside the EU would reduce, positively affecting employment in that sector, including high-skilled jobs. EU-based R&D would also benefit from this, especially regarding biosimilars, a sector in which the EU could then hope to keep its pioneer advantage. All players of the **EU pharmaceutical ecosystem**, including SMEs, would benefit from its sustained strength and dynamism (including for instance sufficient manufacturing capacities, and suitable skills), which is likely to have many outcomes including promoting the creation and growth of EU start-ups.

— **Originators (SPC holders)** would face slightly increased competition in unprotected markets (namely from EU-based manufacturers of generics/biosimilars) (1) for export purposes during the SPC term, and/or (depending notably on whether the waiver would be for export and/or for stockpiling purposes) (2) for *day-1*-entry purposes. This may lead to some decrease (of slower-than-expected increase) of their sales and of the related employment. However, this increase in competition in unprotected markets is expected to remain low compared to the intense competition already generated today by manufacturers established in ('non-SPC') third countries. It may also be recalled that the core legal protection resulting from SPCs in the EU, providing SPC holders with exclusive rights regarding the placing their products onto the EU market during the SPC term, will not be affected at all. So while there may be a second-order effect there will be no first-order one.

— **EU patients** and Member State **public health systems** (budgets) would benefit from a timely market entry of generics/biosimilars onto the EU market (possibly resulting in lower prices), and also from better security of supply.

— **Public authorities** may need to receive and publish notifications related to anti-diversion measures, potentially leading to a small but manageable administrative workload.

- **Summary of costs and benefits**

I. Overview of Benefits (total for all provisions) – Preferred Option		
Description	Amount	Comments
Direct benefits		
Exports of EU-made generics/ biosimilars during the SPC term, under a waiver that would at least cover export purposes	Increase of the EU pharmaceutical trade balance by EUR 6 -10bn over 10 years for a sample of (117+17) molecules (32% of the relevant medicines) Amount above revised down to EUR 2-3bn	CRA study, section 3.4 OHE-EFPIA
Increased employment by EU-based manufacturers of generics/biosimilars	> 20 000 additional jobs Revised down to 3 000 to 9 400 jobs	CRA study, S. 3.4 OHE-EFPIA
Savings for Member States' national expenditure on pharmaceuticals	~ 4-8 % savings	CRA study
Indirect benefits		
Improvement of the whole EU pharmaceutical ecosystem (also beneficial to originators)	A healthy, vibrant EU pharma ecosystem will clearly be beneficial not only for generics/biosimilars manufacturers but also for originators and research organisations, as well as for the creation and growth of start-ups.	

II.Overview of costs – Preferred option							
		EU-based generics/biosimilars manufacturers		EU-based SPC holders (originators)		Administrations	
		One-off	Recurrent	One-off	Recurrent	One-off	Recurrent
Manufacturing waiver for export purposes	Direct costs	0 Negligible cost of notification of the 1st production	Minor logistical costs relating to specific labelling The related costs could be around EUR 10 000 per product per year[83].0	/	/	A few thousand per EU MS Stablishing an IT solution	0

[83] Considering that the evaluation of *Regulation 953/2003 to avoid trade diversion into the EU of certain key medicines* found that a pharmaceutical company incurred costs of a few hundred thousand euro between 2003-15 for adding a logo on its packs and for getting regulatory authorities to amend/extend marketing authorisations for the medicines due to a change of packaging.

						for e-filing and publication of the notification	
	Indirect costs	/	0	Possible loss of employment by originators[84]	Possible decrease in sales (1) in export markets during the SPC term and (2) in the EU immediately after SPC expiry. Available estimations include: • EUR 139 - 278m for non-biologics and EUR 868m – 1,7bn for biologics (CRA study, S. 3.4) • EUR 191m – EUR 573m for non-biologics (OHE-EFPIA)	/	

[84] The Pugatch study mentions a range of 4,500-7,700 direct job exposes to competition. However, that study does not estimate how many of those jobs exposed to competition might be finally lost due to the waiver.

ANNEX 4: DIFFERENCES BETWEEN GENERIC AND BIOSIMILAR MEDICINAL PRODUCTS

Table A3.1. Differences between generic and biosimilar medicinal products

	Generics	**Biosimilars**
Size and structure of molecule	Simple and small chemical structure that can be fully characterised	Large and complex structures, difficult to fully characterise
Method of production	Chemical synthesis - identical copies can be made by chemists in the lab	Made in living organisms - identical copies cannot be made
Immunogenicity	Lower potential	Higher capacity to produce immune system responses
Assurance of product quality	About 50 tests and controls are required to demonstrate identity, strength, quality, potency and purity.	About 250 tests and controls are required to demonstrate identity, strength, quality, potency and purity.
Development timeline	Few months to very few years	Several years
Cost of development to reach approval	EUR 2m -3m	EUR 70-300m / USD 300m
Additional tests for marketing authorisation purposes	Identical to reference medicine; thus only proof of bioequivalence to the reference product is needed	Similar to, but not identical, to the reference product, thus additional tests (and trials) are required
Authorising agency	National medicines agencies or EMA (European Commission)	Only EMA (European Commission)
Discount over the reference product price after expiry	80-90%	20-30%
Interchangeability with reference medicine	Yes for patients already treated with the reference medicine	No interchangeability or automatic substitution (some Member States are introducing almost automatic substitution)
Value chain location	Relatively easy to delocalise the production, and delink development from manufacturing	The production is difficult to delocalise[85] (i.e., once delocalised, it might not be moved again) as it is highly sensitive to environmental changes; therefore development and manufacturing tend to be close to each other[86]

Sources: Based on CRA Report (2017), Deloitte Report.

[85] According to Medicines for Europe, the minimum cost of relocating the production of a single biological product is EUR 10m and it takes a minimum of 1.5 to 2 years. If the relocation results in the need for additional regulatory approvals to ensure that the safety, quality and efficacy of the product are not affected, the costs easily multiply.

[86] Alcacer, J. and Delgado, M. (2016), 'Spatial organization of firms and location choices through the value chain'. *Management Science*, 62(11), 3213-3234. Analysing locations of new establishments of biopharmaceutical firms in the USA from 1993 to 2005, authors show that collocation of activities varies in the value chain. Although present in all activities, it is larger for R&D and manufacturing than for sales.

ANNEX 5: BIOSIMILARS APPROVED IN THE EU AS OF DECEMBER 2017

Biosimilar Trade Name	Marketer	Active Substance	Reference Drug	Year of Approval
Epoetins				
Abseamed	Medice	epoetin alfa	Eprex/Erypo	2007
Binocrit	Sandoz	epoetin alfa	Eprex/Erypo	2007
Epoetin Alfa Hexal	Hexal	epoetin alfa	Eprex/Erypo	2007
Retacrit (2)	Hospira	epoetin zeta	Eprex/Erypo	2007
Silapo	Stada	epoetin zeta	Eprex/Erypo	2007
Filgrastims				
Accofil	Accord	filgrastim	Neupogen	2014
Filgrastim Hexal	Hexal	filgrastim	Neupogen	2009
Grastofil (3)	Apotex	filgrastim	Neupogen	2013
Nivestim	Hospira	filgrastim	Neupogen	2010
Ratiograstim	Ratiopharm	filgrastim	Neupogen	2008
Tevagrastim	Teva	filgrastim	Neupogen	2008
Zarzio (4)	Sandoz	filgrastim	Neupogen	2009
Follitropins				
Bemfola	Finox	follitropin alfa	GONAL-f	2014
Ovaleap	Teva	follitropin alfa	GONAL-f	2013
Growth Hormones				
Omnitrope (5)	Sandoz	somatropin	Genotropin	2006
Insulins				
Abasaglar (6)	Eli Lilly	insulin glargine	Lantus	2014
Lusduna (7)	Merck	insulin glargine	Lantus	2017
Insulin lispro Sanofi	Sanofi	insulin lispro	Humalog	2017
Low-Molecular Weight Heparins				
Inhixa	Techdow Europe AB	enoxaparin sodium	Clexane	2016
Thorinane	Pharmathen S.A.	enoxaparin sodium	Clexane	2016
Monoclonal Antibodies				
Amgevita/Solymbic (8)	Amgen	adalimumab	Humira	2017
Cyltezo (9)	Boehringer Ingelheim	adalimumab	Humira	2017
Imraldi	Samsung Bioepis	adalimumab	Humira	2017
Flixabi (10)	Samsung Bioepis	infliximab	Remicade	2016
Inflectra (11)	Hospira	infliximab	Remicade	2013
Remsima (11)	Celltrion	infliximab	Remicade	2013
Rixathon/Riximyo (12)	Sandoz	rituximab	MabThera	2017
Truxima/Blitzima/Ritemvia/Rituzena (13)	Celltrion	rituximab	MabThera	2017
Ontruzant (14)	Samsung Bioepis	trastuzumab	Herceptin	2017
Parathyroid Hormone Fragment				
Movymia	STADA Arzneimittel	teriparatide	Forsteo	2017
Terrosa	Gedeon Richter	teriparatide	Forsteo	2017
Fusion Proteins				
Benepali	Samsung Bioepis	etanercept	Enbrel	2016
Erelzi (15)	Sandoz	etanercept	Enbrel	2017

(1) Three additional biosimilars were approved by the EMA but subsequently had their authorisations withdrawn.

(2) An FDA advisory committee recommended approval of Hospira's U.S. biosimilar application in May 2017, but the application was rejected by the FDA in June 2017.

(3) A biosimilar application to market in the USA was accepted for review by the FDA but has not been approved.

(4) Approved in the USA as a biosimilar under the Biosimilar Price Competition and Innovation Act of 2009 (BPCIA) with the trade name Zarxio.

(5) Approved in the USA under the 505(b)(2) pathway.

(6) Original EU trade name was Abasria; it was approved in the USA under the 505(b)(2) pathway with the trade name Basaglar and launched in the USA in December 2016.

(7) In July 2017, Lusduna received tentative approval in the USA under the 505(b)(2) pathway.

(8) Approved in the USA in September 2016 with trade name Amjevita. Amgevita and Solymbic are different trade names for the same monoclonal antibody.

(9) Approved in the USA in August 2017 as a biosimilar under the BPCIA.

(10) Approved in the USA in April 2017 as a biosimilar under the BPCIA under trade name Renflexis.

(11) Inflectra has been approved in the USA as a biosimilar under the BPCIA. Inflectra and Remsima are different trade names for the same monoclonal antibody.

(12) Rixathon and Riximyo are different trade names for the same monoclonal antibody. A biosimilar application to market in the USA has been accepted by the FDA.

(13) Celltrion's MabThera biosimilar was first approved in Europe in February 2017 under the name Truxima. Additional marketing authorisations under the trade names Blitzima, Ritemvia, and Rituzena (previously Tuxella) were granted in July 2017. A biosimilar application to market in the USA has been accepted by the FDA.

(14) Samsung Bioepis announced in November that it had received marketing authorisation in Europe.

(15) Approved in the USA as a biosimilar under the BPCIA.

CHMP Issues Positive Opinions Two additional biosimilars, Amgen/Allergan's Mvasi and Celltrion's Herzuma, have received favorable opinions from EMA's Committee on Medicinal Products for Human Use (CHMP) and may soon be approved in Europe. Mvasi, a biosimilar of Genentech's Avastin (bevacizumab), received a favorable recommendation from CHMP on 9 November 2017. Mvasi was approved as a biosimilar in the USA in September 2017. Celltrion's Herzuma, a biosimilar of Genentech's Herceptin (trastuzumab), received a positive opinion from CHMP on 14 December 2017. If, as anticipated, the Commission follows the recommendation of CHMP, Mvasi and Herzuma likely will be approved in Europe in the coming months.

Pending Biosimilar Applications in Europe Eleven additional biosimilar applications are under evaluation by the EMA as of December 2017: three applications for biosimilars of AbbVie's (adalimumab), one application for a biosimilar of Sanofi's Lantus (insulin glargine), six applications for biosimilars of Amgen's Neulasta (pegfilgrastim), one application for a biosimilar of Janssen's Remicade (infliximab) and four applications for biosimilars of Genentech's Herceptin (trastuzumab).

The six pending applications for biosimilars of Amgen's Neulasta (pegfilgrastim) are particularly notable, since EMA has rejected a number of the previous applications for pegfilgrastim biosimilars and no pegfilgrastim biosimilars have been approved to date. Indeed, two of the currently pending applications for pegfilgrastim biosimilars are resubmissions of rejected applications. Sandoz's resubmitted application was accepted for review in October 2017, while Mylan/Biocon's resubmitted application was accepted for review in November 2017. Other pending applications include applications from Coherus, Spain's Cinfa, and Indian pharmaceutical manufacturer USV.

EMA is also reviewing Mylan/Biocon's application for Ogivri, a biosimilar of Genentech's Herceptin (trastuzumab). Ogivri was approved as a biosimilar in the USA

on December 1, 2017. However, Mylan/Biocon's application for marketing approval for Ogivri in Europe, like its application for its pegfilgrastim biosimilar, ran into problems last summer after a European inspection of Biocon's manufacturing facility. Like the pegfilgrastim application, the Ogivri application was withdrawn in August 2017 but resubmitted in November.

2017 has been a record-setting year for biosimilar approvals in Europe. Although the first biosimilars to the European market were approved in 2006 and 2007, the number of approved biosimilars has doubled in the past two years. These approvals have expanded the market into new therapeutic areas and new classes of biologics.

ANNEX 6: ANALYTICAL METHODS

The analytical methods used in the various studies mentioned in Annex 1 are explained in the text of the respective studies.

ANNEX 7: GENERIC AND BIOSIMILAR MARKET IS EXPANDING

1) *Massive global demand for medicines*

There is a worldwide increasing and massive demand for medicines. This is confirmed by industry (IFPMA and EFPIA) data showing that the total global spending on medicines increased from EUR 950bn in 2012 to EUR 1.1 trillion in 2017, and consistent with the US Commerce Department's similar data pointing out to a global spending of USD 1.3 trillion expected by 2020 with annual growths of 5%.

2) *Shift towards more generics and biosimilars*

In all markets, especially in developing countries, the consumption of medicines is shifting toward generics and biosimilars. Generics and biosimilars could represent 80% of the volume of medicines by 2020 with a future growth forecast at a compound annual growth rate of 6.9%. For the US market, data from US Generic Pharmaceutical Association indicates an increase from 27% in 2012 to 36% of the total sales by 2017 and making 80% of the filled prescription sales[87] of the pharmaceutical market by 2020. In the Union, Medicines for Europe claims that 56% of the volume of medicines supplied correspond to generics and biosimilars. Japan government set a target of 80% market penetration of generics and biosimilars in Japan by 2020.

IFPMA 2017 report[88] highlights that the spending on generic drugs is driving most of the growth in the leading emerging markets, which will contribute to the increase in the share of generic spending. The revenues from generics in 2021 are expected to reach USD 495-505 billion.

There was a growth peak of generics until 2012 driven by a major 'patent cliff'[89]; however, perspectives are bright with a rejuvenated pipeline of blockbuster in part due to biologics, plans to take up generics use in major markets as Japan, strong demand in emerging economies and new generics' opportunities in specialised fields or new delivery technologies. The global market for generic medicines should reach EUR 500bn by 2021 from 330 in 2016 (a 50% increase in 5 years). According to several sources (e.g. CRA study and Deloitte), emerging middle classes in Asia demand branded generics/biosimilars with strong reputation.

The biologics market is booming with annual sales of over EUR 150bn. In the EEA the share of biologics (including biosimilars) in the total pharmaceutical sales was 16% in 2008 and increased to 21% in the 12 months ending in 2014 Q3[90]. Now biologics account for over a third of all new drugs in clinical trials or awaiting FDA

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87 Generic Pharmaceutical Association, Generic Drug Savings in the USA – 7th Annual Edition (2015): http://www.gphaonline.org/media/wysiwyg/PDF/GPhA_Savings_Report_2015.pdf

88 https://www.ifpma.org/wp-content/uploads/2017/02/IFPMA-Facts-And-Figures-2017.pdf

89 A 'patent cliff' refers to the situation that takes place when the legal protection (afforded by a patent or SPC) of one or several successful medicine(s) expires (in a short period of time for all of them), causing a very sharp drop in sales for the right-holder(s).

90 CRA report, page 24.

approval[91]. According to *Medicines for Europe*, by 2018, 50% of pharmaceutical expenditure will relate to biologicals.

As well as biologics, the biosimilars sector is booming. Biosimilars providing new avenues to address key therapy areas such as cancer, orphan conditions and chronic diseases with increasing prevalence at a lower cost for public health authorities and health providers. Biosimilars, despite their complexity and high cost of development (see above) are especially interesting for the pharmaceutical industry at large because:

- The first generation of biologics[92] have started to reach the end of their patent/SPC protection or other forms of market exclusivity in the coming years. According to Baker&McKenzie, by 2019 approximately 50% of the biologics market will be off-patent in the USA; Over EUR 90bn of current reference/innovator products will become susceptible to biosimilar competition by 2020[93]. In the USA only, it is estimated that the biosimilar market may be worth USD 11bn by 2020 (accounting for 4-10% of the biologics market by 2020).
- The best-selling pharmaceuticals in the world today are biologics[94]. For example, blockbuster biologic Humira® (Adalimumab) tops the sales ranking with EUR 8bn in the 1st semester of 2017 according to Bloomberg.
- Price competition in the market of biologics is not as intensive as in the case of classic generic markets. In the EU, the discount of the biosimilar to the biologic has averaged about 20 to 30%[95] (comparing with typically 50 to 80%[96] for classic generics).

3) Traditional originators also interested in biosimilars[97]

As a result, not only traditional companies in the generics sector are developing biosimilars, also traditional pharmaceutical/biotech/R&D innovators companies have obtained marketing authorisations to commercialise biosimilars. EMA databases (details in annex 5) show that 15 out of 33 biosimilars currently in force in the EU were issued directly to classic originators (Amgen, Boehringer, Eli Lilly, Merck, Sanofi) or their biosimilars' divisions (Pfizer-Hospira, Novartis-Sandoz, Novartis-Hexal). Samsung Bioepis and Celltrion count with 6 biosimilars authorisations at

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[91] See US Commerce Department-International Trade Administration, 2016 Top Markets Report Pharmaceuticals.

[92] More than 400 biopharmaceutical products, including over 140 recombinant proteins approved in the USA and Europe. Over 40 recombinant proteins have blockbuster (over USD 1bn a year) markets.

[93] This is consistent with other estimations signalling around USD 81bn – see Rovira, J., *et al*, *The impact of Biosimilars' entry in the EU Market*. Granada (Spain): Andalusian School of Public Health (2011).

[94] http://www.expansion.com/empresas/2017/08/08/5988c908e5fdea32328b4627.html

[95] Footnote 92 of CRA study. See Grabowski H., Guha R., and Salgado, M. (2014), *Biosimilar competition: Lessons from Europe*, *Nature Reviews*, Drug Discovery, Feb 2014, Vol. 13; or *Pricing of biosimilars*, Gabi Online, 23 March 2012 available at http://gabionline.net/Biosimilars/Research/Pricing-of-biosimilars).

[96] Danzon P.M. and Furukawa M.F. (2014), '*Cross-national evidence on generic pharmaceuticals: pharmacy vs physician-driven markets*', NBER working paper no. 17226 and Charles River Associates (2016).

[97] https://www.dcatvci.org/5058-biosimilars-opportunities-and-challenges-in-the-us-and-eu

EMA that often manufacture and license to originators. FDA databases show that 6 out of 9 biosimilars are registered by originators (Amgen, Boehringer, Pfizer and Novartis-Sandoz).

4) *Global competition in the pharmaceutical industry; EU lead advantage on biosimilars fading*

Expecting growth is also strong in emerging markets (the so-called 'pharmerging' countries). China is now the second market for pharmaceuticals ahead of Europe. This scenario of strong demand is accompanied by an increasing R&D and manufacturing capacity and know-how in third-countries to compete on pharmaceutical market[98]. Therefore the pharmaceutical industry operates in a highly competitive and global market.

The EU was pioneering in introducing regulatory procedures for approval of biosimilars (the EMA authorised the 1st biosimilar in 2006, 9 years before the FDA[99] authorised the first biosimilar in 2015) and therefore the EU gained a competitive advantage in the development of biosimilars, however, other trade blocs, including BRICS, have updated their regulatory rules and are becoming increasingly attractive for investments in biosimilars[100] (IMS Health identified in 2011 South Korea, India and Brazil as key macroeconomic drivers of growth, attracting foreign capital by creating manufacturing and R&D centres of excellence for biosimilars[101]; In South Korea, 35% of the national medical R&D budget was invested into biosimilars development in 2012 according to Deloitte report).

5) *First mover advantage in the market of generics and biosimilars*

As the pharmaceutical market is global and highly competitive, the 'first generic/biosimilar mover(s)' usually takes most of the market share where patent/SPC expires (see third driver in section 2 below). Indeed, regarding the first-mover advantage in the off-patent/SPC EU market, DG GROW studies show that in the EU, generic firms entering 1 year after the first generic entrant only capture 11% of first entrant market share during the first year, and 20% of first entrant market share after being 2 years in the market. Late entrants in biosimilar industry also face competitiveness disadvantage. Studies show that in 2016, first biosimilars to market captured 72% market share, while 2nd and 3rd entrants only captured 30% and 5% respectively.

6) *EU giving the longest SPC protection*

Despite that positive pioneering effect in the EU, and the efforts being made via FTA negotiations to get trade partners to introduce EU SPC type protection, it is a fact that the EU frequently gives longer patent and SPC protection for pharmaceutical

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[98] See footnotes related to pages 7 and 8 of Deloitte report 2015. See page 3 of this US Commerce Department-International Trade Administration, 2016 Top Markets Report Pharmaceuticals: https://www.trade.gov/topmarkets/pdf/Pharmaceuticals_Executive_Summary.pdf

[99] The *Patient Protection and Affordable Care Act* signed into law on March 2010 authorised the FDA to approve biosimilars that were approved under the Public Health Service Act of 1944 or the Federal Food, Drug, and Cosmetic Act (FFDCA). In 2015, Zarxio became the first biosimilar product approved by the FDA: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm

[100] See pages 7 and 8 of Deloitte report 2015.

[101] https://weinberggroup.com/pdfs/Shaping_the_biosimiliars_opportunity_A_global_perspective_on_the_evolving_biosimiliars_landscape.pdf

products than its trade partners. This differential might hinder investment in biosimilars and generics in the EU.

ANNEX 8: IMPACTS OF THE CURRENT SPC REGIME (BASELINE SCENARIO)

The following table summarises the main impacts of the current EU SPC regime (cf. Reg. 469/2009) on various stakeholders *during the SPC protection period*:

Note: 'G/Bs' means 'generics/biosimilars'

Impact on stakeholders ↓ according to their location →	**… located in a Member State…**		**… located in a non-EU country …**	
	… where an SPC has been granted	**… where no SPC has been granted**	**… where IP protection is in force**	**… where no IP protection is in force**
SPC holders (originators) … (holding IP protection)	The effects of the basic patent are extended by up to 5 (½) years, allowing originators to prevent any local manufacturing and marketing of G/Bs, thereby resulting in increased sales and profits.	Originators cannot prevent competitors from manufacturing and marketing G/Bs.	Originators can prevent competitors from manufacturing and marketing G/Bs.	Originators cannot prevent competitors from manufacturing and marketing G/Bs.
Manufacturers of generics or biosimilars … ('G/Bs')	G/Bs are prevented from manufacturing and marketing G/Bs. This also prevents G/Bs (1) from manufacturing for export, even to countries where no IP protection is in force, and (2) from being ready to supply the (SPC-covered) EU market from *day-1*, if at all[104].	G/Bs are free to manufacture if they have manufacturing capacity and market G/Bs, for domestic use or for export (to countries without IP protection), or so as to be ready to supply the EU market[102] on *day-1*.	G/Bs are prevented from manufacturing and marketing G/Bs, including for export purposes if there is not a manufacturing waiver.	G/Bs are free to manufacture and market G/Bs, for domestic use or for export (to other countries without IP protection), or so as to be ready to supply the EU market from *day-1*.
Patients …	Patients cannot access G/Bs during the SPC term of protection. Moreover they may be unable to access EU-made G/Bs until some time after SPC expiry in the EU[103], if at all[104].	Patients can access G/Bs manufactured domestically (if there is manufacturing capacity) or, more likely[104], imported from non-EU countries where there is no IP protection (anymore).	Patients cannot access G/Bs. Moreover they may be unable to access EU-made G/Bs until some time after SPC expiry in the EU[103], if at all[104].	Patients can access G/Bs manufactured domestically (or imported from similar countries). However, they may not be able to access EU-made G/Bs until some time after SPC expiry in the EU[103], if at all[104].

[102] Including SPC-covered Member States (which could not be supplied during the SPC term).

[103] Depending on the time EU-based manufacturers of generics/biosimilars will need to make preparations to be ready to supply the EU market after SPC expiry.

[104] Considering the strong 'first mover' advantage associated with generics entry, it may well happen that for a certain medicine no EU-based manufacturer of G/Bs – even when legally free to do so – will actually capture a meaningful share of the EU market, leaving all/most of the market to G/Bs located in non-SPC non-EU countries, even after SPC expiry. It is possible that some of the EU market may be captured by G/Bs based in Member States where no SPC applies; however, today SPC protection is filed on average in 20 Member States, which means that for most (successful) medicines very few Member States are SPC-free, and in those Member States it is not guaranteed that there is adequate G/Bs manufacturing capacity.

ANNEX 9: COMPARISON OF SPC PROTECTION EXPIRY DATES

There is no publicly available data that would allow an assessment of the scope of different expiry dates across different regions in the world for medicinal products whose molecules are under SPC protection in Member States. Below, we discuss the SPC expiry dates for the sample of molecules that were provided by Medicines for Europe and that were used in the CRA study.

Differences in expiry dates

In their note on manufacturing waiver (October, 2017), Medicines for Europe provided Commission services with data on 109 molecules with the SPC expiry dates (including paediatric extensions where applicable) in the EU and five other countries – the USA, South Korea, China, India and Canada. The list of molecules along with the SPC expiry dates of the related *substance patents* can be found at the end of this Annex.

Table 1 below provides an overview of Medicines for Europe data coverage and the differences in expiry dates. For most of these molecules, protection expires in the Member States later than in at least one other region. This is the case only for the USA and South Korea, as China, India and Canada do not provide for SPC protection. Focusing only on those molecules for which expiry dates are later in the EU, the average difference is above two years in the USA and South Korea and above three years in CN, IN and CA. This is consistent with results provided by the CRA (2016) where, based on a sample of 70 molecules, authors show that the protection expiry difference between five Member States (France, Germany, Italy, Spain and UK) ranges between 2.23 (for the USA) and 3.85 years (for Canada).

Table 1: Differences in SPC expiry dates between Member States and third country

Country	Molecules with expiry date	Molecules with expiry date earlier than in the EU	Difference in expiry date between EU and third country (in years)		
			Average	Min	Max
US	109	93	2.06	0.01	5.50
KR	44	40	2.86	0.16	5.65
CN	41	41	3.31	0.16	6.47
IN	22	22	3.07	0.16	5.31
CA	40	40	3.53	0.16	6.56

Source: Calculations based on the data provided by Medicines for Europe.

Note: The maximum difference of expiry date can be as long as 6.5 years. This is due to the fact that the duration of SPC is calculated based on application filing date and not the priority filing date.

Representativeness

The representativeness of the Medicines for Europe list is assessed using *Alice de Pastors* database. For consistent comparison between two databases, this assessment focuses on molecules for which SPC protection (including paediatric extension) in the EU expires in 2018 or later and those approved between 2 000 and 2014. This leaves a sample of 97 molecules of the Medicines for Europe list[105]. Those molecules represent 22% (24%) of

[105] For 11 molecules the expiry date is before 2018, and one molecule (*sonidegic*) has been first approved in the EU only in 2015.

all medicinal products (with EMA authorisation) approved between 2 000 and 2014 for which SPC will expire in the future[106].

A closer look at the data shows that the molecules listed on Medicines for Europe cover only few ATC classes (level-3) when compared to the Alice de Pastors data. Considering only those therapeutic indications which appear on the Medicines for Europe list, the representativeness of this list increases to 39%.

Table 2: SPC expiry dates in the EU and other regions for selected molecules

Product Name	EU	US	KR	CN	IN	CA
ABATACEPT	23-Nov-22	02-Jul-21	07-Feb-21	07-Feb-21		07-Feb-21
ABIRATERONE	15-Mar-18	13-Dec-16				
ADALIMUMAB	16-Oct-18	31-Jul-17	01-Apr-19	02-Oct-17		02-Oct-17
AFATINIB	12-Dec-26	22-Jan-22	02-Sep-26	12-Dec-21	12-Dec-21	12-Dec-21
AFLIBERCEPT (EYLEA)	23-May-25	18-Nov-23				
AFLIBERCEPT (ZALTRAP)	01-Feb-28	02-Dec-25	12-Feb-25	12-Feb-25	12-Feb-25	12-Feb-25
ALEMTUZUMAB (LEMTRADA)	16-Sep-28	24-Aug-29	09-Nov-27	09-Nov-27	09-Nov-27	09-Nov-27
ALISKIREN	07-Apr-20	21-Jul-18				
ALISKIREN + AMLODIPINE	07-Apr-20	21-Jul-18				
ALISKIREN + HYDROCHLOROTHIAZIDE	07-Apr-20	21-Jul-18				
ALOGLIPTIN	15-Mar-18	13-Dec-16				
ALOGLIPTIN + METFORMIN	23-Sep-28	27-Jun-28				
AMBRISENTAN	03-Oct-20	29-Jul-18	10-Jul-15	10-Jul-15		10-Jul-15
ANIDULAFUNGIN	18-Mar-18	17-Feb-20				
APREPITANT	13-May-19	17-Apr-15				
ATAZANAVIR SULFATE	04-Mar-19	20-Dec-17				
ATOMOXETINE	28-May-19	26-May-17		01-Apr-16		01-Apr-16
ATORVASTATIN + EZETIMIBE	15-Sep-19	25-Apr-17				
BAZEDOXIFENE	16-Apr-22	04-Apr-17				
BELATACEPT	23-May-26	15-Jun-25				
BELIMUMAB	15-Jun-26	17-Jul-23				
BEVACIZUMAB	16-Dec-19	04-Jul-19	04-Mar-18	04-Mar-18		04-Mar-18
BILASTINE	03-Jun-22	04-Jun-17		06-Apr-17	06-Apr-17	06-Apr-17
BORTEZOMIB	26-Apr-19	03-Nov-17				
BRENTUXIMAB VEDOTIN	25-Oct-27	18-Jan-25				
CANAKINUMAB	26-Aug-28	02-Nov-27				
CASPOFUNGIN	25-Oct-16	26-Jul-15	03-Oct-14	03-Oct-14		03-Oct-14
CERTOLIZUMAB	01-Oct-24	13-Apr-24	06-May-21	06-May-21		06-May-21
CEFTAROLINE FOSAMIL	17-Dec-23	11-Apr-22				
CINACALCET	26-Oct-19	08-Mar-18	05-Sep-17			
CLEVIDIPINE	03-Nov-19	05-Jan-21	11-Mar-14	11-Mar-14		11-Mar-14
DABIGATRAN ETEXILATE	17-Feb-23	28-Dec-21			02-Dec-18	
DARIFENACIN	17-Mar-15	13-Mar-15	11-Jan-11			

[106] There are 441 medicinal products approved between 2000-14 for which the SPC will expire in 2018 and later.

DARUNAVIR	24-Feb-19	09-May-17				
DASATINIB	22-Nov-21	28-Jun-20	04-Dec-20	04-Dec-20	04-Dec-20	04-Dec-20
DEFERASIROX	02-Sep-21	05-Apr-19				
DENOSUMAB	26-May-25	19-Feb-25				
DERQUANTEL	25-Jun-21	27-Jun-16				
DRONEDARONE	06-Aug-11	26-Jul-16	09-Aug-15			
DULOXETINE	11-Aug-18	18-Jan-15				
ECULIZUMAB	01-May-20	16-Mar-21	05-Jan-15			05-Jan-15
EFAVIRENZ+EMTRICITABINE +TENOFOVIR	03-Aug-18	21-Nov-13	08-Jun-13	08-Jun-13		
EMTRICITABINE + TENOFOVIR	24-Feb-20	25-Jan-18	11-Sep-17			
ERLOTINIB	21-Mar-20	08-May-19				06-Jun-15
ETRAVIRINE	01-Sep-23	13-Dec-20	12-Jan-19			
EVEROLIMUS	19-Jan-19	09-Mar-20				
EZETIMIBE	18-Apr-18	25-Apr-17	07-Jan-14	07-Jan-14		
EZETIMIBE + ROSUVASTATIN	15-Sep-19	25-Apr-17				
EZETIMIBE + SIMVASTATIN	02-Apr-19	25-Apr-17				
FESOTERODINE	24-Apr-22	11-May-19		05-Nov-19		05-Nov-19
FINGOLIMOD	18-Oct-18	18-Feb-19				
FLUTICASONE FUROATE	16-Jan-23	03-Aug-21		08-Mar-21	08-Mar-21	08-Mar-21
FOSAPREPITANT	28-Feb-20	04-Mar-19				
GEFITINIB	04-Mar-19	05-May-17	12-Jan-16			
GLIMEPIRIDE + PIOGLITAZONE	21-Jun-21	19-Jun-16				
IMATINIB	21-Dec-16	04-Jul-15	06-Mar-13	04-Feb-13		04-Jan-13
GOLIMUMAB	05-Apr-25	03-Feb-24	08-Jul-21	08-Jul-21	08-Jul-21	08-Jul-21
INSULIN DETEMIR	04-Dec-19	16-Jun-19				
INSULIN GLARGINE	06-May-15	12-Feb-15	02-Jun-16			04-Jan-14
INSULIN GLULISINE	01-May-20	18-Jun-18				
IPILIMUMAB	24-Aug-25	25-Mar-25				
IVABRADINE	25-Mar-18	25-Sep-12				
LACOSAMIDE	30-Aug-23	19-Mar-22				
LAPATINIB	12-Jun-23	29-Sep-20	06-Nov-19	01-Aug-19	01-Aug-19	01-Aug-19
LASOFOXIFENE	24-Apr-20	09-Jan-15	01-Aug-16	01-Aug-16		
LENALIDOMIDE	23-Jul-22	04-Oct-19				
LINAGLIPTIN	24-Apr-22	24-Apr-17				
LINEZOLID	16-Mar-17	18-May-15				
MARAVIROC	20-Sep-22	06-Aug-21	11-Sep-21	05-Sep-21	05-Sep-21	05-Sep-21
METFORMIN + SITAGLIPTIN	08-Apr-23	26-Jul-22	07-May-22	07-May-22	07-May-22	07-May-22
METFORMIN + VILDAGLIPTIN	05-Nov-24	09-Dec-19	03-Apr-22	12-Sep-19	12-Sep-19	12-Sep-19
MICAFUNGIN	29-Sep-20	17-Mar-19	07-Jun-17		10-Jun-15	
MIRABEGRON	01-Jan-28	04-Nov-23		11-Apr-23	11-Apr-23	11-Apr-23
NATALIZUMAB	25-Jan-20	16-Mar-16				
OMALIZUMAB	14-Aug-17	30-Nov-16				
PALIPERIDONE	02-Feb-15	27-Apr-10				
PEGFILGRASTIM	25-Aug-17	20-Oct-15	02-Aug-15	02-Aug-15		
PERTUZUMAB	23-Jun-25	15-Jul-25				

POSACONAZOLE	20-Dec-19	19-Jul-19	10-Oct-15			
PRASUGREL	27-Feb-19	14-Oct-17		09-Sep-12		09-Aug-12
PRUCALOPRIDE	16-Nov-20	16-Nov-15				
RALTEGRAVIR	02-Jan-23	03-Oct-23				
RANIBIZUMAB	23-Jan-22	04-Jul-19	04-Mar-18	04-Mar-18		04-Mar-18
RASAGILINE	12-Oct-19	07-Feb-17				10-Dec-14
RIVAROXABAN	02-Oct-23	28-Aug-24	10-Mar-21	12-Nov-20	12-Nov-20	12-Nov-20
ROFLUMILAST	02-Jul-19	27-Jan-20	07-Feb-19	07-Feb-14		07-Feb-14
ROMIPLOSTIM	05-Feb-24	19-Jan-22				
SAXAGLIPTIN	04-Oct-24	31-Jul-23	12-Dec-22	03-May-21	03-May-21	03-May-21
SEVELAMER	10-Aug-19	16-Sep-14	08-Oct-14			08-Oct-14
SILODOSIN	26-Nov-18	30-Nov-18				12-Jan-13
SITAGLIPTIN	05-Jul-22	26-Jul-22	09-Jan-23	07-May-22	07-May-22	07-May-22
SOLIFENACIN	16-Dec-18	19-Nov-18	07-Mar-17			
SONIDEGIB	18-Aug-30	25-Jul-29	05-Apr-27	05-Apr-27	05-Apr-27	05-Apr-27
SORAFENIB	21-Jul-21	12-Jan-20		01-Dec-20	01-Dec-20	
SUNITINIB	24-Jul-21	15-Feb-21				
TAFLUPROST	22-Dec-22	18-Dec-22				
TEDUGLUTIDE	11-Apr-22	14-Apr-20		04-Nov-17		04-Nov-17
TEMSIROLIMUS	14-Apr-20	15-Aug-19				
TIGECYCLINE	21-Feb-18	09-Apr-16		10-Mar-12		10-Mar-12
TOCILIZUMAB	16-Jan-24	30-Jul-24				
TRABECTEDIN	20-Sep-22	28-Jun-27				
TRASTUZUMAB	27-Aug-28	12-Oct-27	03-May-24	03-May-24	03-May-24	03-May-24
TRASTUZUMAB EMTANSINE	19-Nov-28	02-Jul-28	10-Dec-24	10-Dec-24	10-Dec-24	10-Dec-24
TULATHROMYCIN	13-Nov-18	24-May-19				
VARENICLINE	28-Sep-21	10-May-20	02-Aug-21	02-Aug-21		
VILDAGLIPTIN	27-Sep-22	09-Dec-19	03-Apr-22	12-Sep-19	12-Sep-19	12-Sep-19
VINFLUNINE	19-Jul-19	19-Jul-14				
VORICONAZOLE	24-Jul-16	24-May-16		02-Feb-11		
ZOLEDRONIC ACID	16-May-13	02-Mar-13	12-Oct-11			

Source: Medicines for Europe

ANNEX 10: ASSESSMENT OF WAIVER TIMING SCENARIOS

If an SPC manufacturing waiver was introduced, different scenarios could be envisaged in respect of its time-related applicability, as mentioned in the main text.

To evaluate the impact of the proposed scenarios 1 and 2 on the number of existing SPCs that would be actually affected by the waiver, this assessment relies on information provided in the *Alice de Pastors* database. The sample is limited to SPCs filed with reference to a first marketing authorisation granted in the EU until end 2015 and to those SPC for which the basic patent expires before 1 January 2026. Croatia, where SPC protection became available only recently, is excluded. SPCs are national rights and their geographical scope of protection differs as illustrated in Mejer (2017). In the assessment that follows, we are therefore looking at the number of distinct *basic patent-product pairs* for which the SPC was applied for in the EU (i.e. number of SPC bundles). For each *basic patent-product pair* we consider the first expiry date in the EU. Finally we assume that the amended Regulation will enter into force as of 1 May 2019.

There are 481 *basic patent-product pairs* for which the SPC will expire on 1 May 2019 and later. The distribution of those pairs by the basic patent expiry year is presented in graph below, with the red line indicating 1 May 2019.

Scenario 1: *Immediate effect*. This option will directly impact 136 SPC bundles which will be in effect as of 1 May 2019, and then progressively 28 additional bundles still in 2019, then with an average of 52 bundles per year between 2020 and 2025.

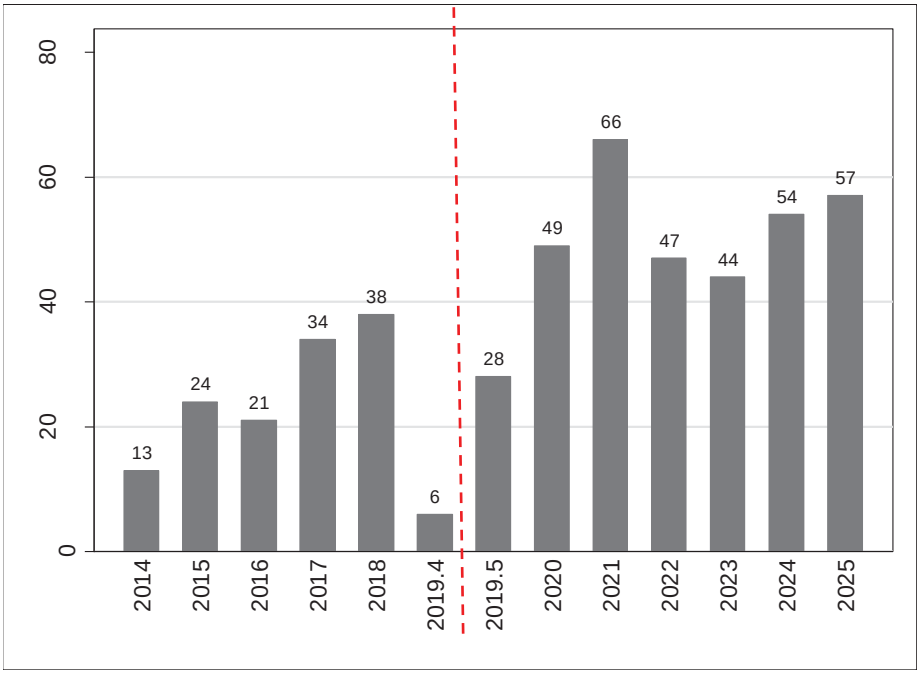
Scenario 2: Only those SPC bundles for whose SPCs *will enter into effect* on or after 1 May 2019 will be subject to the waiver i.e. those for which the basic patent protection will expire on or after 30 April 2019. This will be about 52 bundles per year between 2020 and 2025.

Scenario 3: We do not have data on SPC grant dates (which vary between Member States due to procedural differences). Still, assuming that an SPC is granted on average five years before patent expiry, the waiver would, on average, be available from 2025.

Scenario 4: SPCs are filed on average 9 years after the basic patent filing (Kyle, 2017; Copenhagen Economics, 2018). Assuming that the Regulation enters into force on 1 May 2019, the main impact of manufacturing waiver would be on patents expiring in or after 2028[107].

[107] It could be that few SPCs enter into effect very rapidly after they are applied for.

Graph: Number of SPC bundles by the basic patent term expiry year



Note: The graph above shows the number of SPC bundles (i.e. *basic patent-product pairs*) by year of basic patent expiry, i.e. year when SPC protection begins. The dashed red line indicates the assumed date of the entry into the force of Regulation (1st May 2019). Only those bundles with first SPC expiry after 1st May 2019 are considered. Source: own calculations based on *Alice de Pastors Database*.

ANNEX 11: BIOPHARMACEUTICALS R&D AND MANUFACTURING ACTIVITIES

This Annex provides an overview of the structure of the pharmaceutical industry in the EU, by looking at the manufacturing, R&D, trade, FDI and EMA-compliance manufacturing sites.

Production in the EU

Data Box: Pharmaceutical manufacturing in the EU

The analysis presented below is based on the ESTAT database for structural business statistics (SBS) and size class data, all of which are published annually. It presents an overview of statistics for the pharmaceuticals manufacturing sector in the EU, as covered by NACE Rev. 2 Division 21.

- In 2015 there were around 4 000 enterprises throughout the EU-28 for which pharmaceuticals manufacturing was their principal activity. They employed nearly 570 000 persons. The value of production amounted to EUR 260bn in 2015 and the value added generated was EUR 84bn, a little more than one third of the turnover generated.
- The pharmaceuticals manufacturing (Division 21) sector in the EU-27 is characterised by its small number of very large, capital-intensive enterprises. The manufacturing is very international as 60% of production is generated by firms with foreign ownership (i.e. with a controlling company located outside the reporting country).
- Pharmaceutical production in the EU is quite concentrated as 62% of EU-28 production takes place in four Member States: Germany, Ireland, France and Italy. 55% of the overall value added in the sector is generated in those economies (cf. Table 2 below).
- Four small Member States appear to be specialised in pharmaceutical manufacturing: Ireland, Belgium, Denmark and Slovenia. In 2014, the contribution of value added in pharmaceutical manufacturing relative to the total manufacturing ranges between 10-20% and is the highest for Ireland (34%) (cf. Table 2).

Innovation within the pharmaceuticals manufacturing sector

Data Box: R&D in pharmaceutical manufacturing

R&D data have been collected according to 2002 guidelines of the Frascati Manual. This table presents research and development (R&D) expenditure statistics performed in the business enterprise sector by industry according to the International Standard Industrial Classification (ISIC) revision 4. Depending on the country, R&D institutes serving enterprises are either classified with the industry concerned, or grouped under 'Research and Development' (ISIC rev.4, Division 72). When these R&D institutes are classified with the industry served, the evaluation of R&D in these industries is more accurate and more comparable between countries for the industries concerned. This results, however, in an underestimation of the percentage of BERD performed by the service sector as compared with other countries.

The data covers 21 Member States. The following are missing: Bulgaria, Croatia, Cyprus, Malta, Luxembourg, Latvia and Lithuania.

- In 2013, among the Member States for which data is available for pharmaceutical sector, intra-mural expenditure was USD 15 billion and put the EU-28 and

represented 16% of overall R&D spending in manufacturing in OECD countries, China, Romania and Singapore.

- For the sample of counties reported, R&D spending grew by 26% from its values in 2009 to 2013.
- EU-28 is the second larger R&D spender behind the USA. But its relative importance is decreasing vis-a-vis China. The data indicates that R&D manufacturing expenditure in China more than doubled from the level of USD 4.2 billion in 2009 to USD 9.8 billion in 2013, while to level of expenditure in Germany increased by 10% from USD 4.8 billion in 2009 to USD 5.2 billion in 2013.
- In Belgium, Denmark, Hungary as well as Slovenia, R&D expenditure in pharmaceutical manufacturing accounted for about one third of all R&D expenditure in manufacturing. In contrast, this share was well below 10 % in Germany, France and the United Kingdom.

International trade

Data Box: International trade in pharmaceutical and medical products

The data used in this section comes from Eurostat' COMEXT database for the Member States and in United Nations' COMTRADE database for the non-EU countries. The focus is on Division 54 'Medicinal and pharmaceutical products' of the Standard international trade classification revision 4 (SITC Rev. 4)[108].

Bias in the data: Extra-EU imports and exports are reported by the Member State where the customs declaration is lodged, usually the place where the goods cross the EU external frontier (here referred to as the exit/entry Member State). This is not necessarily the Member State of actual import or export. The geographical allocation of an extra-EU flow is biased in the case the entry/exit Member State is not the actual importing/exporting Member State. This issue particularly impacts the extra-EU imports of Member States having important ports for transhipment (e.g. Antwerp in Belgium or Rotterdam in the Netherlands). Furthermore, differences in the VAT schemes.

Limitations: Trade statistics do not fully reflect the globalised nature of the pharmaceutical industry where value chain is fragmented. Intermediate input (e.g. products and substances) may cross borders at several points in the manufacturing chains. This is particularly true for the simple products being produced in chemical synthesis. Furthermore, existing classification does not allow distinguishing between patent protected and off-patent products or the production process i.e. chemical v. biological.

- Trade in medicinal and pharmaceutical products has been growing steadily since 2002. Extra-EU trade almost tripled from EUR 76 billion in 2002 to EUR 220 billion in 2016 which translates to an average annual growth of 7.8%. In the same period, intra-EU trade more than doubled from EUR 156 billion to EUR 327 billion, equivalent to an average annual growth of 5.4 %.

  Increasing demand in the developing countries and medicinal products going off patent in the developed world are drivers behind this increase.

- In 2002, both intra-EU and extra-EU trade in medicinal and pharmaceutical products accounted for 4.2 % of total intra-EU and extra-EU trade. These remained fairly close between 2002 and 2014 but started diverging in 2015. In

[108] http://ec.europa.eu/eurostat/statistics-explained/index.php/International_trade_in_medicinal_and_pharmaceutical_products

2016, the share was more than 1% higher in extra-EU trade (6.4 %) than in intra-EU trade (5.3 %).

- The EU was by far the major world trader in medicinal and pharmaceutical products (SITC division 54) in 2016.
- The EU export pharmaceutical products to highly regulated markets with strong patent protection and high per-capita spending on healthcare. The USA stands out as the EU's main trading partner over the period 2001-2016. 50% of Extra-EU export concentrated in three countries: the USA (33.6%), Switzerland (11.4%), and Japan (6.1 %). Those countries are suitable for high-quality, complex medicines for which the EU has comparative advantage in manufacturing. On fourth place there is China (5.7%) followed by Russia (4.3 %) and Australia (3.1%) (see Table 1 for details).
- Switzerland and the USA were however not the countries with the annual highest growth rates. Market growth is shifting toward emerging markets in Asia, Latin America and elsewhere, where pharmaceutical sales are forecast to expand at double digit rates (see Annex 7 for the data on trends in global demand for medicines).
- For extra-EU exports both China (21 %) and Russia (10 %) had higher annual growth than the USA (9.2 %). Strong export growth rates were also present in Brazil (8.7%) and Singapore (8.6%). Further reforms of legislative systems, especially regarding patent protection and enforcement, as well as improving regulatory conditions, will make these markets increasingly attractive for EU industry, which competes on quality, not on prices.
- In imports to the EU double digit growth was found in Singapore (17.8 %), Brazil (13.5 %), Canada (12.4 %), China (11.4 %) and Israel (11.3 %) while Switzerland (8.3 %) and the USA (7.0 %) grew somewhat less strongly. Medicinal products going off patent in the EU as well as increasing ability to compete from these countries contribute to increased importation into the EU market.
- While for the EU15 the main trading partners are developed economies, many of the Member States who joined the Union in and after 2004 Russia remains a key trading partner, along with other former Soviet Republics.
- Finally, looking at the relative importance of intra-EU exports to extra-EU exports shows that for the largest Member States who joined the Union in and after 2004 (i.e. Hungary, Poland and Romania), the value of their export to the EU is more than double than export to non-EU markets. The opposite holds for the western and northern Member States (and, amongst those, in particular for the Nordic Member States).

Table 1: Extra EU-28 exports of medicinal and pharmaceutical products, top 10 trading partners, 2001, 2006, 2011 and 2016 (EUR million)

	Export						Import					
	2001	2006	2011	2016	Average annual growth 2001-2016	Share of exports by country 2016	2001	2006	2011	2016	Average annual growth 2001-2016	Share of imports by country 2016
EU-28	40.860	66.813	103.400	144.200	8,8%	100,0%	23.528	35.314	53.137	75.386	8,1%	100,0%
USA	12.985	23.525	30.722	48.408	9,2%	33,6%	11.526	15.416	19.149	31.658	7,0%	42,0%
Switzerland	4.946	9.334	11.503	16.431	8,3%	11,4%	7.901	13.731	19.771	26.171	8,3%	34,7%
Japan	2.750	3.081	6.297	8.789	8,1%	6,1%	1.148	1.222	1.310	1.279	0,7%	1,7%
China	466	863	3.981	8.256	21,1%	5,7%	578	890	2.355	2.912	11,4%	3,9%
Russia	1.428	3.658	7.292	6.240	10,3%	4,3%	9	8	19	24	6,5%	0,0%
Australia	1.513	2.414	3.875	4.446	7,5%	3,1%	381	414	326	326	-1,0%	0,4%
Canada	1.771	3.266	3.412	4.206	5,9%	2,9%	193	746	1.002	1.113	12,4%	1,5%
Brazil	907	1.014	2.593	3.175	8,7%	2,2%	41	111	446	277	13,5%	0,4%
Israel	434	432	762	1.214	7,1%	0,8%	581	410	1.961	2.889	11,3%	3,8%
Singapore	351	650	1.220	1.213	8,6%	0,8%	227	780	2.925	2.656	17,8%	3,5%

Source: Eurostat, Trade Statistics.

Foreign Direct Investments

Data Box: FDI in development and manufacturing of medicinal products

The Financial Times, a leading global daily business and economic publication, tracks **worldwide announcements for investments** by companies across all industries and activities through its FDI Intelligence (FDI) database.

In this section information the focus is on pharmaceuticals and biotechnology industries with the activities related to manufacturing and development (i.e. 'R&D' as well as 'Design, Development and Testing').

- FDI data indicates that between 2003 and 2015, nearly 2,400 investments have been announced in the activities related to development and manufacturing of medicinal products totalling approximately USD 140 billion around the world and creating over 275 000 jobs in 98 countries.
- Investments and announcements have been primarily concentrated in a number of the emerging economies and established markets. Combined, the 80% of the invested dollars have been invested in the EU (32%)[109], the USA (24%), China (13%), Singapore (7%), and India (5%). 76% of the global announcements took place in these regions (see Table 2 for details).

Table 2: Summary of Worldwide announcements of FDI projects, 2003-2016

	Total value (million USD)		Announcements (number)		Jobs estimated (number)*	
	total	share	total	share	total	share
EU-28	45,086	32%	860	36%	63,469	27%
US	33,322	24%	490	21%	61,646	26%
CN	18,495	13%	220	9%	29,476	12%
SG	10,307	7%	91	4%	9,353	4%
IN	7,516	5%	151	6%	25,579	11%
CH	3,397	2%	30	1%	3,019	1%
CA	3,197	2%	64	3%	5,894	2%
RU	2,236	2%	42	2%	-	-
BR	1,999	1%	44	2%	6,436	3%
MY	1,331	1%	27	1%	3,075	1%
KR	1,058	1%	14	1%	2,306	1%
Rest of the World	11,241	8%	333	14%	28,426	12%
TOTAL	139,185	100%	2,366	100%	238,679	100%

Source: FT fDi database. *where the data is available

- Within the EU, 75% of the value of FDI announcements was for the following receiving Member States: Ireland, Germany, France, UK, Belgium, Spain and Italy.
- The vast majority of announcements concerned pharmaceuticals. Over the last decade, 77% of announced projects in the field of medicine development and

[109] The figures above take into account cross-border investments of European firms in Europe. About 50% of the FDI in Europe is coming from Europe.

production with the value of announced capital investment amounted to 79% of planned capital investment took place in pharmaceuticals.

- There is relatively more new greenfield investment in biotechnology when compared to pharmaceuticals. (Table 3).

Table 3: Projects announced in pharmaceuticals and biotechnology by their type

	Pharmaceuticals	Biotechnology
Number of countries	**85**	**45**
Total announcements:	**1705**	**517**
Collocation (share in Total)	*5%*	*4%*
Expansion (share in Total)	*37%*	*26%*
New (share in Total)	*58%*	*70%*

*Source: FT fDi database. *where the data is available*

- The EU is very attractive as a place for biotechnology investments with the 31% of the value announcement concerning this region. It is followed by the USA (28.5%), China (15.4%), Singapore (6.8%), Switzerland (5.8%) and India (3.8%).
- While FDI in pharmaceutical R&D and manufacturing are widely spread across the globe (95 countries), projects in biotechnology are more geographically concentrated (50 countries, including 18 Member States).

Location of Biopharmaceutical manufacturing sites

Data Box: EudraGMP database

The data provides complete information on all pharmaceutical manufacturers who are compliant with Good Manufacturing Practice (GMP). The GMP is a code of standards concerning the manufacture, processing, packing, release and holding of a medicine. Any manufacturer of medicines intended for the EU market, no matter where in the world it is located, must comply with GMP. We are considering only Good Manufacturing Practice (GMP) compliance for authorized sites in the EEA and in in third countries and limited to 'Manufacturing operations'. Sites that produce biological products are identify as sites for which the certificate has been granted for manufacturing of 'Biotechnology products (1.3.1.5)'.

Table 4: Global distribution of FDI projects and European GMP-compliance for biotechnology manufacturing of medicinal products

	Number of FDI projects (2003-2015)	Number of sites that are EU GMP compliant
EU-28	193	234
US	156	69
SG	23	4
KR	4	3
JP	7	3
BR	2	1
TR	2	1
IR	0	1
TW	1	1
IN	32	1
CN	47	1
IL	6	1

CA	12	1

Note 1: Biotechnology is used to produce medicinal products for complex therapeutic purposes when they cannot be synthesized chemically or produced in sufficient amounts from biological material by simple extraction. Source: FT fDi database and EudraGMP database.

Note 2: The number of EU GMP compliant plants in China, India and Canada are expected to increased (from one plant in each of those countries in 2015) in view of the number of FDI projects (47 in China, 32 in India, and 12 in Canada).

Table 5: Overview of the biopharmaceutical R&D and manufacturing activities

Year	Indicator	Source	Unit	EU28	AT	BE	BG	CY	CZ	DE	DK	EE	EL	ES	FI	FR	GB	HR
	INDUSTRY STRUCTURE																	
2015	**Enterprises**	EUROSTAT	number of enterprises	4,000	84	100	50	7	78	554	102	14	90	343	34	335	574	49
2015	**Employment**	EUROSTAT	persons employed	572,976	14,159	23,938	8,448	1,487	9,376	128,545	32,837	319	9,039	39,121	4,555	*n.a*	*n.a*	4,859
2015	**Value of production**	EUROSTAT	million EUR	260,004	3,907	17,868	*n.a*	205	1,286	44,219	13,251	44	1,447	13,043	1,678	35,238	17,521	726
2015	*- as share in EU pharmaceutical*	*EUROSTAT*		*100%*	*1.5%*	*6.9%*		*0.1%*	*0.5%*	*17.0%*	*5.1%*	*0.0%*	*0.6%*	*5.0%*	*0.7%*	*13.6%*	*6.7%*	*0.3%*
2015	*- as share in total National manufacturing*	*EUROSTAT*			*2.3%*	*8.0%*		*8.0%*	*0.9%*	*2.4%*	*13.4%*	*0.4%*	*3.1%*	*2.9%*	*1.6%*	*4.5%*	*2.7%*	*4.6%*
2015	**Value added**	EUROSTAT	million EUR	90,958	1,796	6,226	*n.a*	89	436	16,020	6,539	8	555	4,595	1,064	10,107	7,481	243
2015	*- as share in EU pharmaceutical*	*EUROSTAT*		*100%*	*2.0%*	*6.8%*		*0.1%*	*0.5%*	*17.6%*	*7.2%*	*0.0%*	*0.6%*	*5.1%*	*1.3%*	*11.1%*	*8.2%*	*0.3%*
2015	**Value of production by foreign**	EUROSTAT	million EUR		3,450	14,584	*n.a*	-	1,042	22,568	599	43	468	7,921	894	10,397	5,506	568
2015	*- as share in National pharmaceutical production*	*EUROSTAT*			*88.3%*	*81.6%*		*0.0%*	*81.0%*	*51.0%*	*5.1%*	*96.8%*	*32.3%*	*60.7%*	*53.3%*	*29.5%*	*36.0%*	*78.2%*
	RESEARCH & DEVELOPMENT																	
2013	**R&D in pharmaceutical manufacturing**	OECD	million EUR	11,347	269	1,817	*n.a*	n.a	58	3,964	849	1	70	634	100	747	496	n.a
	- as share in EU pharmaceutical R&D	*OECD*			*2.4%*	*16.0%*			*0.5%*	*34.9%*	*7.5%*	*0.0%*	*0.6%*	*5.6%*	*0.9%*	*6.6%*	*4.4%*	
	- as share in total National manufacturing R&D	*OECD*		*11%*	*6.8%*	*46.9%*			*4.1%*	*8.8%*	*39.3%*	*1.8%*	*33.4%*	*18.3%*	*3.7%*	*5.2%*	*6.3%*	
2016	Share of project by development stage in 2016	IMS, R&D Focus	share of projects	*100%*	*1.1%*	*3.4%*	*0.0%*	*0.0%*		*17.5%*	*5.1%*	*0.0%*	*0.1%*	*3.9%*	*1.1%*	*19.8%*	*32.0%*	*0.0%*
	TRADE																	
2015	Extra-EU Export	EUROSTAT	million EUR	143,185	4,176	19,407	328	151	383	33,872	7,304	8	149	5,452	573	14,185	19,138	243
2015	Extra-EU Import	EUROSTAT	million EUR	72,567	4,121	15,246	147	56	354	10,656	776	28	392	3,729	311	5,428	7,701	193
2015	**Extra-EU Ballance**	**EUROSTAT**	**million EUR**	**70,618**	**55**	**4,162**	**181**	**95**	**29**	**23,216**	**6,528**	**-19**	**-244**	**1,724**	**262**	**8,757**	**11,438**	**50**
2015	*Intra-EU Export*	EUROSTAT	million EUR	162,577	4,295	21,596	491	104	1,766	34,835	4,233	56	869	5,482	279	14,076	14,204	319
2015	*Intra-EU Import*	EUROSTAT	million EUR	163,165	3,881	19,448	1,004	166	3,324	31,627	2,816	333	2,398	10,097	1,700	18,259	22,802	610
2015	*Inta-EU Ballance*	EUROSTAT	million EUR	-589	415	2,148	-514	-62	-1,558	3,208	1,417	-277	-1,529	-4,615	-1,420	-4,182	-8,598	-291
	Intra-EU Export / Extra EU Export			1.1	1.0	1.1	1.5	0.7	4.6	1.0	0.6	6.9	5.8	1.0	0.5	1.0	0.7	1.3
	PHARMA & BIOTECH																	
2003-2015	FDI Total Announcements	FI fDi	number of projects	860	31	52	7	-	15	99	15	1	-	78	9	109	165	6
2003-2015	- FDI Biotechnology Announcements	FI fDi	number of projects	193	7	20	-	-	5	24	4	1	-	8	1	20	55	1
	EU GMP for biotechnology manufacturing	Eudra GMP	number of sites	234	9	16	-	-	-	45	14	-	-	6	1	29	56	2

Notes: Pharmaceutical manufacturing refers to activities performed in the business enterprises which report *pharmaceutical manufacturing* as their primary activity (C21 in NACE Rev. 2 and ISIC Rev. 4. The OECD data on R&D refers to R&D expenditure statistics performed in the *pharmaceutical manufacturing* companies. Data on R&D projects comes from IMS, R&D Focus (see Table 3 in Kyle study). IMS R&D Focus includes information on drug development projects, including the organizations involved in each project and their respective roles. The projects are report by country of leading company headquarter. Trade statistics comes from Eurostat' COMEXT and United Nations' COMTRADE databases. The focus is on Division 54 - *Medicinal and pharmaceutical products*. FT fDi Intelligence is a source of FDI data. Pharmaceutical and biotechnology projects in 'Life science' cluster are taken into account. Statistics reported refer to FDI project announcements in manufacturing and R&D - i.e. 'R&D' as well as 'Design, Development and Testing' - of medicinal products.

Table 5 (cont.) Overview of the biopharmaceutical R&D and manufacturing activities

Year	Indicator	Source	Unit	EU28	HU	IE	IT	LT	LU	LV	MT	NL	PL	PT	RO	SE	SI	SK
	INDUSTRY STRUCTURE																	
2015	**Enterprises**	EUROSTAT	number of enterprises	4,000	83	155	453	22	1	28	17	218	329	134	131	146	25	30
2015	**Employment**	EUROSTAT	persons employed	572,976	17,452	16,137	57,569	662	*n.a*	2,042	1,165	12,744	23,015	6,302	9,270	12,732		2,222
2015	**Value of production**	EUROSTAT	million EUR	260,004	2,919	43,686	24,151	193				5,089	3,738	1,064	760	9,626	1,837	192
2015	*- as share in EU pharmaceutical*	*EUROSTAT*		*100%*	*1.1%*	*19.0%*	*9.3%*	*0.1%*				*2.0%*	*1.4%*	*0.4%*	*0.3%*	*3.7%*	*0.8%*	*0.1%*
2015	*- as share in total National manufacturing*	*EUROSTAT*			*3.2%*	*37.4%*	*2.8%*	*1.1%*				*1.7%*	*1.4%*	*1.4%*	*1.1%*	*5.5%*	*8.2%*	*0.3%*
2015	**Value added**	EUROSTAT	million EUR	90,958	1,297	12,658	8,050	122				2,027	1,165	437	294	4,280	805	55
2015	*- as share in EU pharmaceutical*	*EUROSTAT*		*100%*	*1.4%*	*15.0%*	*8.9%*	*0.1%*				*2.2%*	*1.3%*	*0.5%*	*0.3%*	*4.7%*	*1.0%*	*0.1%*
2015	**Value of production by foreign**	EUROSTAT	million EUR		1,857	41,929	14,051	177				4,165	2,527	499	400	7,727	n.a.	n.a.
2015	*- as share in National pharmaceutical production*	*EUROSTAT*			*63.6%*	*96.0%*	*58.2%*	*91.5%*				*81.8%*	*67.6%*	*46.9%*	*52.7%*	*80.3%*		
	RESEARCH & DEVELOPMENT																	
2013	**R&D in pharmaceutical manufacturing**	OECD	million EUR	11,347	362	153	556	n.a				230	93	109	18	610	206	3
	- as share in EU pharmaceutical R&D	*OECD*			*3.2%*	*1.3%*	*4.9%*					*2.0%*	*0.8%*	*1.0%*	*0.2%*	*5.4%*	*1.8%*	*0.0%*
	- as share in total National manufacturing R&D	*OECD*		*11%*	*36.3%*	*19.4%*	*6.6%*					*5.9%*	*7.8%*	*19.9%*	*10.2%*	*11.5%*	*34.6%*	*1.3%*
2016	Share of project by development stage in 2016	IMS, R&D Focus	share of projects	*100%*	*0.3%*	*1.1%*	*6.5%*		*0.0%*	*0.0%*		*2.4%*	*0.3%*	*0.5%*	*0.0%*	*4.0%*		
	TRADE																	
2015	Extra-EU Export	EUROSTAT	million EUR	143,185	1,353	13,442	6,632	221	0	161	94	9,183	755	435	220	4,073	1,210	36
2015	Extra-EU Import	EUROSTAT	million EUR	72,567	669	2,648	7,048	55	27	91	60	10,514	647	232	359	507	372	201
2015	**Extra-EU Ballance**	**EUROSTAT**	**million EUR**	**70,618**	**684**	**10,795**	**-416**	**166**	**-26**	**70**	**33**	**-1,331**	**108**	**203**	**-139**	**3,567**	**838**	**-166**
2015	*Intra-EU Export*	EUROSTAT	million EUR	162,577	3,095	16,789	12,421	411	299	171	156	18,253	2,086	484	631	3,527	1,203	445
2015	*Intra-EU Import*	EUROSTAT	million EUR	163,165	2,978	3,104	14,324	909	363	418	75	8,666	4,266	2,125	2,255	3,070	687	1,459
2015	*Inta-EU Ballance*	EUROSTAT	million EUR	-589	116	13,685	-1,904	-497	-64	-247	81	9,587	-2,179	-1,641	-1,624	457	516	-1,015
	Intra-EU Export / Extra EU Export			1.1	2.3	1.2	1.9	1.9		1.1	1.7	2.0	2.8	1.1	2.9	0.9	1.0	12.5
	PHARMA & BIOTECH																	
2003-2015	FDI Total Announcements	FI fDi	number of projects	860	29	101	29	5	-	-	7	22	25	5	15	24	8	3
2003-2015	- FDI Biotechnology Announcements	FI fDi	number of projects	193	2	19	7	4	-	-	-	10	-	-	-	3	2	-
	EU GMP for biotechnology manufacturing	Eudra GMP	number of sites	234	3	16	5	2	-	-	-	14	4	2	-	8	1	1

Notes: Pharmaceutical manufacturing refers to activities performed in the business enterprises which report *pharmaceutical manufacturing* as their primary activity (C21 in NACE Rev. 2 and ISIC Rev. 4. The OECD data on R&D refers to R&D expenditure statistics performed in the *pharmaceutical manufacturing* companies. Data on R&D projects comes from IMS, R&D Focus (see Table 3 in Kyle study). IMS R&D Focus includes information on drug development projects, including the organizations involved in each project and their respective roles. The projects are report by country of leading company headquarter. Trade statistics comes from Eurostat' COMEXT and United Nations' COMTRADE databases. The focus is on Division 54 - *Medicinal and pharmaceutical products*. FT fDi Intelligence is a source of FDI data. Pharmaceutical and biotechnology projects in 'Life science' cluster are taken into account. Statistics reported refer to FDI project announcement in manufacturing and R&D - i.e. 'R&D' as well as 'Design, Development and Testing' - of medicinal products.

ANNEX 12: STUDIES ON THE MANUFACTURING WAIVER

This impact assessment draws on eight studies that evaluate or discuss the impact of a manufacturing waiver: one contracted by the Commission, two sponsored by generic/ biosimilar manufacturers and five by SPC-holders.

- CRA (2017), *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe* (European Commission)
- Office of Health Economics (2018), *Review of CRA's Report* (EFPIA)
- European Economics (2018), *Impacts of Reducing Patent and Extended Protections against Manufacturing for Stockpiling and Export* (EuropaBio)
- Vicente, V., & Simões, S. (2014). *Manufacturing and export provisions: Impact on the competitiveness of European pharmaceutical manufacturers and on the creation of jobs in Europe*. Journal of Generic Medicines (BluePharma)
- Sussell, J. A., Tebeka, M. G., Jena, A. B., & Vanderpuye-Orgle, J. (2017). *Reconsidering the economic impact of the EU manufacturing and export provisions*. Journal of Generic Medicines (AbbVie)
- Roland Berger (2015), *Extension of the Bolar exemption regarding production for export and launch preparation*. (Pro Generica)
- Logendra *et al* (2017), *Assessing the impact of proposals for a Supplementary Protection Certificate (SPC) Manufacturing Exemption in the EU*. Quintiles IMS (EFPIA)
- Pugatch Consillium (2017), *Unintended Consequences* (AbbVie, La Roche & US Chamber of Commerce)

The table below provides an overview of these studies and summarizes the main strengths and weakness of each of them. A detailed discussion follows.

Table 12.1: **Overview of the economic studies evaluating the manufacturing waiver**

Study	Funding	Type of study	Coverage	Strengths	Weaknesses
CRA (2017)	European Commission	Quantitative : micro data (117 molecules with expiry dates 2015-2025)	Export waiver Stockpiling	Assumptions well-grounded in the literature and supported by data Counterfactual scenario	Limited data on the biosimilar market
Office of Health Economics (2018)	EFPIA	Sensitivity analysis of CRA	-	Assumptions based on case studies (ref. to Quintiles IMS)	Biased assumptions to minimise the effects estimated in CRA
European Economics (2017)	EuropaBio	Critical discussion of CRA	-	Critical review	Fails to offer solution/alternative data to address limitations
Quintiles IMS (2017) also cited as Logendra *et al* (2017)	EFPIA	Case study: 25 medicinal products (23 molecules)	Export waiver	Identifies specific barriers to enter in 3rd countries	Biased sample does not reflect reality of SPC landscape in the EU: MA prior enlargement, products with invalidated SPCs.
Pugatch Consillium (2017)	AbbVie, La Roche & US Chamber of Commerce	Quantitative: approximation from global demand for medicines	Export waiver	Illustrates the strong evolution of pharma market	Over-interpretation of results: *sales at risk = 'lost sales'*
Vincente & Simoes (2014)	BluePharma	Quantitative: micro data (55 molecules)	Export waiver Stockpiling	Assumptions base on the information from generic producers	Lack of counterfactual scenario
Sussel *et al* (2017)	AbbVie	Sensitivity analysis of V&S	-	Counterfactual	Not transparent about assumptions
Roland Berger (2015)	Progenerica	Quantitative: micro data	Export waiver	Difficult to assess as no methodological annex is available; still, results in line with CRA	

CRA (2017) Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe (European Commission)

The CRA estimates that an SPC manufacturing for 'export-only purposes' could result in additional export sales by EU-based production of those generics of EUR 7.6bn and for EU-based production of those biosimilars of between EUR 463m and EUR 2.97bn over 10 years.

CRA estimates, for that sample, the potential negative impact of this waiver on EU SPC holders' sales in EUR 139m to EUR 278m for the generics market and in between EUR 868m to EUR 1.7bn for biologics over a 10 years period. Therefore, the net additional trade balance for the EU pharmaceutical industry represented by the sample of CRA would be between EUR 6 - 10bn over 10 years.

The estimations are based on the sample of 117 non-biological molecules and 17 biological molecules whose SPC protection in Europe expires during the period 2016-2030 and earlier in at least one of 8 third countries considered (i.e. Australia, Brazil, Canada, China, Japan, Russia, Turkey and US) which account for 60% of the EU export in the pharmaceuticals. The 117 molecules represent 32% (by count) of all molecules whose SPCs expire in Europe during the period 2016-2030.

To estimate the impact of the SPC export waiver to third countries the CRA deducts the estimated sales achieved by European generics producers in third countries without the waiver from the sales achieved under an SPC export waiver. This simplifies to the sum of lost sales during the SPC term in Europe, plus the benefit of first mover advantage from earlier entry under the export waiver.

In their analysis of manufacturing waiver the CRA makes assumptions about market structure, price dynamics and sales volumes that could be achieved by generic and innovator firms located in the EU. These assumptions are made for each export market separately and are based on results of the studies published in peer-reviewed journals or in Reports.

Due to the lack the detailed data on the individual drug sales in export markets the CRA made assumptions at the country level - in a way averaging over medicinal products with different characteristics.

Another limitation is the estimation of the impact of manufacturing waiver for biological molecules. The CRA has information on 17 molecules only. The issue is that biologic revolution came in the late 1990s but the biosimilar entry - i.e. marketing authorization procedures to show that the biosimilar drug is therapeutically equivalent to an already approved original biologic drug – have only been approved recently: in 2006 in the EU and in 2015 in the United States.

Underlying assumptions of CRA Study have been critically reviewed by Office of Health Economics (2018) and European Economic (2018) Reports. The Commission has analysed the different critical remarks. Below we discuss the main criticisms in detail.

Office of Health Economics (2018)

- Claims that SPC protection is not often the longest in Europe

  Relying on the finding of the case studies in Logendra *et al* (2017), the OHE claims that only 2 out of 25 molecules expire later in the EU than in three or more non EU-countries. However, the same case study analysis also shows that 14 out of 25 molecules expire in at least one out of six non-EU countries before the EU. Taking into account the high volume of sales derived from one product only, plus the fact that

this sample only considers 25 molecules for only 6 export markets, we consider that OHE does not prove that opportunities for export markets are not relevant or significant.

Relying on the finding of the case studies in Logendra *et al* (2017), the OHE claims that only 1 out of 25 molecules has earlier expiry date in the USA compared to the EU. From this, it is derived that only 4% of the molecules could benefit from an export waiver in 3rd countries, implying that an export waiver would result in net gains of only EUR 2bn. This figure has been misinterpreted by other position papers who stated, in turn, that only 4% of molecules will have market opportunities in all third countries. The OHE study, based only on 25 molecules expiring in the EU vis-à-vis the USA, offers less robustness than the 117 samples examined in the CRA study, which includes 8 different export countries.

It also needs to be noticed that OHE paper is based on the results of Quintiles IMS study (Logendra *et al* 2017), which presents biased expiry dates for SPC protection in the Union because it includes Poland and Slovenia (which introduced SPC protection only after 2004). Therefore, any reference to expiry dates offered by Logendra *et al* does not reflect the current situation where the SPC can be applied for in all Member States.

- Claims that estimates of markets shares are not consistent across countries

  Estimations from US, Canada, Australia, & Japan come from the IMS Institute for Healthcare Informatics November 2013 Report on '*The Global use of medicines: Outlook through 2017',* which bases its estimations also on IMS Health Midas data (2013). Therefore, all estimations, based on primary and secondary information, come from the same source, IMS data.

- Claims that CRA fails to take account of erosion curves for generics

  Given the long-term nature of diseases treated by biosimilars, switching between reference product and biosimilar are slower. This is why CRA puts a specific emphasis on erosion curves for biosimilars. Switching rates between reference products and generics are faster. Generic market erosion is not as gradual as for biosimilars, therefore first-move advantage is likely to have a bigger impact. CRA models the market share adapting it to the specificities of each market.

  Therefore, market shares addressed in the CRA cannot be deemed incorrect, they are modelled according to the mains dynamics which characterise each market.

- Claims that potential market shares for generics in 3rd countries are exaggerated

  OHE refers once more to case studies in Logendra *et al* (2017) to exemplify, based on a sample of five molecules, that the potential market share for generics is overestimated in third countries. These five molecules are treatments for chronical use in cardiovascular domain. Given the chronic nature of these therapies and the initiating specialist prescription, slow generic entry is justified for these cases[110]. The market

[110] Example of low take-up of Losartan in European market, same molecule used in Quintiles IMS. In this case, low generic take-up is not only an export market characteristic, but a product characteristic: http://www.gabionline.net/Generics/Research/Impact-of-delisting-ARBs-in-Denmark

shares of these case studies is used to reduce by 4 percentage points the market shares put forward in the CRA study (sample of 117 molecules).

While we acknowledge market shares to be different depending on the molecule, and the export country, we do not find justified to claim CRA market shares are not correct, especially when comparing those to a selected sample of five molecules which have very particular characteristics that are not representative of the overall market.

- Claims that the first-mover advantage is not proven

  OHE questions the validity of a first-mover advantage by arguing that this is a very country specific effect and that it cannot be assumed to exist in other countries different than Canada.

  What literature points out, is that the magnitude of the first mover advantage depends on different factors. The nuances will vary depending on the market context, such as prescriber characteristics, route of administration, competitive dynamics, capabilities, lead time and product label. First-mover advantage can be difficult to surmount, but it is not always impossible, especially for 2nd market entrants having experience and large resources. Strong clinical developments and commercial strategies are also important factors for determining market advantage[111].

  The CRA study already takes a conservative approach by estimating a first mover advantage of limited impact: it is only estimated over two years and the magnitude is limited. On top of that, no first mover advantage is modelled in the study when quantifying the benefits of a possible waiver for biosimilars.

  Removing completely the effect of a first mover advantage from the model is not deemed appropriate or realistic, especially considering the already conservative approach taken by the CRA study.

Relying on the information from case studies discussed in Logendra *et al* (2017) OHE revises downward the CRA estimates: for the generic gains on export from EUR 7.6bn in CRA down to EUR 1.3bn and on the potential losses for SPC holders from EUR 139m in CRA up to EUR 573m according to OHE. This recalculation by OHE does not, however, contradict CRA's conclusions: namely those generic gains on exports - and losses for SPC holders will largely compensate any potential losses for the SPC holders.

In 2018, **Europe Economics**, sponsored by EuropaBio, published another review of CRA's study. This study offer critique similar to the OHE (2018) but no alternative quantification is provided. The final conclusion of Europe Economics (2018) is that CRA study could be overestimating the benefits of an export waiver, but their main concern is the possibility that a manufacturing waiver will undermine the sustainability of protection against stockpiling.

The issue of the sustainability of protection raised by industry is not addressed in the CRA report, since it was not the objective of this study, but it has been properly addressed in this impact assessment with the possibility of introduction of anti-diversion measures.

[111] https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/pharmas-first-to-market-advantage

Logendra *et al* (2017) Assessing the impact of proposals for a Supplementary Protection Certificate (SPC) Manufacturing exemption in the EU, Quintiles IMS

Analysing 25 case studies, Logendra *et al* (also quoted as Quintiles IMS), sponsored by EFPIA, argues that there would be potential losses to European originators in the form of decreased export value for the EU, if an SPC manufacturing exemption is introduced. This study argues that an export model based on a 'SPC manufacturing waiver' would not yield much result for different reasons.

Several arguments are brought to justify their claims: 1) market opportunities for generics in 3rd countries are little; 2) European generics will erode sales of European innovative products in 3rd countries because they will compete on the European brand; 3) the potential opportunities for molecules having a later expiry date in the EU than in the rest of the world is very limited; 4) API production is already located in a cost-efficient way.

1) One of the main critics of the study is that opportunities for generics in 3rd countries are few, mostly because of high take-up of local generic products in 3rd countries, incentivized by localization policies. In order to support its argument, the authors present case studies of five molecules for chronic use in cardiovascular diseases in 4 different market shares.

This factor is already acknowledged in the CRA study, which presents a sensitive analysis reducing the possibility of export for European generic firms in 3rd markets (see pages 121 and 132 of the CRA Report). The final impacts show that when assuming that sales of European generic firms can only attain 10% market share in 3rd markets, the additional sales obtained are only 12% (for generics) and 5-6% (for biosimilars) lower than the original estimates.

Firstly, while the few case studies that Quintiles show that different market shares might exist depending on the molecule, they fail to provide solid justification on why the estimation provided by CRA is not valid.

Secondly, if new European generics cannot enter export markets, European innovators should not experience any erosion. An export waiver in any case would then create a substitution effect between generics to the advantage of EU generics by speeding the entrance of European generic in export markets.

2) The study presents the idea that European generics will mostly take sales at the expense of European innovative companies, by competing with branded generic products in 3rd countries post patent expiry. The report grounds this argument on few case studies which show that originators' brands retain some volume share after patent expiry. From this evidence, it is extrapolated that generics manufactured in the EU would capitalise on their 'European brand value' and go on to compete with originators' exports.

On one hand, considering the chronic nature of the diseases represented by the molecules analysed by Logendra *et al*, one could expect a low rate of switching between the reference product and the generic (whether that generic were imported from the EU or from another developed country, or produced locally), as patients' established medication is not easily subject to switching (this phenomenon can also be observed in the EU).

On the other hand, where significant market opportunities are expected, the Logendra *et al* study does not take into account that originators' exports would anyway face competition from branded generics produced in other developed countries such as Canada, or generics production outsourced by EU firms to non-EU countries.

3) The report argues that SPC protection expires earlier in a sample of analysed Member States than in export markets. A close look into their data shows that more than 50% of the molecules considered have an earlier expiry date in a non-European country. In addition, it needs to be noticed that earlier SPC expiry in the chosen EU sample is due to the inclusion of Poland and Slovenia (which introduced SPC protection after 2004). As this means that this study relied on now-outdated data, its conclusions are no longer valid.

4) Finally, the study argues that APIs are currently sourced mostly from China and India because of cost-effectiveness decisions. However, the study fails to acknowledge that this competitiveness advantage is reducing over time[112]. This proposal does not aim to promote European API production per se, but to ensure that if this competitiveness advantage from 3rd countries currently supplying API disappears, Europe will not be constrained by regulation to keep importing from less cost-efficient countries.

Pugatch Consilium (2017) Unintended consequences

The Pugatch study (2017) sponsored by AbbVie, La Roche and the US Chamber of Commerce estimates that with an EU SPC manufacturing waiver between USD 1.34bn to USD 2.27bn of annual exports of European originators (0,61% to 1.04% of their total global sales, corresponding to 4.600 to 7.750 originators' jobs in the Europe) would be exposed to generic and biosimilar competition in export markets.

On one hand, this study seems to assume that all innovators sales open to competition are sales at risk. This assumption would imply that currently SPC-holder do not face competition from other countries in 3rd markets on the off-patent period. As Logendra *et al* (2017) study shows, currently European generic firms face strong competition from the rest of the world.

On the other hand, the study seems to suggest that the totality of sales at risk, are potential sales which can be lost because of the increased competition of the export waiver. As reasoned above, it is unrealistic to assume that the totality of EUR 1.34bn – EUR 2.27bn will be lost, because they are already currently open to competition from other non-European countries, and because the waiver would also benefit their own EU-based manufacturing of biosimilars and generics (for exports and EU *day-1* entry).

The Pugatch study attempts to quantify the potential job losses that could be derived from the export waiver. In order to do so, they assume that the reduction of R&D jobs will be by the same magnitude that the share of sales at risk – 0.61 – 1.04%.

Finally, the Pugatch study fails to acknowledge that, as shown in Annex 5, the waiver will also benefit EU-based generics & biosimilars branches of originators as most biosimilars approved by EMA and FDA as of December 2017 are commercialised by the main innovative companies (originators).

Vicente and Simões (2014). Manufacturing and export provisions: Impact on the competitiveness of European pharmaceutical manufacturers and on the creation of jobs in Europe. Journal of Generic Medicines

In 2014, the *Journal of Generic Medicines* published a study by Vicente & Simões, sponsored by the European generics and biosimilars association (*Medicines for Europe*). This study analysed the potential impacts of introducing a manufacturing and an export waiver in the EU.

[112] Competition in the World API's market, Chemical Pharmaceutical Generic Association, 2015.

Based on a sample of 55 generics, 5 European markets (France, Germany, Italy, Spain and UK), and considering only export markets in Latin America, the implementation of an SPC manufacturing and export waiver would create 8 890 direct jobs and 30 000 additional indirect jobs within 8 years. Disaggregating both effects, manufacturing provision only accounts for the creation of 8 000 jobs direct jobs, 24 000 – 32 000 indirect jobs.

The methodology behind the study relies on the first mover advantage. Considering the limited sample and the omission of a counterfactual, generalisation of these results should be taken carefully. Even though this study presents some limitations, such as lack of evidence for the parameters provided or the omission of a counterfactual, its merits lies on settling the grounds for a controversial debate, which was later replicated by others researchers.

In 2017, the *Journal of Generic Medicines* published a study by **Sussell *et al***, financed by AbbVie, that replicates the model used in the study of Viente & Simoes (see above), applying a number of adjustments. Those adjustments include an arithmetical correction[113], the introduction of a counterfactual[114], a revision of the parameters and a sensitivity analysis. While some of these adjustments are well justified - such as the arithmetical correction or the introduction of a counterfactual – others (e.g. the revision of the parameters) present the same weaknesses since no clear evidence is presented to justify their validity[115].

This study considers that the effects of an SPC manufacturing waiver would be smaller those reported by Vicente & Simoes (2014): 30% less additional production in the EU and 1.898 new direct jobs (and 6,642 new indirect jobs). The results of the study were also notorious because under some scenarios, the authors claim that the number of job losses in the innovative sector could be higher than the job creation in the generics sector. However, this result relies on an important assumption: after patent expiry, competition of generics will not drive prices of innovative products down, thus post-patent innovative products will be sold at their pre-generic price. Evidence shows that, while branded generic products can hold a higher price than generics after patent expiry, market competition drive prices down once the patent has expired[116]. It also needs to be observed that, in order to obtain a negative net effect on job creation, the authors compare an upper bound estimation of 2,490 jobs loss in the innovative sector (as acknowledge by the authors) with a lower bound for the creation of jobs in the generic sector (1,890 jobs).

Based on the limited evidence provided by Sussell *et al* as regards their estimates and the type of calculations used, no robust results can be inferred on positive or negative net effects on job creation. The study only offers a counterfactual and arithmetic correction and alternative parameters which are used as a robust test to criticise Vicente and Simoes study.

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[113] In their arithmetical calculation, Vicente & Simões (2014) duplicate the business volume to be captured by generics after the 3rd of patent expiry. This leads to an overestimate of the calculations.

[114] Predicted decrease of market share due to one month delay after entry of 1st generic manufacturer is taken from the results of Hollis *et al* (2002).

[115] Robustness checks are a valid and a common measure to validate the results of obtained through models. However, usually some insight or reasoning is given in order change the parameters. In this case, Sussell *et al* do not offer any explanation which justifies the magnitude of the variation of the parameters.

[116] Copenhagen Economics, 'Study of the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe'.

Roland Berger (2015) Extension of the Bolar exemption regarding production for export and launch preparation

In 2015, Roland Berger consultants finalised a study contracted by Progenerika (the German association of generic manufacturers) that estimates the highly positive impact of a patent/SPC manufacturing waiver for export purposes in additional EUR 4.7bn exports for the German industry over a decade and additional 6 900 jobs.

ANNEX 13: NUMBER OF MARKETING AUTHORIZATION REFERRED TO IN SPC APPLICATIONS

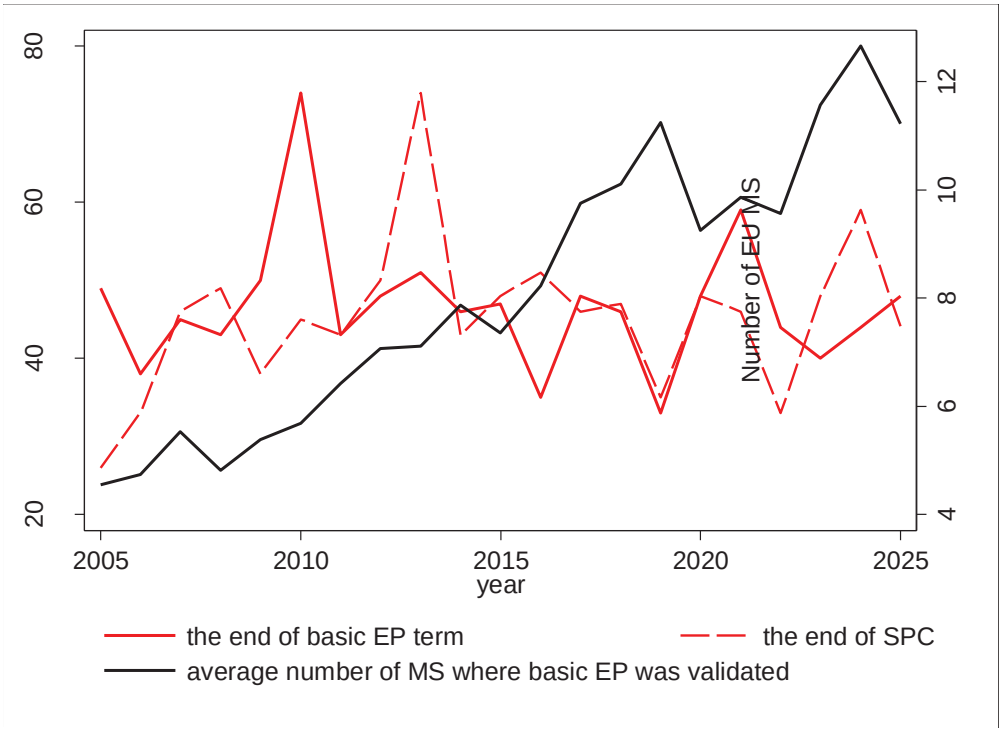
Table 22.1: Number of marketing authorisations (MA) granted between 1995 and 2014 that have been listed in SPC applications

Year of 1st MA in the EU	MA with SPC (all)	MA with SPC (Biologicals only)
1995	35	1
1996	41	2
1997	39	3
1998	36	2
1999	43	8
2000	36	9
2001	42	10
2002	37	7
2003	28	2
2004	41	6
2005	26	3
2006	40	9
2007	37	9
2008	29	1
2009	40	13
2010	24	5
2011	45	6
2012	36	5
2013	56	14
2014	44	9
Total:	755	124

Source: Alice de Pastors database and EMA website.

ANNEX 14: PATENT CLIFF AND GEOGRAPHICAL SCOPE OF SPC PROTECTION

Graph 23.1: Number of SPC bundles and the geographical scope of protection in the EU



Note: The Graph shows the number of SPC bundles by the year of patent term expiry (solid red line) and the year of the SPC expiry (dash red line). Solid black line shows the average number of Member States where the basic patent has been validated. There are two periods where the patent term ends for substantial number of patents – 60 and above - i.e. 2010 and 2021. The black line shows that the geographical coverage of protection in the EU is increasing over time indicating that the SPC protection in the EU is getting mainstreamed.

The data used to develop this graph comes from the Alice de Pastors database. We consider only those SPCs that were applied with reference to EP patent. We exclude SPC that were rejected in the granting process or withdrawn by the applicant. Similar to Annex 10, we count distinct *basic patent-product pairs* for which the SPC was applied for in the EU (i.e. number of SPC bundles). As the expiry dates differ from one Member State to another, for each *basic patent-product pair* we assume that SPC expires 3 years after the end of patent term.

The geographical scope of protection is the number of countries where the SPC was applied for the same basic-patent product pair. The average shown in the graph should be considered as a lower bound for the following reasons. First, Member States are not obliged to cite the EP patent application number. Second, for 20% of the products the SPC was applied for with reference to more than one basic patent in at least one Member State and we are not able to identify the product patents. Finally, depending on patent availability the same product may be protected by two different patents in two different geographical regions.

To illustrate the point, the graph shows that average geographical scope of protection with the basic patent terms expiry in 2024 is about 13 Member States. Still, according to Mejer (2017) and Kyle (2017) the average geographical scope of SPC protection for the medical products approved in 2014 was about 20 Member States.

ANNEX 15: IMPACT OF A POSSIBLE SPC MANUFACTURING WAIVER ON R&D IN THE EU

	Originators / SPC holders		**G/B manufacturers**	
	Classical medicines (non-biologics / 'small molecules')	**Biologics**	**Generics**	**Biosimilars**
R&D requirements	Very high (need for clinical trials; up to EUR 2 000m per medicine; high risk of failure) For biologics: Mixed location factors as manufacturing and R&D tend to be co-located		Low (no need for clinical trials; minor risk of failure; EUR 2-3 m development cost)	High (need for some clinical trials; medium to high risk of failure; up to EUR 300 m R&D cost)
Impact of a SPC manufacturing waiver on R&D conducted in the EU	- Many factors other than IPR-related (e.g. skills, tax incentives) determine R&D location and EU will remain attractive due to excellent ecosystem and infrastructure to conduct R&D. - Other EU pharmaceutical-specific incentives will not vary with the waiver (e.g., orphan incentives). - The global IPR protection and enforcement framework in the EU remains the strongest worldwide;		High positive impact is expected since the waiver would help retain and promote generics manufacturing in the EU.	Positive impact is expected since, for biosimilars, as R&D and manufacturing tend to be co-located.

ANNEX 16: SME TEST

The Union aims to improve the overall approach to entrepreneurship, and has permanently anchored the 'Think Small First' principle in policy making to promote growth of SMEs (and start-ups in particular). SMEs are the backbone of the EU economy, creating more than 85% of new jobs in Europe. Also in the pharmaceutical sector, SMEs play a key role.

The potential impacts of the proposed initiative on SMEs have therefore been considered; they are reported throughout the impact assessment and below in an aggregated format.

This impact assessment and the preferred policy option have taken into account the pharmaceutical SMEs, and an SME-test has been conducted in line with the 4-steps foreseen in the Commission's Better Regulation policy.

Step-1: Identification of affected businesses

There are various types of SMEs active in the pharmaceutical sector. For the purpose of assessing the effects of this proposal, the following types of SMEs active in the pharmaceutical sector can be distinguished:

1. *SMEs engaged in manufacturing activities related to generics and biosimilars*

   They include companies manufacturing on their own behalf as well as companies working as a subcontractor (e.g. such as contract development and manufacturing organisations, 'CDMOs').

2. *SMEs engaged in research supporting the development of biosimilars[117];*

3. *SMEs engaging in R&D with a view to developing innovative pharmaceutical products (i.e. potential future SPC holders), and SMEs manufacturing those products.*

The SMEs covered by points 1 and 2 above are the main beneficiaries of the proposal. The impact of the proposal on SMEs covered by point 3 needs to be assessed.

- *SMEs engaged in manufacturing activities related to generics and biosimilars*

According to Eurostat, in 2015 in the EU28 there were 3 724 SMEs active in pharmaceutical manufacturing, representing 88% of the firms and 22% of the workforce, in the pharmaceutical sector[118]. This includes only those SMEs whose primary activity is pharmaceutical manufacturing[119], and does not necessarily capture SMEs specialized in other activities[120] such as pharmaceutical R&D, commercialisation of generics[121] or innovative products (for the later type of SMEs see data below).

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[117] As explained in the impact assessment, biosimilars are highly intensive on R&D investments (in the range of several hundred million euro per molecule).

[118] Annex 4, 7 and 11 of this impact assessment describe more general the pharmaceutical sector and its weight in the EU economy (export, employment, FDI).

[119] It includes both SMEs manufacturing original as well as generic/biosimilar products.

[120] Another statistical source of pharmaceutical SMEs (not limited to manufacturing activities) in the EU is the register of the SME office of the EMA. This register contains over 1,500 companies registered as active in the pharmaceutical sector in the EEA having the SMEs status. This presents a sharp increase (10 times more than in 2006). Pharmaceutical enterprises can apply for SME status at the EMA before requesting financial or

A high number of SMEs manufacture generics in the EU, and to a lesser extent biosimilars (the 1st biosimilar was approved in the EU in 2006, and biosimilars require higher investments and risks[122]).

Recent decades have seen a steep shift towards outsourcing of manufacturing to reduce the risk of onerous overcapacities. Thus, manufacturing outsourcing to 'contract development and manufacturing organisations' (CDMOs) represented a USD 62bn market in 2016. Industry's annual growth rate was almost 7% (slightly above the growth of the pharmaceutical sector as a whole which is almost 6%)[123]. Despite an on-going trend towards concentration in the CDMO sector, it still remains fragmented with a majority of CDMO being privately owned (small family-run or mid-market companies).

Export performance of European SMEs: the Table below provides an overview of exporting activities by SMEs focused on pharmaceutical manufacturing. About half of the 3,724 SMEs in pharmaceutical manufacturing (i.e. 1 765 firms) are exporting, 77% of these exporting companies export outside the EU.

The exporting activities of these SMEs vary from one Member State to another. The share of exporting firms is the highest in Germany, Belgium, Austria and Spain (with more than 60% of SMEs exporting outside the country of production) and lowest in in Poland, Denmark or UK (less than 35%). Exporting SMEs in Poland, Hungary, Austria and UK are relatively more focused on the EU market than non-EU[124]. In 2015 about 40% of the turnover generated by SMEs has been exported out of this 50% outside the EU. SMEs in Denmark, Hungary and Spain exported more than 50% of their turnover.

Table 16.1: Overview of EU SMEs activities in pharmaceutical manufacturing, 2015

	Number of SMEs					Turnover (EUR m)	Export by SMEs (EUR m)	
	Total	Exporting	*Share Exporting*	Exporting outside EU	*Share exporting outside EU*		Total	Extra-EU
AT	74	50	*68%*	34	*68%*	*n.a.*	1234	644
BE	87	61	*70%*	45	*74%*	806	275	82
CZ	69	33	*48%*	26	*79%*	278	111	23
DE	459	362	*79%*	262	*72%*	4916	1323	630
DK	92	28	*30%*	25	*89%*	357	182	93
EL	81	49	*60%*	38	*78%*	764	68	34
ES	296	197	*67%*	177	*90%*	3904	2396	1227

administrative assistance from the EMA. For the EMA SME Register see: https://fmapps.ema.europa.eu/SME/search_advanced2.php

[121] Of the 282 SMEs in the EMA register that gave their consent to publish their data, 247 are developing and commercializing generic medicines (of which 70 SMEs in 'early manufacturing/Research & Discovery stage', 76 in 'development stage' and 195 in 'Commercialisation/Marketing stage (EU/Non-EU)).

[122] According to the Eudra GMP database 234 sites in the EU are GMP compliant for biotechnological manufacturing. This is much smaller than the overall number of 4 000 of pharmaceutical manufacturing companies as reported in Eurostat (cf. Annex 11).

[123] http://www.ey.com/Publication/vwLUAssets/ey-study-opportunities-in-the-consolidating-cdmo-industry/$File/ey-study-opportunities-in-the-consolidating-cdmo-industry.pdf

[124] This is under the assumption that all companies which export outside the EU also trade within the EU.

FR	274	133	*49%*	125	*94%*	*n.a.*	733	294
HR	45	17	*38%*	17	*100%*	64	91	15
HU	75	31	*41%*	20	*65%*	246	127	55
IE	*n.a.*	53	*n.a.*	41	*77%*	*n.a.*	5130	4518
IT	394	234	*59%*	195	*83%*	6661	2366	1081
NL	208	102	*49%*	60	*59%*	1371	736	170
PL	301	82	*27%*	51	*62%*	444	83	17
PT	127	50	*39%*	37	*74%*	622	144	84
RO	121	43	*36%*	36	*84%*	368	226	20
SE	138	64	*46%*	53	*83%*	725	270	167
UK	531	176	*33%*	120	*68%*	2527	1195	756
Total	3372	1765		1362		24051	16691	9909

Source: Eurostat. Only Member States for which data is available are included in the Table.

- SMEs engaged in research supporting the development of biosimilars

In the EU, biosimilars are evaluated by the EMA (annex 5 shows that, so far, only 36 have been authorised in the EU).

The EMA SME-register shows that 23 SMEs are registered under the product category 'biosimilars', 9 in 'early manufacturing/Research & Discovery stage'[125], 14 in 'development stage'[126], and 13 in 'Commercialisation/Marketing stage (EU/Non-EU)'[127].

- SMEs doing research with the view to view to developing innovative pharmaceutical products (i.e. potential future SPC holders)

In the field of pharmaceutical innovation, start-ups and SMEs are playing an important role, especially in the initial steps of innovation. The Commission's pharmaceutical sector inquiry reported that approximately 25% of molecules in clinical development were acquired from other companies, including SMEs. This shows that pharmaceutical companies are increasingly externalising their R&D. According to EBE, when the EMA analysed the origin of new medicines, 27% of all new medicines, and 61% of new medicines for orphan indications originated from SME. Newer figures confirm that significant medical innovation comes from SMEs. The cumulative figures from the EMA's PRIME scheme indicate that 44% (15 out of 34) of PRIME applications granted in 2017 came from SMEs.

The SMEs register of the EMA has 185 SMEs registered with a focus on new formulations/delivery methods, and 2 SMEs developing complex biologically derived proteins and peptides. We can observe a high number (256) of SMEs specialised in orphan treatments (these category of SMEs especially relies on orphan incentives, under Regulation

[125] These 9 companies are located in BE (2 employees), FR (3 employees), ES (201 employees), DE (68 employees), PL (102 employees), HU (two companies with 38 employees), IE (85 employees), and AT (69 employees).

[126] These 14 companies are located in CY (85 employees), UK (11 employees, 83 employees), BE (2 employees, and 18 employees) FR (3 employees), ES (201 employees), DE (68 employees, and 26 employees), PL (102 employees), HU (two companies with 38 employees), IE (85 employees), SE (10 employees) and AT (69 employees).

[127] These 13 companies are located in GR (1 employee), CY (85 employees), DK (5 employees), SI (13), DE (three companies with 47, 7 and 26 employees), PL (102 employees), HU (two companies with 38 employees), IE (85 employees), LV (1 employee and 5 employees).

(EC) No 141/2000 on orphan medicinal products, for their investments in innovation). We can also observe a high number, 118, of SMEs specialised in paediatric treatments. 77 of these SMEs are also involved in orphan treatments, with a majority of them having less than 10 employees. 159 SMEs are registered as active in the medical devices field.

IP protection is very important for these SMEs. The European Patent Office (EPO), for instance, has produced a series of case studies on European SMEs, including SMEs dealing with biotechnology and medical devices, which are leveraging the power of patents and other IP rights to achieve business success. The resulting case studies illustrate how new and established SMEs have developed the IP management capabilities they need, and how they are using IP to their advantage.

Step-2: Consultations that captures the SME angle

This impact assessment has been elaborated paying due consideration to all inputs provided by stakeholders. The SME angle has been taken into account throughout the consultation process, visits to industrial sites, bilateral meetings, and the participation of the Commission services in seminars/round tables, as explained below.

i) Commission's public consultation on SPCs and patent research exemptions

This public consultation included a set of six specific sub-questionnaires for the six groups of stakeholders, including (II) originators industry/associations and (III) generics and biosimilars industry/associations, both of which included SMEs.

The questionnaires addressed to these industrial-related stakeholders (groups (II) and (III) above) included identification-related questions allowing for the identification of submissions corresponding to start-ups and SMEs. In the case of SMEs, following the EU definition of SME (Small/medium company (except start-up), fewer than 250 employees, annual turnover of EUR 50m or less, and annual balance sheet of equal to EUR 43m or less) and start-up).

The statistics corresponding to respondents identified as SME or start-up profiles are the following:

- Among the 63 respondents defining themselves as mostly manufacturers of generics/biosimilars (group III), 12 respondents identified themselves as an SME and 1 as a start-up. The table below reflects the answers of those 13 SMEs and start-ups (they are anonymised) to the questions related to the problems defined in the impact assessment (and related questions).

Anonymised respondents→	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Agreement with problem 1 (export losses)?	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes	-	Yes	Yes
Agreement with problem 2 (EU *day-1*)?	Yes	Yes	Yes	N/A	Yes	N/A	Yes	Yes	Yes	Yes	-	Yes	Yes
Over-reliance on import of APIs?	Yes	Yes	Yes	N/A	Yes	No	N/A	Yes	Yes	Yes	-	Yes	Yes
SPC triggers delocalisation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-	Yes	Yes
Biosimilar R&D and manufacturing tend to be placed together?	N/A	N/A	Yes	N/A	Yes	N/A	N/A	N/A	Yes	Yes	-	Yes	N/A

- Among the 71 respondents defining themselves as mostly originators (group II), only 2 respondents identified themselves as an SME involved in medicines biotechnology and one as a start-up in the field of biopesticides. The table below reflects the answers of those 3 companies (they are anonymised) to the questions related to the problems defined in the impact assessment (and related questions):

	Do you agree with problem 1 (loss of export)?	**Do you agree with problem 2 (EU *day-1*)?**	**Are problems 1 and 2 more relevant for biosimilars?**
SME respondent 1 (biologics)	Yes	No answer (N/A)	N/A
SME respondent 2 (start-up biotech)	Yes	Yes	Yes
SME respondent 3 (biopesticides)	N/A	N/A	-

In addition, several European pharmaceutical associations such as Medicines for Europe, EUCOPE, EBE, and EuropaBio conveyed the views of their start-ups and SME members in their submissions and accompanying letters sent to the Commission during the public consultation. A few national pharmaceutical associations with start-ups and SMEs-members also provided their views.

ii) Max Planck Institute's SPC stakeholders consultation

The terms of reference for the study on the legal aspects of the SPC that the Commission contracted to the Max Planck Institute (MPI) flagged the need to pay attention to the needs of SMEs in biopharmaceutical sector. The final report of the study discusses a few aspects of the SPC that specifically affect SMEs (e.g. the issue of 'third party holders of marketing authorisations', the scope of the Bolar exemption regarding third party supply of APIs that seems to affect especially to SMEs). Some SMEs and universities replied to the consultation launched by MPI in the context of the study. Some respondents to the consultation highlighted the potential benefits of a manufacturing waiver for SMEs[128].

iii) Visits to premises of pharmaceutical SMEs

As part of the Commission services' SME experience, a representative of DG GROW involved in this initiative visited two pharmaceutical SMEs in Barcelona in November 2015.

iv) Participation of the Commission in round tables and seminars

The Commission was active in participating in events organised, or co-organised, by representatives of pharmaceutical SMEs, as follows:

- 12th EGA Legal Affairs Conference, 8-9 March 2016, Brussels
- European Parliament SME Intergroup in cooperation with Medicines for Europe, Boosting SMEs through the Supplementary Protection Certificate (SPC) Waiver, 27 September 2017
- EuropaBio's roundtable on 'The important role of SMEs in fostering healthcare biotech innovation', 28 September 2017

[128] Question 67 of the questionnaire addressed by the MPI and the IfD Allensbach to industry asked: 'What do you think of the idea of introducing such an 'SPC waiver'?' cf. Annex to the Final Report.

- EUCOPE Members' meeting: revision of the EU framework for SPCs, 17 October 2018
- *Bundesverband der Pharmazeutischen Industrie* (BPI) 10th parliamentary evening 'Sustainable Healthcare Systems and a competitive pharmaceutical industry – A mission impossible?' on 18/10/2017
- Presentation on SPCs – at an event organised by White&Case, which counted with the participation of pharmaceutical stakeholders such as EUCOPE, 3 November 2017
- Small and Medium Entrepreneurs of the European People's Party, in cooperation with EUCOPE, 'How to foster Europe as an R&D hub of pharmaceutical SMEs?', 28 November 2017
- European Parliament - SME Europe, in cooperation with the European Association for Bioindustries: The Future of Medicine: Promoting an Innovative Ecosystem to Position. European Biotech SMEs at the Forefront of Cutting-Edge Science, 11 April 2018
- Workshop at the European Parliament 'Boosting jobs, growth, competitiveness and consumer rights in Europe through the Supplementary Protection Certificate Manufacturing Waiver' organized by EPP in association with Polish Union of Employees in Pharmaceutical Industry on 21 February 2018

The Commission representatives have attended additional workshop on issues related to the SPC, that involved SMEs, organised *inter alia* by the Permanent Representations before the EU of Denmark, Hungary and Poland, (bio)Pharma Ireland high-level seminar in Brussels, EuropaBio Healthcare Council meeting attended by senior industry representatives, or the 7th European Innovation Summit in the European Parliament (with EuropaBio as co-organiser).

v) Bilateral meetings of the Commission representatives with pharmaceutical industry representatives

Commission representatives have had numerous bilateral meetings with representatives from the pharmaceutical industry, who conveyed the position of pharmaceutical SMEs involved in manufacturing of generics and biosimilars and innovative medicines.

vi) Letters send by SMEs and start ups

Following the publication of the Single Market Strategy in October 2015, and especially in the context of the public consultation on SPCs, international, European and national pharmaceutical associations with significant members representing SME, start-ups and universities sent letters to the Commission stating their position on the SPC manufacturing waiver (confirming the position provided by the SPC-holders, generics and biosimilar manufacturers during the public consultation). These associations included the International Council of Biotechnology Associations (ICBA), Medicines for Europe, The European Biopharmaceutical Enterprises (EBE), European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), Aschimfarma, BioM Biotech Cluster Development, and BIO Belgium.

Step-3: Measurement of the impact on SMEs

The impact assessment analyses a number of policy options, which pay particular attention to the SME-angle.

- *The baseline scenario (status quo/option 0 of the impact assessment)*

No policy action would continue to result in a number of negative consequences for manufacturers of generics or biosimilars (loss of competitiveness), especially for SMEs that manufacture in the Union (either on their own behalf or as a subcontractor). Manufacturers of generics and biosimilars highlight that SMEs cannot easily circumvent the unintended consequence of lack of an intellectual property protection level playing field, vis-à-vis non EU-based competitors, by delocalising production. SMEs have less financial resources and a more limited negotiating position when it comes to outsource production to third countries. Some large manufacturers of generics and biosimilars can make use of their factories located in third counties with shorter or no SPC protection to duly enter export markets and the EU *day-1* market.

Therefore, not doing anything would especially affected to EU-based SMEs in the generics and biosimilar sector.

- *New had-hoc licensing measures*

SME might also not have the same negotiating position when negotiating license fees with SPC-holders as larger companies, nor can easily engage in a process of application for a licence[129] as the decision of the granting authority could be subject multiple administrative and judicial appeals until the decision is firm potentially years after the upfront investment in manufacturing is needed.

- *Cutting down the duration of the SPC*

As indicated by associations representing SPC-holders, a reduction of the term of SPC protection would have a direct negative impact on the ability of SMEs active in R&D and/or manufacturing of original products to secure sufficient funding.

- *Soft-law approaches (including voluntary agreements) (option 1 of the impact assessment)*

As explained in the main text, soft law approaches have already been tested at national level but are considered not effective. They might be of very little interest in particular for SMEs that engage in generics and biosimilars manufacturing. SMEs cannot advance investments or make them subject to subject to future case-by-case agreements, in particular not where complex products like biosimilars are at stake. In general, SMEs are less resilient to uncertainty.

For SMEs, voluntary agreement could only work if there were to be a strong involvement of public authorities (national authorities and/or the Commission) to support the participation of SMEs in these types of initiatives. SMEs have limited human resources to engage in cooperation agreements with third parties, and their negotiating position vis-à-vis large companies holding SPCs might be limited.

- *SPC manufacturing waiver for export and/or stockpiling purposes, without anti-diversion measures (option 2 to 4 of the impact assessment)*

A manufacturing waiver, as a statutory targeted derogation from the scope of protection of the rights conferred by the EU SPC, would exempt from SPC infringement those acts directed to the manufacturing of generic and biosimilar medicines for the purposes of export and/or stockpiling. According to the impact assessment, this statutory derogation would be the most effective and simplest option to tackle the problems identified in the impact assessment. This

[129] E.g. Italian *Decreto legislativo* of 10.2.2005, *n. 30, articoli 81 e 200*.

would be especially true for EU-based SMEs manufacturing generics and would be measured, given their financial, resources and negotiating position limitations, as discussed above.

Throughout the consultation process, associations of SMEs engaged in the research and development (and sometimes manufacturing) of original products (in particular biotech products) have expressed concerns that the introduction of a manufacturing waiver would dilute SPC protection and therefore dilute the financial rewards they would receive for their inventions, as well as their possibility to get funding for their innovative R&D. In particular, representatives of innovative SMEs have expressed the concern that policies reducing the value of their IP will have direct impact on SMEs' ability to secure sufficient funding.

In practice however, these concerns appear to be overstated. As demonstrated in this impact assessment, the economic impact on originators of the introduction of an export waiver is minimal. SPC holders maintain full market exclusivity in Europe during the term of the SPC protection, which on average is amongst the highest in the world. They will, as a result of the waiver, face an increased competition in unprotected markets. However, such competition is increasing anyway (even if it does not come from EU-based manufacturers of medicines, then it comes, or will come, from manufacturers based in third countries).Given that the likely negative impact of the export waiver on SPC holders is limited, it should not adversely affect SMEs engaged in R&D and manufacturing activities.

In addition, given that the scope of a manufacturing waiver proposal is clearly confined and limited, there should be no grounds to assume that access to capital is affected by 'regulatory uncertainty'.

The table below comprises a 'competitiveness analysis' of the policy option of introducing a manufacturing waiver for export (Option 2) and stockpiling (Option 3) in EU legislation, from the perspective of SME:

Table: Impact of Options 2 and 3 on SMEs

SME type	**Option 2:** **Export waiver**	**Option 3:** **Stockpiling waiver**
SMEs with EU-based manufacturing activities in generic and biosimilars	The potential window of opportunity for exporting European generics to non-European markets without SPC protection prior to European SPC expiry is no negligible as the SPC protection in the EU extent the patent life on average of 3.5 years. The waiver will lift the barrier allowing for additional investment in the local production or more efficient use of manufacturing capacity for primary (APIs) and secondary manufacturing. The waiver is also expected to improve access to the APIs and make the supply chain stronger. 40% of the SMEs manufacturers of medicines in the EU (1 362 firms) who are currently exporting outside the EU will directly benefit from this measure. Part of the 60% SMEs not currently engaged in extra-EU export might scale up	For SME manufacturers that are currently not exporting outside the EU, and do not plan to scale up to export outside the EU, a stockpiling waiver would assist in scaling up production to be ready for timely entry into domestic or to other Member State market upon SPC expiry.

	production for export purposes taking advantage of the export waiver. Indirectly, the export waiver will support SMEs who currently export outside the EU, and those that will take advantage of the export waiver to scale up production for extra-EU export, and scale up additional production as of EU *day-1*.	
SMEs with EU-based R&I core activities	• For innovative products, there should be very little to no impact on the reward to innovation (given that SPC holders maintain the core of their SPC rights and are exposed to a limited additional competition only). Thus, any negative impact on innovation incentives and the possibility to get funding should be minimal. • For biosimilars, a legal barrier to investment in generics/biosimilars production in the EU would be lifted. This would have a huge positive impact on biosimilars R&D, which might otherwise delocalise (given that for biosimilars R&D and manufacture tends to happen at the same location)	

Note: The qualitative impact on competitiveness in terms of exports and job-creation is analysed in detailed in the impact assessment and its annex on the studies (Annex 12). For the general assessment of options see Section 7 of the impact assessment

Foregoing option with anti-diversion measures

While opinions differ regarding the risks of diversion, anti-diversion measures could usefully be envisaged in order to minimise any additional risk of diversion and provide additional transparency. The impact assessment identifies two preferred anti-diversion measures: a special labelling requirement and a once-off notification of manufacturing under the waiver in each Member State of making.

In order to benefit from the manufacturing waiver with anti-diversion measures, manufacturers of generics and biosimilars, including SMEs, would need to comply with additional labelling requirements, and bear additional administrative costs related to submission of a notification to a public authority.

These anti-diversion measures might not have a positive impact on micro and small SMEs if the cost of the measure or its implementation procedures were cumbersome and of uncertain outcome. The pharmaceutical sector is already highly regulated; SMEs need to comply with the EU strict general regulatory rules, and specific anti-falsified medicines rules as large businesses do. Additionally, the pharmaceutical sector, especially the originators and biosimilar ones, can be highly capital intensive. Therefore additional cost of compliance should be minimised, considering the limitations faced of SMEs.

A proxy to estimate the cost of labelling can be found in the Commission's evaluation of Regulation 953/2003 to avoid trade diversion into the EU of certain key medicines[130] That evaluation found that a pharmaceutical company incurred costs of up to EUR 200 000 between 2003-15 for adding a logo on its packs. However, that cost included fees of EUR 100 000 derived from the obligation of getting regulatory authorities to amend/extend marketing authorisations for the medicines due to a change of packaging, which would not be necessary for the notification scheme proposed in this initiative. Deducting that figure, the

[130] http://trade.ec.europa.eu/doclib/docs/2016/april/tradoc_154437.pdf

cost of labelling on the basis of this initiative would amount to a cost of EUR 10 000 per year. Given that the total turnover of SMEs active in the pharmaceutical sector in 2015 was EUR 24bn, with average per SME of EUR 8m, the labelling cost would impose the cost equal to around 0.1% of annual turnover. Therefore, the potential impact of those safeguards on SMEs is low and would not significantly increase the cost of production. In this light, and given the need to protect originators against illicit diversion of IP-infringing products on the European market, these extra costs appear justified.

The envisaged notification should be simple and should be a once-off exercise in each Member State of making.

- *Preferred option*

Bearing in mind that EU legislation, administrative rules and procedures are meant to be simple and easy to understand, the preferred option for this initiative has taken into account SMEs' interests, by including a set of non-cumbersome labelling and notification requirements..

Step-4: Assessment of alternative options and mitigating measures

The impact assessment and abovementioned analysis shows that SMEs, *as defined in Commission Recommendation 2003/361 and its subsequent amendments*, manufacturing G/B are facing a significant higher burden than large companies in relation to the SPC protection. This is because they cannot easily circumvent the unintended consequences of lack of level playing field in intellectual property protection vis-à-vis non EU-based competitors, by delocalising production. Measures to tackle this issue need to take SMEs into account.

The preferred option of the impact assessment (option 2 bis) envisages mitigating measures to minimise negative impact on SMEs (both SMEs intending to apply for the waiver and SME which hold SPCs). On one hand, it introduces safeguards that are easy to comply with by SMEs, such a simplified reporting obligation (a notification and a simple labelling, bearing in mind that SMEs need already to fulfil labelling requirements for their production). This notification would ideally be conducted via on-line with automatic receipt of submission of the notification with all the required information fields completed. That notification will then be published, so that SMEs holding SPCs can be aware of any manufacturing activity, by a third party, taking place during the term of their SPCs.

Authorities in charge of handling the notification can consider a level of administrative fees in accordance with the size of the companying which files the notification.

It is not appropriate to exempt any category of SME from the transparency/anti-diversion measures related to a manufacturing waiver, i.e. an SPC exemption should be accompanied by measures that minimise risk of illicit diversion of medicines. Finally, an SPC exemption should not entail lower transparency in the pharmaceutical system by comparison with the base line scenario.