Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe

Written by
Raphaël De Coninck, Elina Koustoumpardi,
Roman Fischer, Guillaume Débarbat

February - 2016

EUROPEAN COMMISSION

Directorate-General for Internal Market, Industry, Entrepreneurship and SME
Unit 01 - Chief Economist team

Contact: Malwina Mejer

E-mail: GROW-01@ec.europa.eu

European Commission
B-1049 Brussels

Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe

Directorate-General for Internal Market, Industry, Entrepreneurship and SME

Europe Direct is a service to help you find answers to your questions about the European Union.

Freephone number (*)**:**

00 800 6 7 8 9 10 11

(*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Luxembourg: Publications Office of the European Union, 2017

ISBN: 978-92-79-73301-7
doi: 10.2873/673124

Disclaimer of Charles River Associates

The views expressed herein are the views and opinions of the authors and do not reflect or represent the views of Charles River Associates or any of the organizations with which the authors are affiliated. Any opinion expressed herein shall not amount to any form of guarantee that the authors or Charles River Associates has determined or predicted future events or circumstances, and no such reliance may be inferred or implied. The authors and Charles River Associates accept no duty of care or liability of any kind whatsoever to any party, and no responsibility for damages, if any, suffered by any party as a result of decisions made, or not made, or actions taken, or not taken, based on this paper.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

GLOSSARY

Abbreviation	Description
API	Active Pharmaceutical Ingredient
CEE	Central Eastern European countries
CPA	Italian Chemical Pharmaceutical Association
CRO	Contract Research Organisation
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGA	European Generic Association
EMA	European Medicines Agency
HTA	Health Technology Assessment
IPO	Intellectual Property Office (UK)
LoE	Loss of exclusivity
PPRS	Pharmaceutical Price Regulation Scheme (UK)
SPC	Supplementary Protection Certificate
UPC	Unitary Patent Court
UPP	Unitary Patent Protection

ABSTRACT

In this study we assess the economic impacts of A) extending the scope of the so-called Bolar patent exemption as applied to medicinal products for human use: i) to *any* medicines (not limited to products following an abridged marketing authorisation only), ii) to obtain marketing approvals anywhere in the world, iii) to explicitly allow third party supply of active pharmaceutical ingredients (APIs) within the EU for purposes of tests and trials required to obtain marketing approvals; and B) Allowing manufacturing of medicines for human use protected by Supplementary Protection Certificate (SPC) in protected (domestic) markets for purposes of: i) exporting to third countries where the corresponding patent or SPC has expired, ii) exporting to other EU Member States where the corresponding patent or SPC has expired, and iii) preparing for timely entry in the domestic market subsequent to patent or SPC expiry (stockpiling). We find that:

- Extending the scope of the Bolar exemption to cover any medicines and marketing authorisations in any country would benefit the European pharmaceutical industry by reducing legal costs (e.g. from freedom-to-operate searches, validity opinions, infringement proceedings, etc.), reducing the need to duplicate trials to support marketing authorisations in different jurisdictions, and streamlining the strategic planning process. Extending the Bolar to cover any medicines could result in cost savings from patent screening of up to €23- €34.2 million per year (this represents an upper bound). For illustration purposes, we estimate cost savings between €0.7 million to €4.4 million per case as a result of not having to recruit in additional countries due to widening the scope of the Bolar to cover marketing authorisations in any country. Moreover, the measures are expected to benefit skilled employment in the EU and the patient population through faster introduction of innovative products. It will also eliminate the potential risk of the Unified Patent Court adopting a narrow interpretation of the current wording of the EU Bolar exemption. Such risk could result in additional costs between €62.4 million to €93.6 million for companies currently operating in Member States with a wide Bolar scope.
- Extending the scope of the Bolar to cover third party API supply is likely to benefit EU-based API suppliers. We estimate that sales by third party European generic API producers could increase by 7-29% (€45.2 million to €180.8 million additional annual sales by 2030), depending on the scenario. The combination of an SPC export waiver with an extension of the Bolar exemption to cover the third party supply of APIs within Europe is expected to result in additional EU API sales of up to €254.3 million by 2030. The additional EU API sales correspond to 2,000 new jobs by 2030, assuming no change in worker productivity. EU-based generic producers will also benefit from more choice of locally produced APIs.
- With respect to the SPC export waiver to third countries, considering the impact on both EU based innovators and generics and biosimilars, we estimate that in our base case scenario, it could result in net additional sales of €7.3 billion to €9.5 billion by 2025 for the EU based pharmaceutical industry. These results translate into an EU manufacturing employment increase of 13% to 16% (20,000 to 25,000 additional jobs), assuming no change in worker productivity. Additional savings to EU spending on pharmaceuticals of 4-8% could materialise from a timelier introduction of generics and biosimilars in European markets following SPC expiry in Europe. These numbers are lower bounds as the effects are estimated on a sample of 117 non-biological and 17 biological molecules.

- An SPC export waiver has a potential to increase EU exports from 6% to 18%. These figures are based on a comparison of the additional generic export sales identified above with total (generic and branded) EU export sales to the third countries in our sample. Due to lack of reliable data we cannot make a similar comparison for biosimilar export sales.
- We estimate that an SPC export waiver within Europe could result in net additional sales for the EU based pharmaceutical industry of €208 million to €416 million by 2025, depending on the scenarios, with a beneficial impact on jobs of up to 1,000.
- A stockpiling exemption will benefit EU based generic and biosimilar producers by enabling them to enter domestic markets timely upon protection expiry and will result in savings on pharmaceutical expenditure (1-4%) from the timelier introduction of generics and biosimilars.

EXECUTIVE SUMMARY

We have been commissioned by DG –Internal Market, Industry, Entrepreneurship and SMEs ("DG Growth") to conduct a study to assess the economic impacts on the European pharmaceutical industry as well as wider impacts on employment and spending on pharmaceuticals, of a number of changes to exemption provisions during the patent and Supplementary Protection Certificate (SPC) term in Europe on medicines for human use. These are briefly described below.

1. SUMMARY OF PROPOSED CHANGES TO EXEMPTION PROVISIONS

1.1. Changes to the Bolar exemption

The so-called *Bolar* provision exempts the use of patent protected medicinal products in tests and trials for purposes of obtaining marketing authorisation.[1] At the EU-level, the Bolar exemption is set out in Directive 2001/83/EC, Art. 10(6) as amended, and Directive 2001/82/EC, Art. 13(6) as amended. There is however some variation in the implementation of the Bolar exemption across the EU Member States. Some Member States have adopted a *wide* scope of the exemption that covers the use of a patent protected medicine in order to gain regulatory approval for *any* medicinal product, while others have adopted a *narrower*[2] scope that covers only use of a patent protected medicine for the purposes of the so-called abridged authorisation procedure, used for generics, hybrids and biosimilars.

In countries with narrower Bolar exemptions, the legal status of such trials is not certain, potentially putting innovative companies running clinical trials in these Member States at a risk of infringement. Additionally, the Bolar exemptions in countries with a wider interpretation cover the use of a patent protected product for marketing authorisation procedures in *any* country, while the Bolar exemptions in countries with a narrower interpretation only cover marketing authorisation procedures in an EEA country. Thirdly, the current wording of Article 10(6) of Directive 2001/83/EC as amended and its implementation in individual Member States results in legal uncertainty for European API suppliers wishing to supply APIs to generic firms conducting tests and trials necessary to obtain marketing authorisations. In particular it is not clear whether the Bolar extends to EU-based third party suppliers wishing to supply European generic producers with APIs for purposes of conducting the necessary tests and trials to obtain marketing authorisation.

In this context, we have been asked to assess the economic impacts of extending the scope of the Bolar exemption: i) to *any* medicines (not limited to products following abridged marketing authorisation only), ii) to obtain marketing approvals anywhere in the

---

1 The term Bolar is based on the *Roche Products vs Bolar Pharmaceutical, 733* F.2d. 858 (Fed. Cir. 1984) court case in the US, where the courts found that Bolar Pharmaceuticals in using Roche's patented product to conduct experiments in order to determine that its product was bioequivalent, had infringed the experimental use exemption. Shortly after the decision, the Hatch-Waxman Act was enacted that expressly allowed the use of a patented product for purposes of obtaining regulatory approvals.

2 In this study whenever we use the term *narrow* scope of the Bolar, we refer to a country that has introduced the Bolar exemption in its national laws using the literal wording of Art. 10(6) of Directive 2001/83/EC, as amended, and Art. 13(6) of Directive 2001/82/EC, as amended.

world, iii) to explicitly allow EU-based third party manufacture and supply of protected APIs within the EU for purposes of test and trials required to obtain marketing approvals.

1.2. Changes to the SPC provisions

The SPC provides similar protection to that provided by the patent, therefore under the SPC term the production of the SPC protected medicine is not allowed, even if it is not destined for the domestic SPC protected market. It has been argued that, as a result of this, generic and biosimilar manufacturers located in countries with more relaxed patent protection rules, have a first mover advantage compared to European generic and biosimilar manufacturers. Moreover, during the SPC term, a generic producer cannot manufacture a protected medicine to prepare for day 1 entry in the domestic market following the SPC expiry (stockpiling), which could place European producers at a disadvantage compared to producers that are located in unprotected countries and can prepare stocks for timely entry. In this context, we have been asked to assess the potential impacts of allowing manufacturing of SPC protected medicines in protected (domestic) markets for purposes of: i) exporting to third countries where the corresponding patent or SPC has expired, ii) exporting to other EU Member States where the corresponding patent or SPC has expired, iii) preparing for timely entry in the domestic market subsequent to patent or SPC expiry (stockpiling).

1.3. Effect of the introduction of Unitary Patent Protection and Unitary Patent Court

In 2012 the European Parliament and the Council of the European Union agreed on a package of regulations for the creation of a Unitary Patent Protection (UPP) and 25 Member States signed a Unified Patent Court Agreement for the establishment of a Unified Patent Court (UPC) that would have exclusive jurisdiction on litigation involving European patents with unitary effect or classical European patents validated in different Member States. [3] The Unitary Patent Protection will give patent owners a unitary effect for a European patent in the EU Member States that are part of the legal instruments cited above with a single filing at the European Patent Office (EPO). The UPC agreement contains a Bolar exemption that references the wording of Art. 10 (6) of Directive 2001/83/EC and also contains provisions for SPCs.

For each of these potential changes to the Bolar and SPC provisions, we have been asked to also examine the effect of entering into force of the UPP and the UPC.

2. SUMMARY OF DATA AND SOURCES

To analyse and assess the effect of these measures we relied on:

3 This legislative package contains two regulations creating a unitary patent with unitary effect and its language regime as well as an international agreement among Member States setting up a Unified Patent Court. The first two came into force in January 2014 while the latter has not yet been ratified by all signatories. See http://ec.europa.eu/growth/industry/intellectual-property/patents/unitary-patent/index_en.htm

- IMS Midas data on sales of pharmaceuticals in a number of EEA and non-EEA countries[4],
- Data on 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.[5] The 117 molecules represent 32% (by count) of all molecules whose SPCs expire in Europe during the period 2016-2030. We do not have reliable data to conduct a similar comparison for the 17 biological molecules.
- Data obtained from the European Medicines Agency (EMA) on clinical trials conducted in the EEA for the period May 2004-2015 that EMA feed to the WHO International Clinical Trials Registry.[6]
- Data obtained from the EMA and national medicine agencies on the manufacturing location of the finished product and API for a sample of generic products that entered first upon protection expiry of their reference product.[7]
- Data contained in the CPA report on Global APIs Market, 2015 edition.

We also conducted desk-based research and consulted with the European generic/biosimilar as well as innovative pharmaceutical industry via their industry associations EGA and EFPIA on their views of the potential impacts of these measures through a questionnaire.

3. SUMMARY OF FINDINGS

Our findings are summarised below.

3.1. Scenario 1: Extending the scope of Bolar exemption to cover all medicines

3.1.1. Assessment of effect on the European innovative industry

Using EMA data on clinical trials run in the EEA, we examined whether there is evidence of fewer clinical trials being run in countries with a *narrow* Bolar scope compared to

4 The following EEA countries are covered by the IMS Midas data: Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK. The following non-EEA countries were covered in the IMS Midas data: Switzerland, Russia and Turkey.

5 Australia, Brazil, Canada, China, Japan, Russia, Turkey, US.

6 The clinical trial data covered interventionist clinical trials initiated during May 2004 to early 2015. that EMA feed to the WHO International Clinical Trials Registry http://apps.who.int/trialsearch/ Clinical trials conducted outside the EEA are included if they form part of a paediatric investigational plan or if they are sponsored by a marketing authorisation holder and involve the use of a medicine in the paediatric population as part of an EU marketing authorisation.

7 In addition to the EMA, a request was sent out to 18 national medicine agencies that were members of the CMDh ("*Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human*"). Eleven national medicine agencies responded to our request: Austria, Belgium, Czech Republic, Germany, Greece, Hungary, Poland, Portugal, Romania, Sweden and the UK.

countries with a *wide* scope, while controlling for other factors that could affect the choice of where to conduct a clinical trial. We did not find robust evidence that countries with a wider Bolar scope had more clinical trials, controlling for other factors. These results should not be interpreted as conclusive evidence that a widening of the Bolar scope will have *no effect* on the innovative pharmaceutical industry, as if there was no effect, then it is unlikely that both the UK and Ireland would have amended their patent acts to broaden the scope of the Bolar and research exemptions recently. The lack of identification of an effect is consistent with responses from the industry suggesting that the scope of the Bolar is *one* among *many* factors influencing the location of clinical trials. While we have attempted to control for a number of these other factors, the proxies we have used (based on data availability) are likely not exhaustive[8] and may also be imperfect measures of the true underlying factors.

An extension of the scope of the Bolar is expected to reduce costs incurred by innovative pharmaceutical companies when carrying out trials in countries with a narrow Bolar scope, such as freedom-to-operate (FTO) studies, validity opinions, patent oppositions or costs of infringement proceedings. We estimate that cost savings from FTO studies could amount to €23- €34.2 million per year. These estimates represent an upper bound of cost savings from FTO searches.

3.1.2. Assessment of wider impact of the proposed measure

An extension of the Bolar to apply to any medicines is likely to positively affect incentives to innovate in the EU as it will remove the legal uncertainty associated with running regulatory tests and other trials on medicines that do not follow the abridged marketing authorisation pathway.

Broadening the scope of the Bolar can be expected to increase the number of skilled jobs in a country that switches from a narrow to a wide scope of the Bolar. It is not possible for us to estimate exactly by how much the number of skilled jobs will increase. If additional trials can already largely be supported by existing doctors and other employees through an increase in their productivity, the impact on skilled jobs will be more limited, but the positive impact on the level of expertise and the economy as a result of an increase in productivity will remain.

An additional benefit of widening the Bolar scope to cover any medicine is that it will reduce delays associated with assessing the legal risks when conducting studies and trials in countries with a narrow Bolar scope, resulting in more timely access to innovative medicines for patients.

Last, if the measure leads to more clinical trials in countries with currently a narrow Bolar scope, this will benefit the country patient population, as it has been shown that the adoption of a new medicine is wider in countries where the clinical trial was run, due to information spillovers making physicians more likely to prescribe the new medication.[9]

---

8 For example, due to lack of data for the countries and period considered, we could not include potentially relevant factors such as financial incentives for innovation/R&D, quality and reputation of doctors, presence of patient population with relevance to a particular therapeutic area, country specific factors that could affect the costs of running clinical trials (e.g. protocol amendment requests etc).

9 For a discussion of the literature studying the information spillover effect see "Economic research into the environment for clinical research and development in the UK", a report prepared for Novartis by Europe Economics, 16 October 2012. http://www.novartis.co.uk/downloads/europe-economics-clinical-trials-report.pdf

3.1.3. Effect of introduction of Unitary Patent Protection and Unitary Patent Court

The effect of the introduction of UPP and the UPC on the proposed measure will depend on whether the UPC adopts a narrow or a wide interpretation of the Bolar. If the UPC adopts a narrow interpretation of the Bolar scope, then the benefits discussed above on incentives to innovate, number of clinical trials, skilled jobs and expertise could be reversed. Moreover, a narrow interpretation by the UPC would result in additional legal costs that could amount to €62.4 million to €93.6 million for companies currently operating in Member States with a wide Bolar scope.[10]

If, on the other hand, the harmonisation of the Bolar exemption is implemented via an amendment of Directive 2001/83/EC (as amended in 2004) to explicitly cover any medicine, the effect of the introduction of the UPP and UPC will be consistent with the harmonisation analysed here. This is because, as explained above, the UPC Agreement made a cross-reference to the Directive. If the Directive explicitly covers all medicines, then both national courts and the UPC will have a consistent treatment of patent infringement cases relating to the Bolar exemption. Therefore all the benefits and savings presented in the previous subsection would apply.

3.2. Scenario 2: Extending the scope of Bolar exemption to cover marketing authorisations in any country

3.2.1. Assessment of effects on the European innovative pharmaceutical industry

Our econometric results on the relationship between the number of clinical trials[11], the scope of the Bolar and a number of explanatory variables, do not support a robust conclusion on the effect of the scope of the Bolar on the number of clinical trials run in a country. As explained above, the lack of identification of an effect is consistent with responses from the industry suggesting that the scope of the Bolar is *one* among *many* factors influencing the location of clinical trials. While we have attempted to control for a

10 As an illustration, we estimate the costs of the introduction of the UPP and UPC if it adopts a narrow interpretation of the Bolar, compared to a situation where a wide Bolar scope was harmonised across Europe, focusing on one legal cost element, FTO searches. In the UK consultation the cost of carrying out FTO studies was mentioned by respondents as an additional cost incurred when carrying out trials in countries with a narrow Bolar provision. We assume that no FTO studies would be required for comparator trials that recruited in the EEA under a wide Bolar scope that covered all medicines whereas they would be needed if the UPC adopts a narrow interpretation of the Bolar. These estimates are illustrative. Firstly, only the cost of FTO studies is considered here. Since other costs were also identified in relation to the narrow Bolar scope such as costs related to e.g. opposition proceedings, infringement actions, licensing costs etc., the cost estimates reported above are partial. Secondly, the magnitude of FTO costs per case relate to the UK, but could be different in other EU countries. Thirdly, we assume that an FTO is carried out for each comparative study that uses another medicine as a comparator. This could overestimate the overall cost of FTO studies as it is likely that not all comparative clinical trials that use another medicine as a comparator would carry out such an analysis, as in some cases the comparator may already be known not to be covered by a patent or SPC. Moreover to the extent that FTO studies would need to be carried out anyway, the above estimates could overstate the impact. To the extent that the latter two effects dominate, the estimates should be considered as upper bounds.

11 To assess the effect of this measure, we did not limit the clinical trials to comparative clinical trials where another medicine was used, but we included all clinical trials in the EMA data, as this measure is likely to affect the number of clinical trials irrespective of whether they use a comparator medicine or not.

number of these other factors, the proxies we have used (based on data availability) are likely not exhaustive[12] and may also be imperfect measures of the true underlying factors.

The proposed measure is likely to reduce costs to innovative firms of running clinical trials for a number of reasons:

- Increasing the number of countries from which patients can be recruited to support marketing authorisations in any country, is likely to reduce clinical trial delays associated with patient recruitment[13]. For a blockbuster drug these delays could amount to at least $2.7 million (or €2.4 million using 2015 average USD/EUR exchange rate) per day in lost sales worldwide.[14]
- It is likely to reduce the need to duplicate clinical trials to support marketing authorisations in non-EU countries. The costs of carrying out clinical trials are significant. We estimate indicative cost savings of not having to run a clinical trial in one additional country as a result of this measure of €647,406 to €1.1 million per case, depending on the per-patient cost of the clinical trial.[15] The cost savings of not having to run a clinical trial in four additional countries as a result of this measure could be €2.6 million to €4.4 million per case, depending on the per patient cost of the clinical trial.[16]
- It will reduce the need to make early decisions about where to launch first. While we cannot monetise the savings associated with this, it is likely to benefit innovative companies, as by delaying the decision of where to launch first, the companies can benefit from additional information that could become available that affects the expected profitability of launching in that market.[17]

---

12 For example, due to lack of data for the countries and period considered, we could not include potentially relevant factors such as financial incentives for innovation/R&D, quality and reputation of doctors, presence of patient population with relevance to a particular therapeutic area or country specific factors that could affect the costs of running clinical trials (e.g. protocol amendment requests etc).

13 Patient recruitment is a primary cause of clinical trial delays.

14 In line with industry norm, we define a blockbuster drug as one that generates sales of at least $1 billion annually, which corresponds to $2.7 million on a daily basis.

15 A 2012 study by Europe Economics prepared on behalf of Novartis provides estimates of per patient costs of clinical trials for 5 EU countries (Germany, Italy, Poland, Spain and the UK) ranging from €5,679 for Poland to €9,758 for the UK. Economic research into the environment for clinical research and development in the UK, a report prepared for Novartis by Europe Economics, 16 October 2012. http://www.novartis.co.uk/downloads/europe-economics-clinical-trials-report.pdf

The average number of patients per country of recruitment for a Phase III clinical trial is 114 based on EMA clinical trial data. We estimated the average number of participants by EU country for Phase III clinical trials, by dividing the target size per clinical trial by the number of countries of recruitment and then taking an average across the EU28 countries.

These cost savings assume that the cost of clinical trials in non-EU countries is similar to the cost in the EU.

16 These savings are indicative and are for a single clinical trial only and are based on EU per patient costs of clinical trials and average EEA number of patients per clinical trial. These cost savings assume that the cost of clinical trials in non-EU countries is similar to the cost in the EU.

17 The option value of waiting has been analysed in a number of economic papers that have found a value of waiting to invest when there is uncertainty regarding the benefits and costs of an investment and when an investment is irreversible. The seminal paper on this was by Robert McDonald, Daniel Siegel, *The value of waiting to invest*, The Quarterly Journal of Economics (1986) 101 (4): 707-727

3.2.2. Assessment of effects on the European generic and biosimilar pharmaceutical industry

As in the case of innovative pharmaceuticals, this proposal is likely to result in cost savings for both the generic and biosimilar industry for the following reasons:

- It will reduce the need to run additional bioequivalence tests to obtain marketing authorisation in other countries. The savings from extending the number of EU countries where bioequivalence tests may be carried out to support marketing authorisations outside the EU, may not be significant, as there are already a number of European countries with a wide Bolar scope within the EU that EU based generic companies can choose for their bioequivalence tests.
- It will reduce the legal risk and need to obtain different legal advice by EU country as to what acts are covered by the Bolar in each Member State. We have no estimates of these costs that would enable us to quantify this saving. These cost savings would apply to innovative as well as generics and biosimilar producers.
- The measure could result in cost savings for biosimilars, as biosimilars need to conduct trials to prove biosimilarity which are more costly than running bioequivalence tests on healthy volunteers. We estimate that the costs of obtaining the reference product only could amount to several millions.[18] Secondly, patient recruitment can be difficult as patients may be reluctant to participate in a study knowing that only some of them will receive the reference medicine and some will receive the biosimilar whose efficacy has not been proven yet.[19]

3.2.3. Assessment of wider impact of the proposed measure

An extension of the Bolar to cover tests and trials for purposes of obtaining marketing authorisation in any country is expected to positively affect incentives to innovate in the EU, by increasing the attractiveness of EU Member States as a location to run clinical trials for originators and biosimilars, and bioequivalence tests for generics. The proposed measure is also likely to benefit Contract Research Organisations (CROs) located in European countries with a narrow Bolar scope that may currently not be preferred for carrying out bioequivalence tests as using the results of such studies for marketing authorisations outside Europe may be found to be infringing the patent(s) of the reference medicine.

It is likely to result in an increase in skilled jobs, though we cannot estimate precisely the magnitude of this effect, as it depends on whether the additional trials and tests can be supported by existing skilled workers through an increase in their productivity or whether additional skilled jobs would be required.

---

18 A study suggests that phase III clinical trial required volumes could range between 2,000 to 10,000 vials or syringes over a two to four year period. By way of example, a 150 mg vial of Herceptin in the UK costs £407.4 according to NICE. A clinical trial for a biosimilar of Herceptin could therefore cost between £814,800 (2,000 times £407.4) and £4.07 million (10,000 times £407.4), only considering the costs of the reference medicine. Michael Cohen, Sourcing innovator products in the age of biosimilar research, posted 01 June 2015 on GaBi online. http://www.gabionline.net/Sponsored-Articles/Sourcing-innovator-products-in-the-age-of-biosimilar-research

19 Erwin A. Blackstone and P. Fuhr Joseph, (2013) *The economics of biosimilars,* American Health and Drug Benefits 2013 Sep-Oct; 6(8). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/

The proposed measure is also likely to benefit the patient population by reducing delays in clinical trials for originators and biosimilars due to patient recruitment problems, as it will increase the number of candidate countries for recruitment. Moreover, as discussed above, running a clinical trial in a specific country benefits the patient population in that country as it makes physicians that worked on the study more likely to prescribe the new medicine.[20]

3.2.4. Effect of Unitary Patent Protection and Unitary Patent Court

Should the UPC adopt a narrow interpretation of the Bolar, the identified benefits could be at least partly reversed.

As we do not know how many clinical trials are conducted with a view to gaining marketing approvals outside the EEA we cannot estimate the additional costs of the introduction of the UPC. However the costs for innovative companies are likely not to be additional to those identified in section 3.1 as e.g. a single FTO study would be needed for each case irrespective of whether a marketing authorisation within the EEA only or also outside the EEA was sought.

Companies (innovators as well as generics and biosimilars) wishing to use results of tests and clinical trials for marketing authorisations outside Europe would incur additional legal costs to determine whether they could be infringing.

A narrow interpretation by the UPC could result in the need to duplicate results of clinical trials for innovative medicines and biosimilars to support marketing authorisations outside Europe, resulting in higher costs of development. Assuming clinical trial costs outside Europe are not very dissimilar to the estimates we have for Europe[21] we estimate additional costs of carrying out clinical trials in more countries between €2.8 million to €4.9 million for one product only.[22] In the case of biosimilars, as mentioned above, the costs relating to the purchase of the reference product only for purposes of the clinical trial could be several million per case.

For EU-based generics, such a change is likely to result in Europe becoming a less attractive location to conduct bioequivalence tests and more bioequivalence tests being conducted outside Europe through e.g. outsourcing to CROs. Such a measure would also negatively impact the EU-based CRO industry.

If the harmonisation of the Bolar exemption is implemented via an amendment of Directive 2001/83/EC (as amended in 2004) to explicitly cover marketing authorisations in any country, the interpretation by the UPC will be consistent with the harmonisation of a wider Bolar. Therefore all the benefits discussed in the previous subsection would apply.

---

20 A summary of the literature on the information spillover effect is available in "Economic research into the environment for clinical research and development in the UK", a report prepared for Novartis by Europe Economics, 16 October 2012. http://www.novartis.co.uk/downloads/europe-economics-clinical-trials-report.pdf

21 As mentioned above, the average per patient cost of a clinical trial for an innovative product was estimated to be in the range of €5,679 for Poland to €9,758 for the UK.

22 These figures assume that a phase III clinical trial would need to be carried out on an additional 500 patients. As explained in section 2.1.2 a Phase III trial is conducted on several hundred to several thousand patients. Therefore our estimates are conservative.

3.3. Scenario 3: Extending the scope of the Bolar exemption to allow the supply of APIs within the EU

An extension of the scope of the Bolar exemption to cover the supply of APIs within Europe for Bolar purposes could result in a higher share of APIs used by European generics producers to be sourced from European API suppliers rather than imports. Other things equal (cost, quality, API physical attributes etc.), it could be expected that more legal certainty regarding third party API supply within Europe would increase European API supply for development purposes. Moreover, according to the EGA, once a generic producer chooses API suppliers[23], it is unusual to switch when the commercial production starts. This is because APIs from a different supplier could have a different stability profile, which could lead to the need for new stability batches, new analytical studies on impurities and so on. Moreover, medicine agencies request documentation for any change in the manufacturing process (including change of API supplier), which could make the process of switching supplier expensive. EGA estimates that for more complex APIs, the cost of switching API suppliers could reach €4 million per case. This suggests that once an API supplier is chosen at the development and pilot batch stage it is unlikely to be changed.

Data collected on the manufacturing location of APIs for a sample of first generic entrants in Europe during the period 2008Q1-2014Q3 suggest that there is a high reliance on imported APIs. As we cannot determine with certainty the effect of this change on the future share of European merchant API suppliers on European generic API sales, we run three scenarios regarding the impact:

1. **Case 1** assumed that their share would increase by 2.5 pct points;
2. **Case 2** assumed that their share would increase by 5 pct points;
3. **Case 3** assumed that their share would increase by 10 pct points.

Focusing on non-biological molecules that will be in the pipelines of generic producers over the next 10 year period (with protection expiries between 2018 and 2027), we estimate that under case 1, European merchant generic API sales could be 7% higher, under case 2 they would be 14% higher and under case 3 they would be 29% higher. In monetary terms we estimate the additional annual sales to European merchant API producers at the end of the 10 year period to amount to €45.2 million (7% increase relative to no impact) under case 1, €90.4 million (14% increase) under case 2 and €180.8 million (29% increase relative to no impact) under case 3.

The combination of an SPC export waiver with an extension of the Bolar exemption to cover the third party supply of APIs within Europe is expected to result in additional EU API sales ranging from €211.8 million to €254.3 million by 2030 depending on the scenario.

The additional EU API sales translate into 1,160 to almost 2,000 additional jobs by 2030.

The cost of procuring raw materials (APIs) at the development and advance manufacturing phase is an important cost for generics. Clarifying and extending the scope of the Bolar exemption to cover the third party supply of APIs within Europe, is likely to lead to lower costs of supply for European generics, by increasing the number of Europe

23 According to the EGA response some companies choose two suppliers to ensure supply availability.

based API suppliers and reducing transport costs as well as customs clearance and other delays associated with imports.[24]

3.3.1. Effect of Unitary Patent Protection and Unitary Patent Court

If the UPC adopts a narrow interpretation of the Bolar, then the positive impact on the European API and generic industry could be reversed, as European generic producers may be unable to source APIs from European API producers during the testing phase as a result of the legal risks. Given the costs of switching suppliers between the development and advanced manufacturing phase, this is likely to reduce sales by European API producers going forward, as these products move to the advanced manufacturing phase.

Relative to a world where a harmonised wide Bolar provision applied in all EU Member States that explicitly covered third party API supply within Europe for Bolar purposes, the introduction of a UPC with a narrow interpretation could result in the European API industry at worst losing the additional estimated sales of between €45.2 million to €180.8 million identified above. Moreover, it would result in a loss between €14-56 million from API sales destined for the export market as a result of the SPC export waiver. There would be a corresponding loss of jobs between 269 and 1,076. These costs represent an upper bound.

A narrow implementation of the Bolar provision by the UPC could result in additional costs of supply for EU based generics as it would reduce their available options for API supply during the testing phase to those that can be imported. Even though most APIs are currently imported from outside Europe (mainly India and China), for some more complex compounds the available third party API supplier options may be more limited.

3.4. Scenario 4: Allowing manufacturing of SPC protected medicines in protected (domestic) markets for purposes of exporting to third countries where the corresponding patent or SPC has expired

3.4.1. Assessment of effect to the European pharmaceutical industry

We expect an SPC export waiver to third countries to lead to increased sales by European generic and biosimilar manufacturers to third countries where the corresponding SPC has expired, as such a provision will enable them to enter these markets without delay.

Based on a sample[25] of molecules for which the SPC term expires later in Europe compared to 8 third countries,[26] we estimated that, in our base case, an SPC export waiver could result in additional export sales by European generics of €7.6 billion. We also considered the potential negative impact that an SPC export waiver could have on export sales by European branded medicines, which we estimated at €139 - €278 million

24 According to a report by FTI, importing APIs adds 14 weeks to the development phase of a pharmaceutical. FTI report, “A narrow interpretation of the Bolar exemption in the EU pharmaceutical industry”, April 2014, paragraph 5.11.

25 Our sample consists of 117 molecules. By comparison the SPC term of 370 non-biological molecules expire in the EU during the period examined (2016-2030). Therefore our sample represents 32% of the 370 molecules.

26 Australia, Brazil, Canada, China, Japan, Turkey, Russia, US.

by 2025, depending on the scenario. Taking into account the potential negative impact on export sales of European branded pharmaceuticals, we estimate net additional sales to the European non-biological (generics and branded) pharmaceutical industry as a result of an SPC export waiver for the sample of molecules and third countries considered of €7.3 billion to €7.4 billion by 2025. Expressed in annualised terms, they represent between 6-18% of total (generic and originator) EEA non-biological export sales to the third countries analysed.[27]

For biosimilars, based on a sample of 17 molecules with later SPC expiries in Europe compared to at least one of the 8 third countries mentioned above, we estimated that as a result of an SPC export waiver, EU based biosimilar producers could achieve additional export sales of €2.97 billion assuming a fast biosimilar penetration in the export markets and €463 million assuming a slow biosimilar penetration by 2025.[28] The impact on biosimilars is low because our sample is small. If we had data on all molecules and countries, the size would be correspondingly larger, e.g. if the true available market size in third countries was €20 billion, the additional sales by EU biosimilar producers could be €5.7 billion (29% of €20 billion).[29] The net impact of the SPC export waiver on the European biological pharmaceutical industry, taking into account a potential reduction in export sales of the European innovative biological industry (which we estimate at €868 million to €1.7 billion) is estimated to be between €1.2 billion to €2.1 billion in additional export sales by 2025 in the fast penetration case for the sample of molecules and countries considered. In the slow biosimilar penetration case the estimated impact to the EU-based biological industry (branded and biosimilars) could reach *up to* €463 million by 2025 for the sample of molecules and countries examined.

3.4.2. Assessment of wider impact

Since the proposed measure does not enable generic or biosimilar competition *during* the patent or patent extension term but only *after* protection has expired, it cannot be expected to lead to a reduction in incentives to innovate relative to what was intended by the design of the patent and patent extension terms in Europe and other countries. The proposed measure could only negatively affect incentives to innovate if it resulted in generic or biosimilar products destined for export markets to leak into domestic European

---

27 Based on Comtrade statistics, EEA exports to Brazil, Canada, China, Japan, Russia, Turkey and the US amounted to €40 billion in 2014. The €7.3 - €7.4 billion in cumulative sales during the period of SPC protection in Europe, correspond to almost €2.3 billion in cumulative annualised sales, representing a 6% share of €40 billion in 2014. Since our sample represents 32% of the molecules whose SPC expires in Europe during the period 2016-2030, the impact could range between 6% to 18% (3 times 6%).

28 In the fast penetration scenario we assumed that biosimilar penetration for the molecules in our sample in the third countries considered would be similar to that achieved by filgrastim in the EU5 countries (France, Germany, Italy, Spain and the UK). In the slow penetration scenario we assumed that biosimilar penetration for the molecules in our sample in the third countries considered would be similar to that achieved by somatropin and epoetin in the EU5 countries.

29 29% is the share we estimate EU based biosimilar producers could achieve in the third country markets in our sample. Considering more third countries could change the weighted average share that EU based biosimilars can achieve in export markets (given that the 29% is based on the 8 third countries considered). The purpose of the above illustration is to show that the effect would be correspondingly higher if we had a fuller dataset rather than a sample. We do not have reliable data on all the biological molecules whose protection expires in Europe in the period 2016-2030 to compute the relative size of our sample, as we do for non-biological molecules.

markets during the period of patent or SPC protection. However, the risk of infringement is likely to dissuade companies from engaging in such activities.[30]

The proposed measure is likely to result in increased employment in the European pharmaceutical industry as a result of increased sales by European generic and biosimilar producers. We estimate the potential employment effect associated with the additional sales to be between approximately 20,000 to 25,000 additional jobs by 2025, assuming no change in worker productivity.[31] To put these figures in perspective, according to the EGA the EU generic and biosimilar industry directly employs 160,000 people, therefore an additional 20,000-25,000 jobs represent a 13-16% increase in employment. It should be noted that this effect on employment is calculated based on a sample of 117 non-biologic and 17 biologic molecules only and therefore represents a lower bound. Additional manufacturing and R&D employment can be expected to materialise in the future, as generic and biosimilar producers are more likely to invest in Europe if they are allowed to compete timely in export markets from EU manufacturing locations.

A manufacturing export waiver during the SPC term could moreover result in speedier entry of European generics and biosimilars following protection expiry in the EU markets. A biosimilar or generic manufacturer based in Europe who has already set up large scale manufacturing for export would be ready to start selling in the domestic market upon SPC expiry, compared to a manufacturer that is only allowed to start large scale production after the SPC expiry in his domestic market. The benefit could be particularly important for biosimilars, as scaling up production is more complex and consequently requires more time. For illustrative purposes we estimate that if an SPC export waiver resulted in generic entry occurring immediately after protection expiry in the domestic market this would result in savings on pharmaceutical expenditures of €1.6 billion to €3.1 billion over three years for the sample of molecules examined or 4% to 8% depending on when we assume generic entry would occur without an SPC export waiver.[32] If, as a result of the SPC export waiver, biosimilars in Europe entered with a 6-month delay (relative to 1 year delay without an SPC export waiver) following SPC protection expiry in Europe, we estimate savings on pharmaceutical expenditures of €0.6 billion for the sample of molecules examined or a 2% saving.

30 Generic entry at risk (i.e. during the period of protection) is possible even without an SPC export waiver and given the infringement risk, it is unlikely that an SPC export waiver will materially increase the incidence of such cases.

31 We use Eurostat data on production and number of employees in the EU pharmaceutical industry (NACE R2 – Manufacturing of basic pharmaceutical products and pharmaceutical preparations) for the EU28 countries to calculate average production per employee and divide the additional sales by this figure to arrive an estimate of additional employment assuming no change in productivity. http://appsso.eurostat.ec.europa.eu/nui/submitViewTableAction.do.

32 We estimate expenditures for a sample of molecules with later SPC term expiry in Europe relative to the 8 third countries analysed, if generic entry occurred in the EEA immediately following protection expiry as a result of the SPC export waiver compared to expenditures for these molecules if generic entry occurred: i) in the third quarter following protection expiry (the EU average delay for generics is 8.2 months); ii) in the second quarter following protection expiry, assuming delays will reduce in the future, without an SPC export waiver.

3.4.3. Effect of Unitary Patent Protection and Unitary Patent Court

The Unitary Patent should not have an impact on the benefits arising from an SPC export waiver. However, in the situation without an SPC export waiver, a Unitary SPC may put at a disadvantage the generic manufactures operating in Member States with earlier protection expiry dates.

3.5. Scenario 5: Allowing manufacturing of SPC protected medicines in protected (domestic) markets for purposes of selling to other EU Member States where the corresponding patent or SPC has expired

3.5.1. Assessment of effect to the European pharmaceutical industry

We expect an SPC export waiver within Europe to result in increased sales by European generics and biosimilars manufacturers. However we expect the impact to be smaller than that identified under scenario 4 for the following reasons: a) we expect there to be fewer such opportunities as the SPC term is calculated in a way that tends to eliminate differences in protection expiry dates of the same molecule across the EEA, b) European markets are smaller in size relative to third country markets, b) increased competition will result in cannibalisation of sales by other European pharmaceutical producers and d) such a measure could result in a response by the EU based innovative pharmaceutical industry that would limit opportunities for an SPC export waiver within Europe to have an effect.

We estimate the net additional sales to EU-based generic producers that could result from an SPC export waiver within Europe to range between €207.9 million to €416 million by 2025, depending on assumptions regarding the diversion from other European generic and branded producers. Assuming a response by the European innovative industry to increase the coverage of SPC protection across Member States in Europe, these benefits could be reduced.

We cannot estimate the effect for biosimilars since IMS Midas data only report patent expiry dates and do not report protection expiry dates for biological molecules. However, we expect that an SPC export waiver would benefit EU-based biosimilar producers by allowing them to sell into other EU Member States where there is no longer protection. The benefit could be particularly important for biosimilars, due to the very high costs of relocating production.

3.5.2. Assessment of wider impact

Since the SPC export waiver will enable sales by generic and biosimilar producers to those European countries where the SPC has expired or did not exist in the first place, incentives to innovate should not in principle be affected, as the measure will not result in a reduction in the term of patent or SPC protection of originator products. Incentives to innovate could be adversely affected if the measure results in generic and biosimilar products destined for markets without protection to be diverted to protected markets.

However, this risk is already present[33] and it is unlikely that an SPC export waiver within Europe will materially increase this risk.

The proposed measure is likely to result in increased employment in the European pharmaceutical industry as a result of increased sales by European generic and biosimilar producers. We estimate the potential employment effect associated with the additional sales by EU-based generic producers to range between approximately 548 and 1,095 additional jobs by 2025, assuming no change in worker productivity and no reaction by the EU-based innovative industry.[34] Additional employment benefits could result from increased sales by the EU-based biosimilar producers, though due to data limitations we were not able to quantify the impact. Over the longer term additional employment benefits could arise, should an SPC export waiver result in additional investment by generics and biosimilars in manufacturing and R&D facilities in Europe.

Further, a manufacturing export waiver during the SPC term within Europe could result in speedier entry of EU-based generics and biosimilars following protection expiry in the domestic market. A biosimilar or generic manufacturer based in Europe who has already set up large scale manufacturing for export to other EU countries would be ready to start selling in the domestic market upon SPC expiry, compared to a manufacturer that is only allowed to start large scale production after the SPC has expired in his domestic market. For illustrative purposes, we estimate that if an SPC export waiver resulted in generic entry occurring immediately after protection expiry relative to a delay of up to 8 months (the average delay of generic entry observed in the EEA during our sample period) this would result in savings on pharmaceutical expenditure of €0.4 to €0.7 billion over a three year period for the sample of molecules examined or 4% to 8% depending on when we assume generic entry would occur without an SPC export waiver.[35] These savings on pharmaceutical expenditure consider an SPC export waiver within Europe as a standalone measure. If an SPC export waiver to third countries has also been introduced, the savings on pharmaceutical spend specifically relating to this measure (namely an SPC export waiver within Europe) would be smaller.

3.5.3. Effect of Unitary Patent Protection and Unitary Patent Court

If SPCs will be granted centrally with effect in all participating Member States, then there will eventually be no differences in SPC protection expiry dates for unitary patents within

---

33 Consider a compound that is not SPC protected in Slovenia but covered by an SPC in other EU Member States. A generic company, based in Slovenia, could legally manufacture the product for sale in that market. This situation, which is encountered within Europe, theoretically creates the same risk of leakage into Member States where the product is protected.

34 We use Eurostat data on production and number of employees in the EU pharmaceutical industry (NACE R2 – Manufacturing of basic pharmaceutical products and pharmaceutical preparations) for the EU28 countries to calculate average production per employee and divide the additional sales by this figure to arrive an estimate of additional employment assuming no change in productivity. http://appsso.eurostat.ec.europa.eu/nui/submitViewTableAction.do.

35 We estimate expenditures in our sample of molecules with later SPC expiry dates in some EU Member States compared to others, if generic entry occurred immediately following protection expiry as a result of the SPC export waiver compared to expenditures if generic entry occurred: i) in the third quarter following protection expiry (the EU average delay for generics is 8.2 months); ii) in the second quarter following protection expiry, assuming delays will reduce in the future, without an SPC export waiver. Due to data limitations we have not been able to quantify the effect on pharmaceutical expenditure savings from speedier introduction of biosimilars in the domestic markets, as a result of this measure.

Europe. Consequently the current benefits to the generic industry due to the differences in protection expiry and related employment and pharmaceutical expenditure savings identified above will also decline over time.

If SPCs on unitary patents continue to be granted Member State by Member State, then there will continue to be differences in SPC expiry dates between Member States and scope for an SPC export waiver within Europe.

3.6. Scenario 6: Allowing manufacturing of SPC protected medicines in protected (domestic) markets for purposes of preparing for entry in the domestic market (with minimal delay) subsequent to patent or SPC expiration i.e. stockpiling

3.6.1. Assessment of effects on the European generic and biosimilar industry

A stockpiling exemption is likely to benefit the European generic and biosimilar pharmaceutical manufacturing industry by allowing domestic producers to enter timely in markets where the SPC term of the reference product has expired, putting them on an equal footing to compete in these markets with generic and biosimilar producers located in countries without SPC protection (within as well as outside the EU).

The effect of a stockpiling exemption on delays to generic and biosimilar entry will depend on other factors, such as regulatory delays related to pricing and reimbursement negotiations and other regulatory approvals as well as demand side and supply side policies on generics.

To help determine whether manufacturers located in countries where there is no SPC protection or where the protection has already expired, have an advantage in entering first in protected markets upon protection expiry, we examined data obtained from the EMA and national medicine agencies on the manufacturing location of finished products for a sample of first generic entrants following protection expiry during the period 2008Q1 to 2014Q3. The results suggest that manufacturers located in countries where the protection has expired earlier or did not exist in the first place have an advantage in entering first upon protection expiry compared to e.g. domestic producers. This is also confirmed by the finding that European generics manufacturers based in EU Member States with no SPC protection during the analysed period were not significantly disadvantaged compared to non-European ones.[36]

We examined the time to generic entry based on generic entry events during the period 2008Q1 to 2014Q3. We find that for more lucrative markets, entry is already speedy, though there are still some markets where entry does not occur within the first quarter. Our results also suggest that larger generic manufacturers (measured by their EEA-wide generic sales), who are more likely to have a network of manufacturing facilities, are faster to enter upon protection expiry compared to smaller ones. Therefore, a stockpiling exemption may help smaller European generic producers in entering more timely upon protection expiry, by levelling the playing field between large generic companies that have

36 This relates mostly to the CEE countries that joined the EU later (in 2004) and introduced SPC regulation then. As a result some products analysed did not have SPC protection in these countries.

already ramped up production in a less protected market and domestic generic manufacturers.

For biosimilars there is a longer delay to enter following protection expiry, in large part due to the complexity of developing biosimilar products, however the delay has reduced over time. A stockpiling exemption can be expected to also benefit biosimilar producers, as ramping up production is more difficult for biosimilar producers due to the complexity of the production process.

3.6.2. Assessment of wider impact

A stockpiling exemption is also likely to increase incentives by generic and biosimilar producers to invest in manufacturing and R&D production in Europe, by enabling them to compete timely in unprotected or no longer protected markets from European facilities. The combined effect of an SPC export waiver and a stockpiling exemption can be expected to be mutually reinforcing.

A stockpiling exemption could reduce expenditures on pharmaceuticals by lowering delays in entry by generic and biosimilar producers, thus resulting in a speedier decline in prices. For illustrative purposes we estimate the impact on pharmaceutical expenditures if observed delays in generic and biosimilar entry during our sample period (2008Q1 to 2014Q3) were reduced by up to 6 months. Our analysis indicates that if generic entry was brought forward by 6 months, savings on pharmaceutical expenditure (at fixed pre-protection expiry volumes) would amount to €1.1 billion over a three year period for the sample examined as a result of the faster decline in prices, a 4% saving relative to actual generic entry delays during our sample period. If biosimilar entry was brought forward by 6 month, savings on pharmaceutical expenditure would amount to €15 million over a three year period for the sample examined as a result of the faster decline in prices, a 1% saving relative to actual biosimilar entry delays during our sample period. The low impact is the result of a relatively low biosimilar penetration and the fact that there were only a few biosimilar entry events during our sample period. As biosimilar penetration increases over time, the beneficial effects on pharmaceutical expenditure will also increase.

3.6.3. Effect of Unitary Patent Protection and Unitary Patent Court

The effects of UPP and the UPC will depend on whether SPCs on unitary patents become effective in all Member States that have ratified the UPC Agreement with a single filing or whether they will continue to be granted separately by Member State.

If SPCs on unitary patents become effective with a single filing, then SPC protection coverage is likely to increase in Europe over time. The potential beneficial effects of a stockpiling exemption will therefore be amplified as such an exemption would benefit generic and biosimilar producers in more Member States compared to a situation where products are not covered by SPCs in some Member States. If SPCs on unitary patents continue to be granted on a Member State by Member State basis, then situations where products are not covered by SPC in some Member States could continue to arise. A stockpiling exemption will not affect generic or biosimilar producers in countries where an SPC has not been granted.

1. INTRODUCTION

It is generally accepted that well defined patent protection rights promote innovation, particularly in R&D intensive industries such as the pharmaceutical industry, where the costs and time to discover and develop a product are significant. Patent protection offers innovators a period of protection from direct competition, during which they can recoup and earn a return on their R&D costs. In Europe the maximum patent protection term is 20 years from the date of patent application. For pharmaceutical products, an extension to the patent protection term is available through the Supplementary Protection Certificate (SPC).[37] This is offered to compensate innovators for delays in the marketing authorisation process that reduce the effective protection term of the patent. The maximum SPC term is 5 years, plus an additional 6 month period of paediatric extension.

Innovation in the pharmaceutical sector results in significant benefits to society as it enables the discovery and development of medicines to treat chronic and life threatening diseases, reducing mortality and prolonging better quality life. The financial cost and time to develop a new medicine are considerable. A recent study by the Tufts Centre estimates the cost at $2,558 million in 2013 USD (or €1,949 million in 2013 EUR) and the length of time to reach the market 'longer than a decade'.[38] The development of biological medicines for the treatment of chronic and life threatening diseases is an important new area of research. Biological medicines are considered more efficient in treating certain diseases (e.g. cancer), however their cost of treatment is significantly higher compared to chemically synthesised molecules.[39]

An ageing population has resulted in an escalation of public healthcare costs for the Western World. A 2014 European Commission Strategy document on the pharmaceutical industry notes that public spending on health accounts for 7% of GDP in the EU and is expected to increase to between 8.5-9.1% of GDP by 2060.[40] Generics and to a lesser extent biosimilars are considered a key driver in reducing these costs going forward as

37 EC Regulation No. 1768/92 repealed by EC Regulation No. 469/2009, concerning the supplementary protection certificate for medicinal products.

38 See http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study

39 According to NICE, on average, biologic medicines for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology cost around £9,500 per patient per year compared to £450 per patient per year for conventional therapies. Commissioning biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology, NICE https://www.nice.org.uk/proxy/?sourceurl=http://www.nice.org.uk/usingguidance/commissioningguides/biologicaltherapies/commissioningbiologicdrugs.jsp

40 European Commission Staff Working Document, "Pharmaceutical industry: a strategic sector for the European economy", 2014.

they are sold at a significantly lower price than the originator product. [41] Their speedy entry following patent expiry is therefore an important contributing factor towards reduced healthcare costs.

In order to be marketed, a new product requires to obtain marketing authorisation from the relevant authorities.[42] Whereas innovative products need to demonstrate through clinical trials that they are safe to be used in humans and efficient in treating the illness, generic products follow a so-called abridged marketing authorisation procedure and can rely on the data from clinical trials of the reference product as long as they can demonstrate bioequivalence to the reference product (or in the case of biosimilars, biosimilarity to the reference product). The abridged marketing authorisation procedure was developed in order to facilitate the timely entry of generics and biosimilars. To prove bioequivalence or (biosimilarity) generics (biosimilars) need to undergo tests using the reference product that may still be patent protected. The so-called *Bolar* provisions allow such use for the purposes of obtaining marketing authorisation.[43] In Europe, the Bolar exemption is set out in Directive EC/2001/83, Art. 10(6) as amended, and Directive 2001/82/EC, Art. 13(6) as amended. There is however variation in the implementation of the Bolar exemption across EU Member States. Some Member States have adopted a *wide* interpretation of the Bolar exemption that covers the use of a patent protected medicine in order to gain regulatory approval for any medicinal product, while others have adopted a *narrower*[44] scope that covers only use of a patent protected medicine for the purposes of the so-

41 A number of papers and articles suggests that biosimilars sell at a discount of 20-30% in Europe. See for example, *Pricing of biosimilars,* Gabi Online, 23 March 2012 that suggests an average discount of 30% (http://gabionline.net/Biosimilars/Research/Pricing-of-biosimilars). Henry Grabowski, Rahul Guha and Maria Salgado, (2014), *Biosimilar competition: Lessons from Europe*, Nature Reviews, Drug Discovery, Feb 2014, Vol. 13, suggest average discounts in Europe of less than 25% (not taking into account rebates offered to hospitals). But in some cases the discount is substantially higher, especially if rebates to hospitals are taken into account. For example, a recent article notes that a biosimilar for Remicade in the UK has reduced price by 25% relative to the originator. The same article notes that if NHS discounts are taken into account the discounts of biosimilars to Remicade for the NHS are 40-50% and go up to 60% if money returned to the government via the Pharmaceutical Price Regulation Scheme (PPRS) is also taken into account. According to Merck, the marketing authorisation holder for Remicade, biosimilars for Remicade trade at an average discount of 45% to Remicade in the EU. In Norway the discount of a biosimilar to Remicade has reached almost 70% http://www.fiercepharma.com/story/merck-discounts-remicade-uk-it-tries-fend-biosimilars/2015-10-26 The average discounts of generics to their reference products are higher (more than 50%, see Danzon P.M., Furukawa M.F. (2014), "Cross-national evidence on generic pharmaceuticals: pharmacy vs physician-driven markets", NBER working paper no. 17226)

42 As explained in more detail in section 3, a marketing authorisation in the EEA can either be obtained centrally from the European Medicines Agency (EMA) or nationally from the relevant authorities.

43 The term Bolar is based on the *Roche Products vs Bolar Pharmaceutical 733* F.2d. 858 (Fed. Cir. 1984) court case in the US, where the courts found that Bolar Pharmaceuticals in using Roche's patented product to conduct experiments in order to determine that its product was bioequivalent, had infringed the experimental use exemption. Shortly after the decision, the Hatch-Waxman Act was enacted that expressly allowed the use of a patented product for purposes of obtaining regulatory approvals.

44 In this study whenever we use the term *narrow* scope of the Bolar, we refer to a country that has introduced the Bolar exemption in its national laws using the literal wording of Art. 10(6) of Directive 2001/83/EC, as amended, and Art. 13(6) of Directive 2001/82/EC, as amended.

called abridged authorisation procedure, used for generics, hybrids[45] and biosimilars. Innovative companies running clinical trials in countries with narrower Bolar exemptions therefore face a legal risk, unlike generic and biosimilar companies. Additionally, the Bolar exemptions in countries with a wider interpretation usually cover the use of a patent protected product for marketing authorisation procedures in any country, while the Bolar exemptions in countries with a narrower interpretation only cover marketing authorisation procedures in an EEA country.

The SPC provides similar protection to that provided by the patent, therefore under the SPC term the production or sale of the SPC protected medicine is not allowed even if it is not destined for the domestic SPC protected market. It has been argued that generic manufacturers located in countries with more relaxed patent protection rules have a first mover advantage compared to European generic manufacturers. Additionally, under the SPC term a generic producer cannot manufacture a protected medicine to prepare for day 1 entry in the domestic market following the SPC expiry.

In 2012 the European Parliament and the Council of the European Union agreed on a package of regulations for the creation of a Unitary Patent Protection (UPP) and 25 Member States signed a Unified Patent Court Agreement for the establishment of a Unified Patent Court (UPC) that would have exclusive jurisdiction on litigation involving European patents with unitary effect or classical European patents validated in different Member States. [46] The Unitary Patent Protection will give patent owners a unitary effect for a European patent in the EU Member States that are part of the legal instruments cited above with a single filing at the EPO. The UPC agreement contains a Bolar exemption that references the wording of Art. 10 (6) of Directive 2001/83/EC and also contains provisions for SPCs.

In light of these issues, we have been commissioned by DG Growth to examine the impact on the pharmaceutical industry and on consumers of potentially extending and harmonising the scope of the Bolar exemption and allowing during the SPC term manufacturing for export and for stockpiling in order to ensure timely entry following patent expiry. In particular we have been asked to examine the likely impacts of the following potential changes:

A. Extending the scope of Bolar exemption:

1. to all drugs, independently of whether they are generic or not i.e. including patented new developments that are based on or that further develop the SPC protected active component.

2. to obtain marketing approvals anywhere in the world.

3. to allow the supply of active pharmaceutical ingredients (APIs) within the EU.

---

45 A hybrid is a chemically synthesised medicinal product that does not fulfil the definition of a generic, i.e. an exact copy of the reference product according to Art. 10 of the Directive or where bioequivalence cannot be demonstrated with bioavailability studies or in case of changes in the active substance, indications, strength, pharmaceutical form etc.

46 This legislative package contains two regulations creating a unitary patent with unitary effect and its language regime as well as an international agreement among Member States setting up a Unified Patent Court. The first two came into force in January 2014 while the latter has not yet been ratified by all signatories. See http://ec.europa.eu/growth/industry/intellectual-property/patents/unitary-patent/index_en.htm

B. Allowing manufacturing of SPC protected medicines in protected (domestic) markets for purposes of:

4. exporting to third countries where the corresponding patent or SPC has expired or does not exist.

5. selling to other EU Member states where the corresponding patent or SPC has expired (if this situation happens).

6. preparing for entry in the domestic market (with minimal delay) subsequent to patent or SPC expiration i.e. stockpiling.

For each of these potential changes we have been asked to also examine the effect of entering into force of the unitary patent protection and the UPC. Whereas the SPC regulation covers both human and veterinary medicinal products and Directive 2001/82/EC on veterinary medicinal products includes in Art. 13(6) a similar provision to the Bolar provision in Art. 10(6) of Directive 2001/83/EC on human medicinal products, in this study we have been asked to consider only human medicines; therefore veterinary medicines fall outside the scope of this study.

The structure of this report is as follows. Section 2 describes the pharmaceutical value chain, making distinctions where relevant, between originator and generic products and between biological and non-biological medicines. Section 3 discusses the legal framework relating to patent protection and the Bolar provisions in Europe, the US and Canada. In section 4 we assess the impacts of extending and harmonising the Bolar provisions and allowing manufacturing for export and stockpiling during the SPC term. Section 5 concludes.

2. EUROPEAN PHARMACEUTICAL MARKET AND REGULATORY FRAMEWORK

The European pharmaceutical industry is comprised of a diverse number of participants active at different stages of the supply chain, with some being vertically integrated. Pharmaceutical producers can be broadly categorised into:

- **Innovator firms** that conduct R&D to identify, develop and market new medicines that in most cases are patent protected. The EU pharmaceutical and biotech industry has the highest R&D intensity (defined as the share of revenues devoted to R&D) among the EU research based industries. In 2013 the pharmaceutical and biotech industry devoted €30.4 billion in R&D representing 14.4% of revenues. By comparison, the second most R&D intensive industry, software and computer services, devoted 10.4% of revenues in R&D. In 2014, R&D expenditure by the European research-based pharmaceutical industry in amounted to €30.5 billion.[47]
- **Generic and biosimilar** producers develop and market medicines that have lost their protection.

47 The Pharmaceutical Industry in Figures 2015, EFPIA. http://www.efpia.eu/uploads/Figures_2015_Key_data.pdf

- **Generic** products are based on the same chemically synthesised API as the originator reference product. Compared to innovative products, the costs of developing a generic product are significantly lower. This is because generic products do not have to undergo the research to identify a new compound (as they are based on the same active compound as the reference product) or to conduct costly clinical trials to prove that their product is safe to be used in humans and efficient in fighting the disease. The top 10 generic producers by 2014 sales in the EEA had an average R&D spend of 6% of revenues.[48]
- **Biosimilar** products on the other hand, because they are not exactly identical to their reference products have higher costs of R&D and are generally more expensive to produce, as explained in more detail below.

Another important distinction is between the products that are based on chemically synthesised and those that are based on biological compounds.

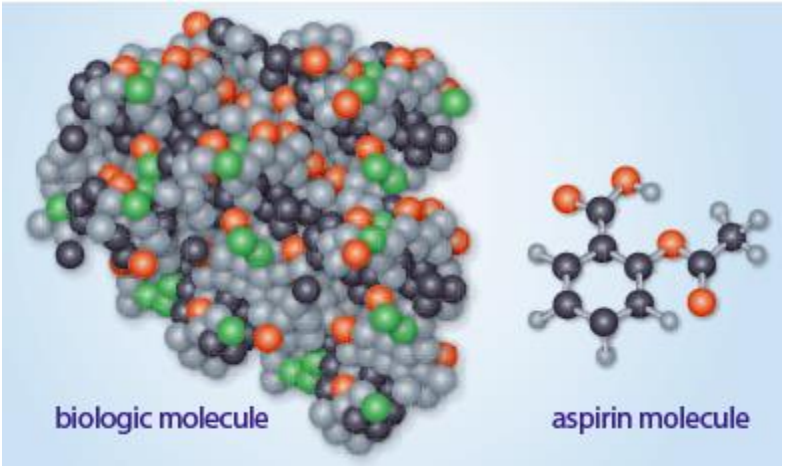
- **Chemically manufactured** active substances (or small molecule drugs) are based on compounds that can be produced in a laboratory through a series of chemical reactions. According to IMS Midas data about 79% of the total sales in the EEA in the last twelve months ending September 2014 are based on chemically manufactured molecules.[49] In 2008, the share was 84% suggesting a gradual decline.
- **Biologics** are drugs based on biological sources, such as e.g. proteins, that have therapeutic properties. Compared to small molecule drugs they are larger and much more complex molecules, made of hundreds of amino-acids. This can be seen graphically in the figure below that compares the molecule structure of the active ingredient in aspirin with the molecule structure of a biologic. Advances in scientific knowledge in the area of genetics and cell processes has led to a new understanding of diseases and to new biologic therapies. Biologics are widely held to be the most promising area of research as they are used to treat chronic and life threatening diseases for which no cure has been found, such as cancer, growth deficiency, rheumatoid arthritis, diabetes, multiple sclerosis etc. In the EEA the share of biological (including biosimilar) molecules in total pharmaceutical sales[50] was 16% in 2008 and increased to 21% in the 12 months ending 2014Q3. According to EGA, by 2018, 50% of pharmaceutical expenditure will relate to biologicals.

48 The top 10 generic companies based on 2014 IMS sales values were Sandoz, Teva, Mylan, Sanofi, Stada, Servier, Aurobindo, Fresenius, KRKA and Actavis. Because Sanofi and Servier have significant originator activities and do not separately report generic R&D, they were not included. Instead the 11th and 12th largest generic companies were included: Sun Pharma and Hospira.

49 Total sales excluding "out of scope" sales, e.g. vitamins, and molecules that are neither classified as biologic nor non-biologic by IMS ("unknown").

50 Total sales excluding "out of scope" sales, e.g. vitamins and molecules that are neither classified as biologic nor non-biologic by IMS ("unknown").

Figure 1: Molecule structure of a biologic versus a small molecule drug (aspirin)



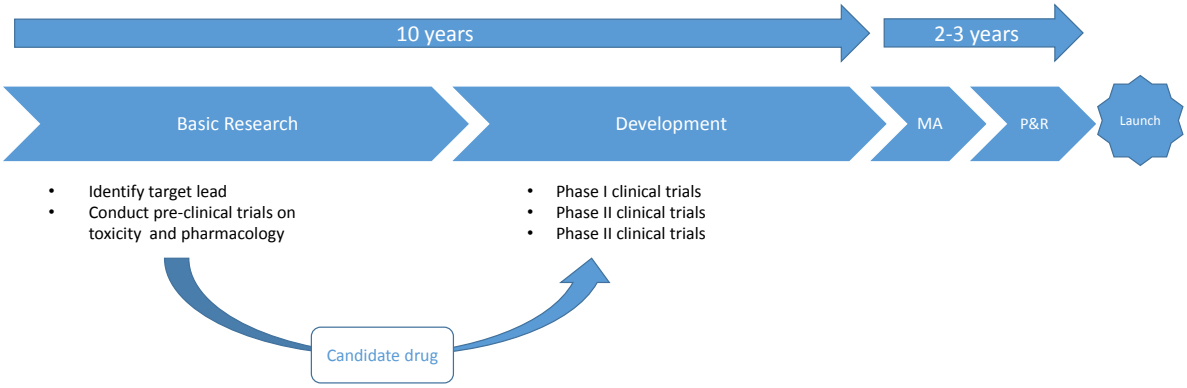
Source: Pharmaceutical Research and Manufacturers of America, "Biologics Medicines in Development" 2013

In Europe, the innovative pharmaceutical industry employs directly 707,000 people, of which approximately 116,000 in the R&D sector and generates 2-3 times more employment indirectly.[51] The generics and biosimilar industry employs directly about 160,000 people with indirect employment exceeding 500 thousand, according to EGA.

The following sections describe the supply chain for innovative versus generic and biosimilar producers, making distinctions between chemically synthesised and biological molecules, were relevant.

2.1. Innovative medicines

The figure below presents the different stages of development of an innovative product before it is launched.



By the time a new compound is first synthesised, on average 12-13 years elapse until it is placed on the market.[52] Moreover, approximately only 1 in 10,000 compounds synthesised in a laboratory will end up into a marketed product.[53] A recent study by the

51 EFPIA, The pharmaceutical industry in figures, 2015 edition. http://www.efpia.eu/uploads/Figures_2015_Key_data.pdf

52 *Ibid.*

53 The Pharmaceutical Industry in Figures 2013, EFPIA. http://www.efpia.eu/uploads/Figures_Key_Data_2013.pdf

Tufts Centre estimates the cost at $2,558 million in 2013 USD (or €1,949 million in 2013 EUR) and the length of time 'longer than a decade'.[54] In a study published in 2003 Tufts estimated the cost per new drug at $802 million (in 2000 USD), which translates to $1,044 USD in 2013 representing an increase in costs of 145% over this period. Reasons for the increased costs of R&D (and the corresponding slower introduction of new chemical entities) include the concentration of R&D in areas where the probability of failure is higher (e.g. in areas of therapy where there are unmet needs and where it may take longer and be more expensive to find a cure)[55], the increase in R&D costs has also been linked to increased regulatory requirements which result in longer reviews, as well as increasingly more complex clinical trials.[56]

As mentioned above, in Europe, the innovative pharmaceutical and biotech industry are the most R&D intensive industries, spending an estimated €30.5 billion in R&D in 2014. According to a Deloitte report commissioned by Janssen Pharmaceutica, the majority of R&D expenditure in pharmaceuticals (59%) is based on private funds with the remaining coming from public funds at the national and European Union level.[57] More than 85% of private health R&D investment in Europe is concentrated in the EU5 countries (France, Germany, Italy, Spain and the UK), Switzerland, Belgium, Denmark, the Netherlands and Austria, which the report attributes among other things to the financial incentives offered for R&D by these countries.

The next subsections describe the steps that innovative pharmaceuticals go through before they can be launched.

2.1.1. Research

Research involves the various steps required to arrive at a candidate drug that is promising to be developed further. Basic research can last up to 6 years and according to EFPIA represents approximately 24% of the R&D investment for an innovative product.[58]

Table 1 presents the various steps in the research phase. Some of these are common across chemically synthesised and biological products, while others differ in their implementation depending on whether the compound is chemically synthesised or biological.

---

54 See http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study

55 Pamolli, Fabio; Magazzini, Laura; Riccaboni, Massimo, "The productivity crisis in pharmaceutical R&D", Nature Reviews Drug Discovery June 2011, 10; 428-438. http://www.nature.com/nrd/journal/v10/n6/full/nrd3405.html

56 Ferrandiz, Jorge Mestre-, Sussex, John and Towse Adrian, "The R&D cost of a new medicine", Office of Health Economics, 2012. According to the authors, the R&D cost varies depending on therapeutic area with the most expensive areas being neurology, respiratory and oncology, firm size and whether a drug is a chemical compound or a biologic. The authors cite a study by DiMasi and Grabowski (2007) that find that the R&D costs of biologics are higher due to longer clinical and approval times. DiMasi, J. and Grabowski, H. (2007), "The cost of biopharmaceutical R&D: Is biotech different?". Managerial and Decision Economics. 28(4-5), 285-291.

57 *Investing in European health R&D, a pathway to sustained innovation and stronger economies,* (2015) a report by Deloitte commissioned by Janssen Pharmaceutica N.V.

58 EFPIA, The pharmaceutical industry in figures, 2015 edition. http://www.efpia.eu/uploads/Figures_2015_Key_data.pdf

Table 1: Basic research steps

Step	Chemically synthesised	Biologicals
1. Target identification	A target is identified through either data mining of biomedical data from publications of patent information, gene expression data and various other biomedical sources.[59] A target is usually a biological agent or process that is thought to be responsible for a disease	
2. Target validation	The target is validated by further studies to ensure it is actually implicated in the disease to be treated and that it can be responsive to a drug. This process involves experimentations in both living cells and animals	
3. Lead identification	Identification of active compounds that can act against the target, through the use of high-throughput screening which involves testing hundreds of thousands of compounds against the target to see which work. This is followed by a choice of a few classes of active compounds that have the greatest potential to be developed into a drug.	DNA is inserted into cells to code for the production of particular protein that can act against the target. Compounds that have the greatest potential to be developed into a drug are chosen.
4. Lead optimisation	Chemists work on synthesising the lead active compounds and try to optimise them in terms of their efficacy against the target, prospects to be able to be synthesised at reasonable costs, formulation and safety.	Specific chemicals are added to control the function of the biologic including its ability to bind onto the target.

Following these steps, a candidate drug is chosen to be further developed. Process and formulation chemists get involved to find a way to synthesise the product in a commercially viable manner, in a formulation that can be effectively administered to the patient and in a physical form that will maximise its stability profile.

In the case of biological products, the cell line that can produce the biologic more effectively is selected for expansion. This cell line is unique to each manufacturer and is the source of all future products. The cell line is grown in bioreactors and the biologic drug is then isolated and purified using sophisticated technology.

2.1.2. Development

Having identified the candidate drug, the pharmaceutical firm begins clinical trials which consist of four phases as set out in the figure below. Phase I-III occur prior to the marketing authorisation, whereas Phase IV occurs following marketing authorisation.

59 Hughes JP, Rees S, Kalindjian SB, Philpott KL, "Principles of early drug discovery", British Journal of Pharmacology, 2011 March, 162(6): 1239-1249. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3058157/

According to EFPIA, the development phase is the most expensive part in the R&D phase, accounting for almost 51% of total R&D expenditure, more than half of which is on Phase III clinical trials. [60]

- Phase I clinical trials: during this phase, the product is administered to a small number of healthy volunteers to determine whether the medicine is safe, if it has the desired effects and what is the more suitable dose. If this is successful, then the product moves to Phase II clinical trials.
- Phase II clinical trials: during this phase the drug is administered to a small number of patients to assess the effectiveness of the product against the disease and identify side-effects. If these are successful the product moves to phase III clinical trials.
- Phase III clinical trials: large scale clinical trials where the product is administered to thousands of patients to monitor the effectiveness and also to assess potential longer term use side effects. These studies also help to determine permitted uses of the medicine, labelling, and whether it is more effective relative to other competing therapies.
- Phase IV: following marketing authorisation pharmaceutical companies continue to monitor efficacy and side-effects following the use in a more diverse population setting. Any new discoveries during this phase must be reported to the European or national medicines agencies.

Figure 2: Clinical trial phases

Stage	Typical number and type of patients	Typical Duration	Purpose
Phase I	20-100 healthy volunteers	Up to 1 year	To ensure the medicine is safe and find the most suitable dose
Phase II	Up to several hundred patients	1-2 years	To assess effectiveness and look for side-effects
Phase III	Several hundred to several thousand patients	2-4 years	To confirm effectiveness and monitor any side-effects from long term use
Phase IV	Variable: commonly several thousand	Variable	To develop new treatment uses, compare with other treatments, determine the clinical effectiveness and long-term safely of the medicine in a wider variety of patient types and/or to satisfy conditions of authorisation

Source: *Intellectual Property and Pharmaceuticals*, EFPIA

Vertical integration versus outsourcing of R&D

Large pharmaceutical companies have in-house capabilities to carry out the research and development of their products.[61] Increasingly however, large pharmaceutical companies

60 EFPIA, The pharmaceutical industry in figures, 2015 edition. http://www.efpia.eu/uploads/Figures_2015_Key_data.pdf

have outsourced some steps in the R&D process to outside organisations. For example, increasingly research is being carried out by universities, biotechnology firms or Contract Research Organisations (CRO).[62] A study by Kneller (2010) finds that about half of the new drugs discovered in the US between 1998 and 2007 originated from public laboratories or biotechnology firms.[63] [64] The European Commission in its pharmaceutical sector inquiry reported that approximately 25% of molecules in clinical development were acquired from other companies, including SMEs.[65]

Another area of outsourcing is clinical trials. Increasingly, pharmaceutical companies are outsourcing clinical trials to CROs and there is a trend of carrying out trials in emerging markets to benefit from their lower costs.[66], [67]

2.1.3. Marketing authorisation

In order to be sold to the public, pharmaceutical companies need to obtain marketing authorisation from competent authorities. In Europe, several routes for the authorisation of medical products are offered to companies:

---

61 Most large pharmaceutical companies have research laboratories in Europe, US and Asia. For example, Novartis has research laboratories in Switzerland, Italy, US, India, Singapore, China and Japan (http://www.novartis.com/innovation/research-development/rd-locations/index.shtml). Pfizer has research laboratories in the US, Canada and the UK (http://www.pfizer.com/research/science_and_technology/rd_locations). GSK has research laboratories in Belgium, France, Germany, Spain, UK, the US and Canada and Singapore and China (http://www.gsk.com/en-gb/research/randd-locations/asia/). Roche has research laboratories in Germany, Sweden, Switzerland, UK, US, China and Japan (http://www.roche.com/research_and_development/who_we_are_how_we_work/rnd_locations.htm).

62 Zhang Jim, "New global pharmaceutical outsourcing trends", Life Science Leader magazine, 29 December 2011. http://www.lifescienceleader.com/doc/new-global-pharmaceutical-outsourcing-trends-0001

63 Kneller, Robert, "The importance of new companies for drug discovery: origins of a decade of new drugs", Nature Reviews Drug Discovery (November 2010), Vol 9; 867-882.

64 Rafols, Ismael *et al*, "Big pharma, little science? A bibliometric perspective on Big Pharma's R&D decline", Submitted to the Technological Forecasting and Social Change, June 2012. http://www.sussex.ac.uk/Users/ir28/pharma/bigpharmalittlescience.pdf

65 *Pharmaceutical Sector Inquiry*, European Commission, 8 July 2009, Part 1.

66 Big pharma ranks China as number one destination in Asia for pharmaceutical outsourcing, finds new PWC report. http://www.fiercebiotech.com/press-releases/big-pharma-ranks-china-number-one-destination-asia-pharmaceutical-outsourcing-finds-n

67 The globalisation of clinical trials and its consequences has been discussed by a number of commentators. For example Glickman et al (2009) find that 1/3 of the phase 3 trials submitted to the US FDA as of November 2007 were conducted outside the US and that the majority of clinical sites (13,521 out of 24,206) were outside the US. Seth W. Glickman, M.D., M.B.A., John G. McHutchison, M.D., Eric D. Peterson, M.D., M.P.H., Charles B. Cairns, M.D., Robert A. Harrington, M.D., Robert M. Califf, M.D., and Kevin A. Schulman, M.D., "Ethical and scientific implications of the globalisation of clinical research", The New England Journal of Medicine 2009, 360: 816-823. Available at http://www.nejm.org/doi/ref/10.1056/NEJMsb0803929#t=article . Similarly, over the period 2005-2011 data from more than 890,000 patients enrolled in pivotal clinical trials submitted to the EMA for purposes of obtaining marketing authorisation. Of these, approximately 38% were in Europe, 34% in the North America, and approximately 28% from the rest of the world (about 9% from Central and South America and 9% from the Middle East, 4% from CIS, 3% from Africa and 2% from Australia and New Zealand). Clinical trials submitted in marketing authorisation applications in the European Medicines Agency, EMA 2013, available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf

- The centralised procedure, whereby the request is made at the EMA. A centralised marketing authorisation procedure is compulsory for biological products, orphan drugs[68], products for the treatment of certain indications[69] and advanced therapy medicines (e.g. gene therapy, somatic cell therapy or tissue engineered medicines). For medicines that do not fall within these categories, companies still have the option of submitting an application for a centralised marketing authorisation to the EMA if the medicinal product constitutes significant therapeutic, scientific or technical innovation or the granting of authorisation is in the interest of patients at the Union level.
- Purely national authorisations for medicinal products to be marketed in one Member State only.
- The mutual recognition procedure (MRP), which is based on the principle of recognition of an already existing national marketing authorisation by one or more Member States.
- A decentralised procedure (DCP) for marketing authorisation applications for a medicinal product submitted simultaneously in several Member States.

For the MRP/DCP, one of Member State is chosen as the "Reference Member State". At the end of the procedure national marketing authorisations are granted in the reference and in the concerned Member States.

A company that obtains a centralised marketing authorisation can sell its products in any EEA Member State. A national marketing authorisation (purely national/MRP/DRP) on the other hand, allows the company to sell its product in the particular Member State that granted it. Any variations such as modifications to the strength, route of administration, pharmaceutical form as well as variations and extensions must also be granted an authorisation or be included in the initial marketing authorisation.

In order to obtain a marketing authorisation (centralised or national), an innovative pharmaceutical product needs to submit detailed information regarding the product, including a description of its manufacturing method and data from pre-clinical and clinical trials demonstrating that the product is safe and efficient to be used in humans.[70]

The issuing of marketing authorisations can take a significant amount of time. In a 2014 study the Escher group found that for 50 MRP/DRP procedures finalised between 2006 and 2013 and corresponding to 635 national licences, the time to national authorisation from the MRP/DRP approval varied considerably among Member States. It was more than 120 days for more than half of the sample and for only about 7% was the national marketing authorisation approved within 30 days as mandated by Article 28(5) of

---

68 Orphan drugs are drugs for the treatment of life threatening or chronically debilitating diseases, where the prevalence is not more than 5 per 10,000 and where it is unlikely that the returns from marketing the medicine would be greater than the cost of developing. A number of incentives are offered to companies that develop such products, such as protocol assistance for clinical trials, scientific advice and 10 year market exclusivity.

69 HIV, AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions and viral diseases. See http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp

70 The details regarding information that needs to be submitted as part of the dossier of an innovative medicine are available in Annex I of the Directive 2001/83/EC.

http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

Directive 2001/83/EC.[71] Reasons for the observed delays include discussions on packaging, brand names, quality of translations of the product information or workload at the competent authority.

Applicants for a marketing authorisation must also ensure that their products comply with the Good Manufacturing Practice (GMP) principles that are set out in Directive 2003/94/EC and must be adhered to within the EEA. Medicine agencies carry out inspections of manufacturing facilities of finished products and APIs in the EEA and in third countries to monitor that manufacturing facilities comply with the GMPs. The GMP principles cover not only the manufacturing of the final medicine but also of the active substances used in the medicine. Applicants should therefore provide information on the name and address of the manufacturing location of the active substances and the finished product as well as the name and address of the proposed sites for the release of the first batches of the finished product in the EEA to the medicines agency as part of their dossier. If the product or active substances are imported, the applicants are required to include information on GMP inspections at those facilities in the last 2-3 years. A medicine cannot be given approval until the agency is satisfied that the manufacturing location of the API and the final product are GMP compliant.[72]

According to Directive 2003/94/EC, the manufacturer must ensure that all the manufacturing operations for medicinal products are carried out in accordance with the information submitted to the authority during the marketing authorisation application. If there are any changes to this process, the marketing authorisation holder is required to notify the authority regarding the modifications. Moreover, any change to the method of production needs to be validated, i.e. tests carried out to ensure that the new production method results in a product that has similar quality characteristics as the one that received the marketing authorisation.[73]

2.1.4. Manufacturing

Already from the development phase, specialists start thinking about the manufacturing process of a pharmaceutical. There is a significant difference in the complexity and costs between manufacturing a medicine based on a chemically synthesised molecule and a medicine based on a biologic compound. These are discussed below.

Chemically synthesised medicines

The production process of chemically synthesised medicines involves the manufacture of the active pharmaceutical ingredient, via chemical reactions of different organic and

---

71 *Improving the EU system for the marketing authorisation of medicines,* Escher TI Pharma (September 2014) http://escher.tipharma.com/fileadmin/media-archive/escher/Reports/Escher_report_IA.pdf

72 Due to a number of cases of quality issues with APIs sourced from China (some of which even led to deaths, e.g. the Herceptin scandal in the US) and increased supply of falsified medicines (medicines that contain low quality ingredients, are fraudulently mislabelled or do not contain the correct amount of the active ingredient), the EU adopted a new Directive in 2011 on falsified medicines which all Member States needed to implement by January 2013. As part of this Directive, the import of APIs must be accompanied by a written confirmation from the regulatory authority of the exporting country that the manufacturing facility complies with EU equivalent GMP standards.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000186.jsp

73 Guide to Good Manufacturing Practice for Medicinal Products, Part I. Available at http://www.picscheme.org/publication.php?id=4

inorganic compounds, the transformation of it in the required formulation (tablets, syrups etc) and dosage, as well as packaging and labelling. Because of their reduced structural complexity, their properties are better defined and are not significantly affected by changes in the manufacturing process.

Most large innovative pharmaceutical companies produce their APIs in-house while some purchase them from third party suppliers. A report on the global API industry by the Italian Chemical Pharmaceutical Association (CPA), estimates the global API market (both captive and merchant) at $120 billion in 2014. Of these approximately $80 billion are branded or originator APIs. Of the $80 billion branded APIs, approximately three quarters (74%) are manufactured in-house and a quarter is purchased from third party suppliers.

Innovative firms usually prefer to outsource the production of APIs for products that are no longer protected. For example, Astra Zeneca in December 2014 decided to close down its Avlon plant in the UK that produced the API for its blockbuster cardiovascular drug Crestor (due to go off patent in 2017 in the UK and Germany and 2016 in the US)[74] and its schizophrenia drug Seroquel (the patent on the API expired in 2012 in a number of countries)[75], and decided to outsource the APIs for these products. Similarly, Pfizer following the patent expiry of Lipitor, its blockbuster cardiovascular drug, sold its manufacturing site in Cork, Ireland which continued to supply it with the API for Lipitor. Merck & Co in the US also sold some of its plants to Contract Manufacturing Organisations (CMOs) which continued to supply it with the APIs.[76]

Biologic medicines

Biologic medicines are produced by living organisms (e.g. genetically modified cells of small organisms) and their production can involve hundreds of steps.[77]

First, DNA is inserted into living cells such as bacteria, yeast or cultured animal cells to code them to start producing a protein. Specific chemicals may be added to control the function of the biologic. The cells that are most effective at producing the desired biologic are selected and then grown and cultivated in bioreactors to produce the desired biologic. Finally, the biologic drug is isolated and purified using sophisticated technology.[78]

Because of the intricate structure of biologics and their complex manufacturing process, it is very difficult to scale up their production and maintain the same quality across different batches.[79] Small differences in temperature or other factors can affect how the product

---

74 http://www.genericsweb.com/index.php?object_id=680

75 http://www.accord-healthcare.eu/quetiapine-sustained-release-patent-invalid-in-the-uk . See also http://www.genericsweb.com/index.php?object_id=972

76 "AstraZeneca will outsource Crestor API following UK plant closure", December 2012, http://www.outsourcing-pharma.com/Contract-Manufacturing/AstraZeneca-will-outsource-Crestor-API-following-UK-plant-closure . See also "Informex 2015: CMOs benefit from changes at big pharma", February 2015, http://borderless.net/content/informex-2015-cmos-benefit-changes-big-pharma

77 *Ibid.*

78 Amgen, "Biologics and biosimilars: an overview. http://www.amgen.com/pdfs/misc/Biologics_and_Biosimilars_Overview.pdf

79 Morrow, Thomas, Felcone, Linda "Defining the difference: what makes biologics unique", Biotechnology Healthcare, 2004 Sep 1(4). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3564302/

will work in patients. Changes in the manufacturing process or facility may therefore require additional testing to determine that the product has the same safety, potency and efficacy as the product that received authorisation.[80] According to the EGA, the minimum cost of relocating the production of a single biological product is approximately €10 million and would take at a minimum 1.5 to 2 years to complete. If additional clinical bridging studies are needed the costs and delay could be multiples of these figures. Moreover, due to the complexity and sensitive nature of the biologic products the R&D usually takes place at the same location as advanced manufacturing, because any change in the manufacturing process from test batches can result in the need for additional regulatory approvals.

Due to the complexity and cost of developing and manufacturing biologics their end cost is significant and the discount to the price of the reference product is lower compared to generics.

2.1.5. Pricing and reimbursement

In most European countries the prices of innovative products are set statutorily, usually at the manufacturer level (e.g. Belgium, Bulgaria, Cyprus, Czech Republic, Greece, Spain, Portugal).[81] In a number of countries prices are set by negotiation between manufacturers and social health insurance funds or national health services (France, Italy, Spain and the UK). In Germany prices are set freely but reimbursement is regulated. In certain cases, usually in the hospital sector, medicines are procured on the basis of tenders with the tender being awarded to the most competitive bidder.

External reference pricing is used by most countries either to set statutory prices or to form the basis of pricing negotiations. External reference pricing involves setting prices by reference to prices in other Member States (basket of countries). There are differences among Member States in how they calculate reference prices and how the reference prices feed into the domestic prices. Some countries use an average price of the reference countries (Austria, Belgium, Cyprus, Denmark, Iceland, Ireland, Portugal, Switzerland and the Netherlands). Other countries set the reference price to be equal to the minimum price among the reference countries (Bulgaria, Hungary, Italy, Romania, Slovenia and Spain) while others use the average of the three or four lowest prices of the reference countries.[82] The following describe the pricing and reimbursement of innovative medicines in the five largest EU countries.[83]

---

80 Medicines in development: Biologics, presented by America's Biopharmaceutical Research Companies, 2013, http://www.phrma.org/sites/default/files/pdf/biologicsoverview2013.pdf

81 "Pricing and reimbursement of medicines: a European overview", Sabine Vogler, Austrian Health Institute, PPRI Conference, Vienna, 30 September 2011. http://whocc.goeg.at/Downloads/Conference2011/PraesentationenPPRIKonferenz/Day2_morning_Festsaal_0900_Vogler.pdf

82 *External reference pricing of medicinal products: simulation based considerations for cross-country coordination*, European Commission, December 2013. http://ec.europa.eu/health/healthcare/docs/erp_reimbursement_medicinal_products_en.pdf

83 *Pricing and reimbursement handbook*, 1st Edition 2011, Baker & McKenzie (http://www.bakermckenzie.com/files/Uploads/Documents/Germany/LifeSciences/EuropeanPricingReimbursement.pdf)

Ispor Global Healthcare Systems Road map, http://www.ispor.org/htaroadmaps/france.asp

In France, marketing authorisation holders apply to be included on positive reimbursement lists so that they can be funded by the public health insurance. There are separate lists for products to be dispensed by pharmacies and for products to be dispensed in hospitals. For new pharmaceutical products a health technology assessment is first carried out to determine the medical benefit provided by the medicine to patients (Service Médical Rendu, "SMR"). This in turn determines the level of reimbursement: the higher the SMR, the higher the reimbursement rate. The reimbursement rate applies to the public price that is fixed by agreement between the Comité Economique des Produits de Santé (CEPS) and the pharmaceutical manufacturers. Influencing factors affecting the level of the fixed price include: the degree of improvement in the medical benefit provided to patients, the price of local or international comparators (mainly from the Germany, Italy, Spain and the UK) and sales forecasts in France. The fixed price is the manufacturer price but distribution margins (of distributors and pharmacies) are also capped. The reimbursement price is set for 5 years from their inclusion in the positive reimbursement list. After the 5 years have passed the price is re-negotiated. For medicinal products administered in hospitals though pricing is not regulated, but their reimbursement is based on predetermined tariff lists through the tarification à l'activité ("T2A") system.

In Germany prices are in principle set freely by manufacturers of new drugs, while the pharmacy and distribution margin is regulated by setting a maximum allowed margin. In practice however, reimbursement prices are regulated and if products are priced above the reimbursement level, the difference is covered by out of pocket payments. Pharmaceutical companies need to provide social security funds with compulsory discounts in order to be reimbursed. Moreover since 2007 pharmacies are required to only dispense prescription medicines that offer rebates to social security funds. Since 2011, all newly licensed medicines are subjected to a health technology assessment that assesses their costs and benefits relative to other therapies. If no added benefit is found, a maximum reimbursement price is set. The price of products that are considered to offer an added benefit over existing therapies is set via negotiations between manufacturers and social security funds that set the reimbursement price at a discount off the list price. For hospitals, prices are determined via negotiations with manufacturers and in many cases hospitals negotiate in groups thereby increasing their buyer power.

In Italy, prices of reimbursable medicinal products are set via negotiations between the manufacturers and the Italian Medicines Agency. A number of criteria are used to inform these negotiations including health technology assessment, price of similar products, patient population size, etc. There are also ceilings on spending for outpatient care which if exceeded result in amendments to the reimbursement price and profit controls.

In Spain, prices for innovative products are set via negotiations between manufacturers and the Ministry of Health. External reference prices are used to form the basis for negotiations for innovative products for which no comparator exists in Spain, whereas internal reference prices are used to determine the price of innovative products for which a comparator exists. A premium to the price of the comparator product is allowed only if the HTA has indicated added benefits compared to costs relative to comparator therapies.[84]

In the UK prices of innovative medicines are set via negotiations between the pharmaceutical industry and the NHS. Under the Pharmaceutical Price Regulation

84 *Pharmaceutical pricing: the use of external reference pricing,* Rand Corporation, 2013. Available at http://www.rand.org/content/dam/rand/pubs/research_reports/RR200/RR240/RAND_RR240.pdf

Scheme (PPRS) profits made by pharmaceutical firms are regulated so that they do not exceed a certain threshold following allowances for R&D and other costs. Price cuts are usually negotiated for older drugs, every 5 years. The NHS can only reimburse medicines that are recommended by the NICE based on a positive Health Technology Assessment. Therefore a positive recommendation from NICE is considered key in the market share that a medicine can achieve in the UK.[85]

In most EU countries, pricing and reimbursement applications can only be made after a marketing authorisation has been granted, however some Member States allow pricing and reimbursement applications before the marketing authorisation is officially granted (e.g. France, Italy, the Netherlands and Sweden). In most EU countries companies require price approval before marketing their products, but in some countries (e.g. Germany, UK) companies are free to set their prices (though reimbursement is still regulated).[86] Such regulatory differences affect firms' decisions regarding where to launch their products first. According to the Directive 89/105/EEC, each one of the pricing and reimbursement decisions must not exceed 90 days (180 days in total). There are limited public data on delays associated with pricing and reimbursement negotiations. EFPIA's WAIT indicator measures delays associated with pricing and reimbursement negotiations since the marketing authorisation (the data used includes new substances authorised centrally by the EMA). The latest WAIT indicator at the time of writing this report was in mid-2011 and shows that for the 66 new medicines with a valid EU marketing authorisation between 1 January 2008 and 31 December 2010, the average time elapsing between the date of EU marketing authorisation and the date of completion of pricing and reimbursement procedures in 20 EU Member States varies from 166 to 550 days.[87]

2.1.6. Distribution

The distribution of pharmaceuticals to hospitals and pharmacies is usually done via wholesalers, as shown in the figure below. In some cases, e.g. in hospital tenders, manufacturers supply hospitals directly. In other cases they can also supply pharmacies directly, particularly in the case of large pharmaceutical chains.[88] The distribution chain of pharmaceuticals is the same for both originator and generic drugs. In some cases, biological products such as vaccines require specialised treatment and storage as they need to be kept at low temperatures.

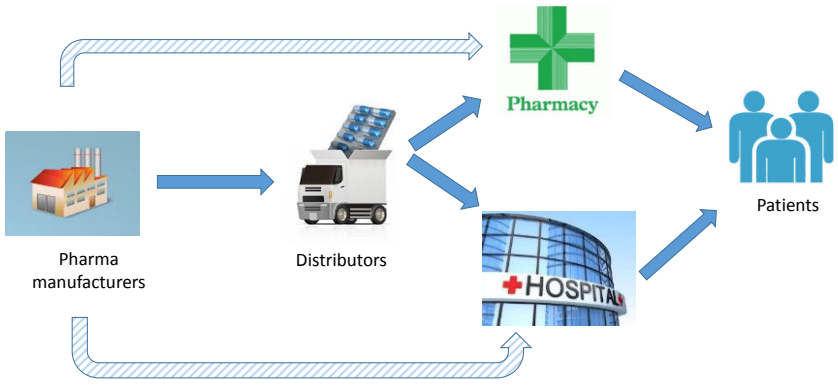
85 Drug Pricing, Houses of Parliament Postnote 364, October 2010. http://www.parliament.uk/documents/post/postpn_364_Drug_Pricing.pdf

UK Reimbursement Process, ISPOR, available at http://www.ispor.org/htaroadmaps/uk.asp

86 *Pharmaceutical Sector Inquiry*, European Commission, p134 and input from EGA.

87 Patients WAIT Indicator, 2011 report EFPIA http://www.efpia.eu/documents/33/64/Market-Access-Delays

88 "Understanding the pharmaceutical value chain", IMS Health, November 2014. http://www.imshealth.com/imshealth/Global/Content/Corporate/IMS%20Health%20Institute/Insights/Understanding_Pharmaceutical_Value_Chain.pdf



2.2. Generics and biosimilars

Generic medicines are copies of products that have lost their patent or SPC protection and for which data protection and market exclusivity have expired. Generics contain the same active ingredient, the same strength and the same pharmaceutical form as the reference product. Article 10.2 of Directive 2001/83/EC defines a generic product as follows:

> *"Generic medicinal product" shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies"*

A biosimilar is a medicine that intends to have the same mechanism of action and is used to treat the same disease as a reference biological medicine. Due to their structural complexity and the complexity of their manufacturing process, biosimilars cannot be identical to their reference products. In Europe, the first biosimilar was authorised in 2006 (somatropin by Sandoz). A total of 19 biosimilars have been authorised by the EMA until February 2015.[89]

According to EGA, by 2020 approximately 75-80% of *dispensed* medicines in Europe are expected to be generics and biosimilars, compared to 56% in 2015.

2.2.1. Research and development

Because generic products are copies of existing products, generic producers do not have to conduct costly research to identify a compound that can act against the disease. Moreover, as explained in more detail below, generic products do not need to conduct expensive clinical trials to prove that they are safe and efficient to be used in humans but can rely on the trials conducted by the innovative reference product.

In the case of hybrid products, clinical data are required in order to obtain marketing authorisation therefore the R&D spend for these products is higher than for pure generics.

Biosimilar products on the other hand have more significant costs of development relative to generic products. Because biologics are developed using living cells, the active

89 EMA website.

ingredient is impossible to recreate exactly. According to Sandoz the development of biosimilars involves the following steps[90]:

- At the first stage, a large number of methods are used to characterise the structure and function of the biologics across hundreds of different specifications. State-of-the art technology is used to understand how the biosimilar compares to the reference product in a non-clinical setting. Moreover, dozens of different batches of the reference product may be used in order to ensure that the biosimilar falls within the variability of the reference product across the different batches.
- Following the identification of a product that exhibits sufficiently similar characteristics to the reference product in a pre-clinical setting, the second stage is the clinical development where the product is administered to humans in clinical trials to assess whether their safety and efficiency profile in humans is the same as that of the reference product.

According to Sandoz, the cost of developing a generic small molecule is around $2-3 million whereas biosimilars are estimated to cost around $75-250 million to reach approval.[91] Due to their higher investment costs, the savings on the price of biosimilars relative to their reference products is relatively modest. A number of papers and industry articles suggests that biosimilars sell at a discount of 20-30% in Europe, though in individual cases the discounts could be significantly larger.[92]

2.2.2. Marketing authorisation

According to Article 10 of Directive 2001 /83/EC, generic and biosimilar products can follow an *abridged* marketing authorisation procedure. The requirements of the abridged authorisation procedure differ for generics and biosimilars.

Generics, because they are copies of their reference products, can rely on the results of pre-clinical and clinical trials of their reference product, provided that they can demonstrate through bioequivalence studies that they are essentially the same as their reference products. Generic applications can rely on the dossier of a patented reference product which has obtained a marketing authorisation in the EEA for at least 8 years. This period of 8 years is the period of *data exclusivity* of an innovative drug. During this

90 http://www.sandoz-biosimilars.com/aboutus/development.shtml

91 Biologics and biosimilars; an overview, Amgen, available at: http://www.amgen.com/pdfs/misc/Biologics_and_Biosimilars_Overview.pdf

92 A number of papers and articles suggests that biosimilars sell at a discount of 20-30% in Europe. See for example, *Pricing of biosimilars,* Gabi Online, 23 March 2012 that suggests an average discount of 30% (http://gabionline.net/Biosimilars/Research/Pricing-of-biosimilars). Henry Grabowski, Rahul Guha and Maria Salgado, (2014), *Biosimilar competition: Lessons from Europe*, Nature Reviews, Drug Discovery, Feb 2014, Vol. 13, suggest average discounts in Europe of less than 25% (not taking into account rebates offered to hospitals). But in some cases the discount is substantially higher, especially if rebates to hospitals are taken into account. For example, a recent article notes that a biosimilar for Remicade in the UK has reduced price by 25% relative to the originator. The same article notes that if NHS discounts are taken into account the discounts of biosimilars to Remicade for the NHS are 40-50% and go up to 60% if money returned to the government via the Pharmaceutical Price Regulation Scheme (PPRS) is taken into account. According to Merck, the marketing authorisation holder for Remicade, biosimilars for Remicade trade at an average discount of 45% to Remicade in the EU. In Norway the discount of a biosimilar to Remicade has reached almost 70% http://www.fiercepharma.com/story/merck-discounts-remicade-uk-it-tries-fend-biosimilars/2015-10-26

period a generic cannot rely on the data from the *dossier* of the reference product when applying for a marketing authorisation.

In addition, a generic product cannot be placed on the market before 10 years have passed from the initial authorisation of the reference product. This can be extended to 11 years if during the first eight years the marketing authorisation holder obtains an authorisation for a new therapeutic indication which holds significant benefits over existing therapies.[93] This period of 10 or eleven years provides a period of "*market exclusivity"* after which generic products can be placed on the market.

Similarly, biosimilars need to submit data from pre-clinical tests and clinical trials demonstrating that there are no significant differences to the reference product in terms of their safety and efficacy profile.[94] As mentioned above, all biotechnology medicines, including biosimilars must be assessed by the EMA, under the centralised procedure.[95]

Europe was the first major economy to set a regulatory pathway for biosimilars (with the 2004 amendment of Directive 2001/83/EC), including detailed guidelines for developing biosimilars (developed by the EMA) that set out the method for comparing biosimilar products to their reference products.[96] By comparison, in the US, the regulatory pathway for biosimilars was only enacted in 2010.

As in the case of innovative products, generic and biosimilar applicants must ensure that they are GMP compliant in order to obtain a marketing authorisation (see discussion in section 2.1.3 above).

2.2.3. Manufacturing

The manufacturing process of generic products is similar to the manufacturing process of chemically synthesised originator products discussed above. The main difference being that generic producers rely more than branded products on APIs sourced from the merchant market as opposed to in-house production. The CPA report estimates that almost 63% of *generic* API sales globally are purchased in the merchant market and the rest are sourced from in-house production.

This is because generic manufacturers typically produce a very large number of different products.[97] Given the large number of APIs needed to produce these products, most generic manufacturers, even if they have capabilities to produce APIs in-house, choose to purchase some of the APIs from third party suppliers. Additionally, a number of smaller

---

93 Directive 2001/83/EC, as amended, Article 10.1.

94 EMA, "Questions and answers on biosimilar medicines", 27 September 2012, available at http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf

95 According to the EMA Procedures for marketing authorisation, biotechnology medicines include medicines developed by i) recombinant DNA, ii) controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transforming mammalian cells and iii) hybridoma and monoclonal antibody methods. EMA "Procedures for marketing authorisation: Centralised procedure", Vol 2A, Chapter 4, available at http://ec.europa.eu/health/files/eudralex/vol-2/a/chap4rev200604_en.pdf

96 European Commission, Consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products.

Amgen, "Biologics and biosimilars: an overview. http://www.amgen.com/pdfs/misc/Biologics_and_Biosimilars_Overview.pdf

97 "Principles of pharmaceutical marketing", 3rd ed. Micky Smith.

generic manufacturers do not have the capabilities to produce the APIs in house and therefore source them from third party suppliers.

The manufacturing process of biosimilars is similar to that of biological products described above. As in the case of biologicals, the characteristics, including the safety and efficacy profile of biosimilars is very sensitive to changes in the conditions of manufacturing. For this reason, it is usually the case that the research and development of the biosimilar product is located at the same place where the advanced manufacturing takes place. Moreover, as described above in the case of biologicals, the costs of relocation of a single biosimilar product are significant, in part due to the fact that a relocation can result in the need for additional regulatory approvals.

2.2.4. Pricing and reimbursement

In most European countries the prices of generics are regulated via an internal pricing reference system, whereby the prices of generics are set by reference to prices of identical products (based on the same active substance) sold in the same market. In many cases the price of generics is required to be a certain percentage below the price of the reference originator product (this is referred to as price linkage). Table 2 adapted from a 2012 article in the GaBI Journal presents the generic price discounts required in different Member States.[98] In other markets, such as Germany, Denmark, the UK and others, generic prices are not regulated, but their reimbursement is. In these markets, national health services reimburse the price of a generic up to a ceiling and if the generic is priced at a higher level, the patient pays the difference.

98 GaBI online, *The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries: an overview*, 2012, Vol. 1, Issue 2. Available at http://gabi-journal.net/the-impact-of-pharmaceutical-pricing-and-reimbursement-policies-on-generics-uptake-implementation-of-policy-options-on-generics-in-29-european-countries%E2%94%80an-overview.html

Table 2: Generic price linkage policy in the EU Member States and Norway

Generic price linkage	Country
Specific policies	AT[99], EE[100], ES[101], LT[102],NO[103]
Generics priced below originator up to (at least) 20%	CZ, EL, IE, IT, LU
Generics priced at least 20-50% lower than originator	BE, CY[104], HU, PL, PT
Generics priced at least 50% lower than originator	FR
No generic price linkage to originator price required	BG, DE, DK, FI[105], HR,[106] LV, MT, NL, RO, SE[107], SI, SK, UK

Source: www.gabi-journal.net/, Data provided and updated by staff and official competent authorities involved in the PPRI/PHIS networks, based on references [6, 18-20]

AT: Austria; BE: Belgium; BG: Bulgaria; CY: Cyprus; CZ: Czech Republic; DE: Germany; DK: Denmark; EE: Estonia; EL: Greece; ES: Spain; FI: Finland; FR: France; HR: Croatia; HU: Hungary; IE: Ireland; IT: Italy; LT: Lithuania; LU: Luxembourg; LV: Latvia; MT: Malta; NL: Netherlands; NO: Norway; PL: Poland; PT: Portugal; RO: Romania; SE: Sweden; SI: Slovenia; SK: Slovakia; UK: United Kingdom.

Biosimilars are not considered as generics and therefore regulations on pricing and reimbursement for generics are not applicable to biosimilars. Below are some more detailed notes on the pricing and reimbursement of generics and biosimilars in some of the largest pharmaceutical European markets.

In France, whereas the reimbursement of generics is set by price linkage to the reference product, where the reimbursement is typically below 50% of the reimbursement of the reference product, the pricing of biosimilars is determined by negotiations between the manufacturer and the Economic Committee for Healthcare products. The reimbursement

99 The first follower is required to be priced at least 48% below the originator. The second follower needs to reduce its price by at least 15% from the price from the first follower and the originator by at least 30% within three months after the inclusion of the first follower into reimbursement. The third follower needs to reduce its price by at least 10% from the price of the second follower. At ths time of writing the article, all of the products in the market h_{ad} to reach the price level of the third follower within three months after the inclusion of the third follower.

100 The first follower is required to be priced 30% below the originator. The second follower needs to reduce its price by at least 10% and the next two followers are 5% lower.

101 The follower needs to be priced below the reference price.

102 New regulation since January 2010: the first follower is required to be priced 30% below the originator. The second and third follower need to reduce their price by at least 10% each.

103 Stepped price model (Trinnprismodellen).

104 For locally produced medicines.

105 In the case of the first follower priced 40% lower than the originator, a faster procedure is offered.

106 Generics to be included into reimbursement are requires to be priced at least 30% than average price in the reference countries and at least 10% lower than the last bioequivalent generics introduced to the list.

107 A price, which is lower or the same as the highest price within a group of substitutable medicines, is accepted without further investigation.

of biosimilars is decided by the Economic Committee for Healthcare products based on the recommendation by the Transparency Commission of the French National Health Authority, which is in turn based on factors such as therapeutic value, seriousness of the disease etc, i.e. factors similar to those considered for the reimbursement of originator products. There are no set rules on how the prices for biosimilars are set.[108]

In Germany, as discussed above, though the price of pharmaceuticals is set freely by the manufacturers, in practice the reimbursement is regulated as manufacturers need to offer discounts to social health funds in order to be reimbursed. Reimbursement prices for generics and biosimilars are set by reference pricing determined by the umbrella organisation of the social health funds.

In the UK, the price of generics is set through negotiations between generic manufacturers and wholesalers. The reimbursement of generics is determined by a drug tariff that sets the reimbursement level depending on the number of available generics with the same active ingredient (international non-proprietary name, "INN"). In the case of biosimilars prices must comply with the Pharmaceutical Price Regulation Scheme (PPRS). As biosimilars are not considered new substances in this context, their prices must be approved by the Department of Health.

To our knowledge there are no recent data published by the EGA on generic delays associated with pricing and reimbursement negotiations. An older study by the EGA found that the average delay for generic companies entering a market as a result of pricing and reimbursement negotiations was 153 days. There was variation among Member States, with some countries (Sweden, Denmark, Netherlands) experiencing shorter delays (less than 50 days), while others (mainly Eastern European) experienced longer delays (more than 250 days).[109] In Germany and the UK generic medicines obtain pricing and reimbursement automatically upon grant of marketing approval.

2.2.5. Distribution

The retail supply chain of generic and biosimilar pharmaceuticals is not different to that of originator products. Pharmaceutical manufacturers usually sell to distributors who then supply pharmacies and hospitals which then dispense the product to final patients. In some cases pharmaceutical companies supply products directly to hospitals, e.g. in cases of tenders and in fewer cases manufacturers supply pharmacies (especially large chains) directly.

108 http://www.taylorwessing.com/synapse/ti_biosimilars.html

109 How to increase patient access to generic medicines in European healthcare systems, a report by the EGA Health Economics Committee, June 2009. http://www.egagenerics.com/images/Website/Market_Barriers_Report_FINAL_update_How_to_Increase_Patient_Access_to_Generic_Medicines.pdf

3. PATENT PROTECTION

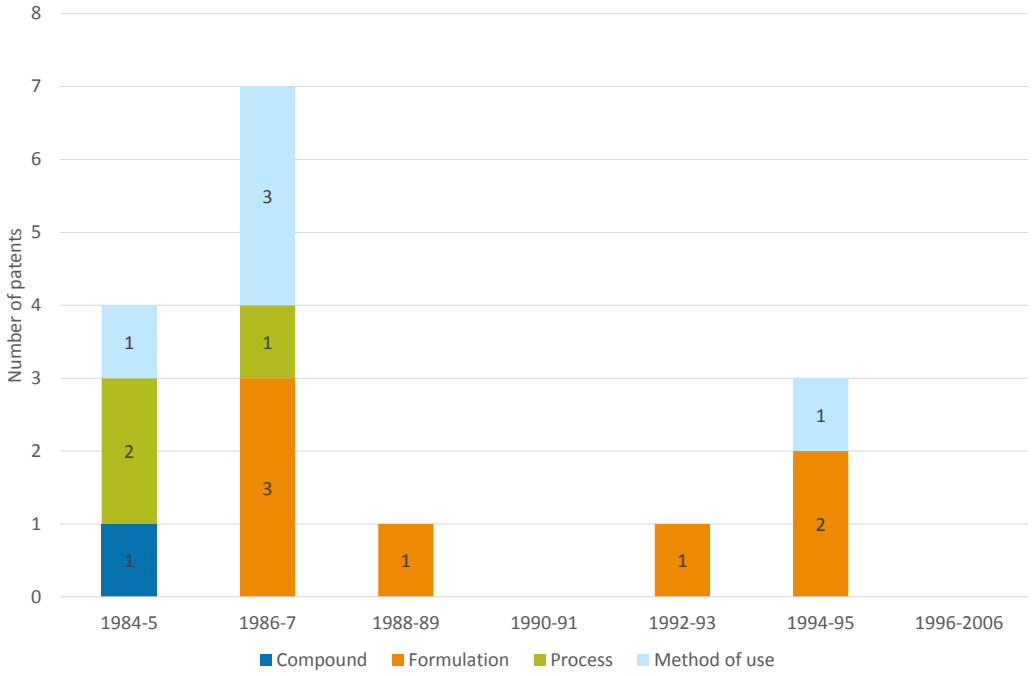
This section describes the regulatory framework relating to patent protection provisions and exemptions in Europe, the US and Canada.

3.1. Europe

3.1.1. Patent protection

The period of patent protection in Europe is 20 years from the date of patent filing. Typically, there are several patents filed for a single medicine. Pharmaceutical companies apply for patent protection as the research and development progresses. They start by patenting their active compounds, then might patent for instance one or several methods of use, formulations and processes. Research for medicines therefore generally leads to the granting of a patent portfolio. Some of these patents (e.g. patents on the active compound) will be more effective at protecting the product from generic competition compared to others, e.g. method of use or formulation.

Figure 3: Illustration of Development of Hypothetical Patent Portfolio over Time



Source: *Intellectual Property and Pharmaceuticals*, EFPIA

Patent applications can be filed either at a national level or at the European Patent Office (EPO). In order to take effect, an EPO filing needs to be validated (within a specified period) at the national level in each Member State in which protection is sought. [110] Some Member States require translations and fees to be paid by a certain date. The enforcement of patent rights, even for a European patent is therefore national. According

110 http://www.epo.org/applying/basics.html

to EFPIA's response to the 2009 EC Pharma sector inquiry, the cost (at the time) of validating a single, relatively short patent document in all EEA countries was €55,000[111] plus another €8,000[112] for maintaining the patent in all EU Member States. Due to the administrative and financial costs associated with national patent validations and renewals, some pharmaceutical companies may decide not to validate a patent in some smaller Member States where the expected benefits of protecting the product from generic competition do not exceed the costs.

In Spain inventions of chemical and pharmaceutical products were not patentable before October 1992, only processes were patentable. Applicants for European patents had to use a different set of claims to validate their patent in Spain, referencing the process of production rather than the compound itself, which were easier to circumvent.[113]

3.1.2. Supplementary Protection Certificates

Since R&D is a lengthy process in the pharmaceutical industry and patents are filed early, products can reach the market 10 years or more after the first patent was granted. This leaves the originator company with only half of the patent protection time. As laid out in the previous section, exclusivity is essential in the pharmaceutical industry due to large R&D costs. To compensate pharmaceutical companies for delays in carrying out the necessary steps to obtain a marketing authorisation, a number of countries have implemented extensions to the patent term through the so-called Supplementary Protection Certificates (SPC). These were implemented in the USA in the mid-1980s, a few years later in Japan and in the 1993 in Europe.[114] After some Member States passed their own SPC regulations, the EC decided to propose a regulation to harmonise it across the EU in 1992 (EC Council Regulation No. 1768/92).

This regulation as well as its amendments were repealed by EC Regulation No 469/2009[115] The preamble states that:

> *"The duration of the protection granted by the certificate should be such as to provide adequate effective protection. For this purpose, the holder of both a patent and a certificate should be able to enjoy an overall maximum of 15 years of exclusivity from the time the medicinal product in question first obtains authorisation to be placed on the market in the Community"*

Though SPC duration and granting conditions are regulated by the EU, national patent offices, not the EPO, grant them.

---

111 This amount includes patent fees of the EU 27 national patent offices, agents' fees and translation costs for each Member State.

112 This figure includes renewal fees plus agent fees.

113 "Chemical-pharmaceutical patent applications filed during the period in which an EPC reservation was in force: has Supreme Court case law become obsolete?", February 2015, Ángel García Vidal, Academic Counsel, Gómez-Acebo & Pombo. http://www.gomezacebo-pombo.com/media/k2/attachments/chemical-pharmaceutical-patent-applications-filed-during-the-period-in-which-an-epc-reservation-was-in-force-has-supreme-court-case-law-become-obsolete.pdf

114 According to the EC Regulation all products authorised for use in the European Community could file for an SPC provided they had been on the market for some period. The length of period that the product should have been on the market to qualify for an SPC differed across Member States. http://www.mpasearch.co.uk/eu-supplementary-protection-certificates

115 Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:152:0001:0010:en:PDF

The SPC term is calculated as follows:

$$SPC\ term_{country\ i} = date\ of\ 1st\ MA\ in\ the\ EEA - date\ of\ patent\ filing_{country\ i} - 5$$

The SPC term cannot exceed 5 years. It can be extended by an additional 6 months, the so called paediatric extension, if a paediatric investigation plan has been submitted.

For example, consider a product that filed a patent in Germany on 01 February 1995 and received its first marketing authorisation in the EEA on 01 February 2004. The patent expires in 30 January 2015 without SPC protection giving an effective protection term of 11 years. If an SPC was applied for in Germany, the SPC term would begin on 01 February 2015 and it would last 4 years, until 30 January 2019.

Generally, the following rule applies regarding the duration of the SPC term:

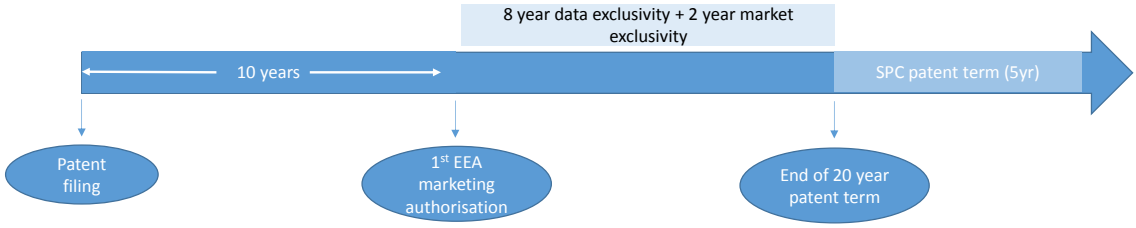
- If the first authorisation for sale in the EU was granted within five years of the patent application, no SPC can be obtained.
- If it was granted between five and ten years, SPC can last between zero and five years.
- Finally, if the first authorisation for sale was granted at least ten years after the first patent application, SPC is automatically obtained for five years.

The way the SPC term is calculated results in a common SPC expiry term across Member States even if the patent filing date is different, as long as the difference between the national patent filing and first EEA marketing authorisation result in a positive SPC term. In practice, however, differences in the SPC term can be observed across Member States. These differences arise for a number of reasons. Differences in the dates that the regulation came into force in different Member States, e.g. in Greece, Spain and Portugal the regulation entered into force in January 1993 but began to apply on January 1998 compared to other western European countries where the regulation applied earlier. Therefore for older products that are still protected we could observe some differences in SPC terms. Moreover, most countries that joined the EU later (CEE and other countries that joined in 2004 or later) only introduced SPC regulation upon their accession to the EU and different transitional arrangements applied to each country, as these were negotiated individually. For example, in Poland, Hungary, Romania and Slovakia, any product covered by a valid patent for which the first marketing authorisation occurred after 1 January 2000, could be granted a certificate provided that the application was made within 6 months of the country's accession (May 2004, January 2007 for Romania) and in the case of Slovakia within 6 months of the first marketing authorisation or 6 months from 01 July 2002. In the Czech Republic any product covered by a valid patent and that received a marketing authorisation after November 1999 could be granted a certificate provided the application was made within 6 months of the date on which the first marketing authorisation was obtained. In Slovenia, Estonia, Cyprus, Latvia, Lithuania and Malta, any product covered by a valid patent for which the first marketing authorisation was obtained before 1 May 2004 could be granted a certificate provided the application was made within 6 months of the country's accession (May 2004) to the EU or in the case of Cyprus within 6 months of the patent grant.[116] These differences in transitional

116 Art. 20 of Regulation EC No. 469/2009.

arrangements could result in differences in protection coverage for older products. Differences could also arise for idiosyncratic reasons, such as, e.g. the SPC lapsing because the annual fees in a certain country were not paid in time or because a company decides not to file for an SPC in a particular country.

The figure below shows graphically the time line from patent filing to protection expiry. As can be seen below, the effect of the SPC term is to extend the protection beyond the end of the patent term to compensate for delays in obtaining marketing authorisation. The figure also shows the period of data exclusivity that lasts 8 years since obtaining marketing authorisation, during which period a generic company cannot rely on the dossier of its reference product for its marketing authorisation and the 10 year period (8+2) of market exclusivity, during which period no generic can enter the market. Of course, if the period of data and market exclusivity expires before the SPC term as shown below, a generic product cannot enter the domestic market until the SPC term expires.



3.1.3. Bolar provisions

Directive 2001/83/EC was amended in 2004 to provide *inter alia* legal certainty concerning the use of patent protected medicines for tests and trials required to obtain a marketing authorisation. As discussed above, a generic application can rely on the results of the reference product's pre-clinical tests and clinical trial data, provided that the generic is demonstrated to be bioequivalent to that reference product. To demonstrate bioequivalence, the applicant needs to perform tests using the reference product. In particular, bioequivalence tests require the administration of the generic product seeking marketing authorisation and its reference product to subjects and the subsequent measurement and comparison of the exposure and absorption of the active substance in subjects that have received the generic product and subjects that have received the reference product.[117] However, the reference product may potentially still be patent protected. The *Bolar* provision set out in Article 10.6 of Directive 2001/83/EC, as amended, allows the use of the patent protected product for purposes of obtaining a marketing authorisation. In particular, Article 10.6 of Directive 2001/83/EC states 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 the patent rights or to supplementary protection certificates for medicinal products.*

117 The best practice guidelines on carrying out bioequivalent studies are set out in "Guideline on the investigation of bioequivalence" by the Committee for Medicinal Products for Human Use, 2010.

Paragraphs 1, 2, 3 and 4 describe the data requirements for obtaining a marketing authorisation for a generic (paragraphs 1 and 2), a hybrid[118] (paragraph 3) and for biosimilars (paragraph 4).

However, this general principle set out in Article 10.6 of Directive 2001/83/EC has been implemented differently in the Member States' national legislation. Some Member States (e.g. the UK up until the recent amendments to its patent legislation, Belgium, the Netherlands and others) have chosen a narrow scope of the Bolar exemption that closely resembles the literal wording of the Directive, while others have chosen a wider scope (e.g. Germany, Denmark, Italy and Spain). In particular, differences arise among Member States on whether the *Bolar* exemptions cover only medicines seeking an abridged marketing authorisation procedure, namely generics, hybrids and biosimilars or also innovative drugs and on whether they cover products seeking marketing authorisation not only in the EEA but also outside the EEA. In addition to the Bolar exemptions provided for in Article 10.6 of Directive 2001/83/EC, most Member States also have experimental use exemptions that cover the experimental use of patented compounds to discover new uses, indications etc. Again, there is significant variation across Member States on what acts are covered by the experimental use exemption.

Table 3 summarises for some European countries whether the Bolar and experimental use exemptions are wide or narrow based on publicly available information.[119] More detailed notes on the scope of the Bolar and experimental use provisions in the EU5 countries plus Ireland which is interesting due to the recent amendment of its patent act are set out in Appendix A.

118 A product that does not satisfy the definition of a generic either because bioequivalence cannot be demonstrated through bioavailability studies or because of changes in the active substance, therapeutic indications, strength, pharmaceutical form etc.

119 Information on the 5 largest EU countries is presented (France, Germany, Italy, Spain and the UK), as well as some additional countries (Belgium, Denmark, Ireland and the Netherlands) where information on the scope of the Bolar and experimental exemptions was available at the AIPPI Working Group Committee Q202 that examined the scope of the experimental use and Bolar exemptions in various countries. https://www.aippi.org/?sel=questions&sub=listingcommittees

Table 3: Summary of scope of experimental use and Bolar exemptions for some EU countries

Country	Bolar/ experimental use covers any medicine (Wide) or only abridged applications (Narrow)?	Bolar covers marketing authorisation procedures in any country (Wide) or only EEA (Narrow)?
Austria	Wide	Wide
Belgium	Narrow	Narrow
Finland	Wide	Wide
Denmark	Wide	Wide
France	Wide	Wide
Germany	Wide	Wide
Hungary	Wide	Wide
Ireland	Wide[1]	Wide[1]
Italy	Wide	Wide
Netherlands	Narrow	Narrow
Portugal	Wide	Wide
Spain	Wide	Wide
Sweden	Narrow	Narrow
UK	Wide[2]	Wide[2]

Source: Responses by relevant national authorities to AIPPI Working Committee Q202, WIPO[120], UK IPO Consultation on amending the UK Patents Act, Irish Department of Jobs, Enterprise and Innovation impact analysis of the research exemption provision.

Notes: 1) A bill was passed in 2014 in Ireland that amended the Irish Patent Act to extend the scope of the Bolar exemption to any medicine; 2) The UK Patent Act was amended effective October 2014 to allow for a wider interpretation of the experimental use exemption that covers not only abridged marketing authorisations but trials carried out by innovative products for purposes of obtaining marketing authorisations in any country or for conducting Health Technology Assessments. Until then, the experimental use and Bolar exemption in the UK had a narrow scope.

The current wording of the Bolar exemption in the Directive as well as in national legislations is not specific with regards to what other acts are covered by the Bolar exemption. In particular, it is not entirely clear as to what parts of the manufacturing process that are related to obtaining marketing approvals are covered by the Bolar. This results in legal uncertainty for generic or biosimilar producers and their suppliers e.g.

120 Facilitating generic drug manufacturing: Bolar exemptions worldwide, June 2014 http://www.wipo.int/wipo_magazine/en/2014/03/article_0004.html

when requiring APIs to conduct bioequivalence tests (see for example the discussion of the Astellas – Polpharma case below) or when they produce batches required for clinical trials (see for example the Sanofi – Lily case in France discussed below).

Polpharma vs Astella

This question arose in the Polpharma vs Astellas case. A Polish API manufacturer, Polpharma advertised the active substance solifenacin succinate in the professional journals SCRIP and Generics Bulletin, as well as on its website. Polpharma supplied 30.5kg of solifenacin succinate at a sales price of EUR 127,000 to Hexal AG, a German manufacturer of generics. Japanese company Astellas Pharma Inc, subsequently sued the Polish manufacturer in both Germany and Poland for patent infringement on its European patent on solifenacin succinate.

Polpharma denied infringement. Its defence was that when concluding the business transactions, it was in agreement with Hexal that the product would only be used in studies and trials whose aim is to produce a solifenacin-based generic drug and to obtain a corresponding marketing authorisation. Whether or not Polpharma's defence is correct therefore depends on the interpretation of the European Bolar provision.

The Regional Court in Dusseldorf (O 282/10) and the Higher Regional Court in Gdansk ruled in June and July 2012 that the Bolar provision did not extend to API manufacturers selling to a testing entity. In both cases the decision was appealed. In October 2013, the Polish Supreme Court upheld the decision, while the Dusseldorf Court of Appeal referred the question to the European Court of Justice.

In the German Appeal case[121], Polpharma argued that the Regional Court's decision adversely affected a number of companies that do not have the ability to manufacture the API themselves, either because they are smaller companies or because they produce a large number of products (like most generic manufacturers) and are thus unable to produce all the active substances themselves. Moreover it adversely affects European API manufacturers relative to non-European ones, as it restricts their ability to sell to companies in the EEA trialling a product, whereas it allows the in-house manufacture and import from outside the EEA of APIs for such use.

The Dusseldorf Court of Appeal in its Order also expressed the view that generic manufacturers that do not have in-house API manufacturing capability should not be placed at a disadvantage compared to those that can produce the APIs in house and it should in principle be as easy for them to procure the amounts of API needed to conduct tests from third parties. The regulatory uncertainty on this issue means that generic manufacturers that do not produce the APIs need to obtain them from API manufacturers in countries where the compound does not have a patent protection.[122] The Dusseldorf Court of Appeal was of the opinion that:

- Commercial third party acts of delivery are principally also subject to the marketing authorisation privilege pursuant to Sec. 11 No. 2b PatG, Art. 10 Para. 6 of Directive 2001/83/EC.

121 An English translation can be found here https://docs.google.com/viewer?a=v&pid=sites&srcid=ZGVmYXVsdGRvbWFpbnxwYWxpdGNhc2VzfGd4OjEwM2Q1ZDUxOGVhOWM2N2I

122 See page 22 of the English translation, *ibid.*

- The third party supplier must be able to assume, given the circumstances (profile of the supplied company, imminent expiration of the patent, small amounts of delivery), that the delivered API will be used for privileged trials and studies for approval.
- The third party must take precautionary measures in order to avoid the non-privileged use of the active substance, through e.g. agreements of use with penalties for inappropriate use etc.

In support of this opinion, the Court noted that

> *The reasons that substantiate the bill concerning Sec. 11 No. 2b PatG support that the marketing authorisation privilege - at least in principle - also extends to those acts of delivery that create the substantive preconditions of the set up for the trials and studies. It derives that the production of medicinal products shall also be subject to this provision to the extent that it is required for the implementation of studies and trials (BT-Drucks. 15/5316 p. 48; Chrocziel/ Hufnagel in Festschrift für Mes, p. 59, 61; Langfinger, VPP circular 1/2011, 53, 57; Fitzner/Lutz/Bodewig/Ensthaler, Patentrechtskommentar, 4th edition, Sec. 11 No. 16). The one conducting the studies and trials under Sec. 11 No. 2b PatG shall thus also be allowed to produce patented medicinal products or active substances to be used in the same studies and trials. The reasons for this law mention that the user of the trial carries out his own acts of delivery while third party deliveries are not mentioned at all. However, this does not necessarily mean that only those acts of preparation are allowed which the user of the trials carries out himself, and that third party acts of delivery are not encompassed. According to the wording of Sec. 11 No. 2b PatGTo third party deliveries can be included as the provision does not refer to the individual who files the application for approval, but merely to the purpose of the conducted trials and studies (c.f. Chrocziel/Hufnagel in Festschrift für Mes, p. 59, 63). The fact that the effects of the patent shall not extend to "the resulting practical requirements" leaves room for the inclusion of third party activity for the company seeking marketing approval (c.f. Hufnagel, PharmR 2006, 209, 213 f.; Chrocziel/Hufnagel in Festschrift für Mes, p. 59, 63). From a purely linguistic point of view, Sec. 11 No. 2b PatG can be regarded as a not just personal, but a substantive privilege without further ado. For its application, it is merely decisive that the trials and studies as well as the therefore necessary deliveries ("practical requirements"), whoever might have delivered them, serve to obtain a marketing authorisation for the medicinal product.[123] (emphasis added)*

The ECJ Judgement on this issue was much awaited as it would have repercussions for all API manufacturers in Europe. However as the case was withdrawn by Astellas, the ECJ will not opine on the subject.

Nevertheless, the Dusseldorf Court of Appeal has provided some clarification on the subject that in principle should cover third party API suppliers wishing to supply protected APIs for Bolar purposes to generics manufacturers in Germany.

Sanofi vs Lilly France

The question of what acts relating to the manufacturing and stocking of protected products at the development phase for Bolar purposes is covered by the Bolar exemption arose in the recent Sanofi-Lilly France case. [124] Sanofi-Aventis held an SPC on insuline

123 See page 19 of the English translation, *ibid.*

124 Sanofi-Aventis vs Lilly France, Order of December 15, 2014, Paris TGI.

gargline that expired in France on 5 May 2015. Lilly France had been preparing a biosimilar insuline gargline and received a marketing authorisation from the EMA on September 2014. In August 2014, Sanofi conducted a raid (*saisie-contrefaçon)* on Lilly France that revealed that Lilly had stocks of insuline gargline. Sanofi filed a preliminary injunction against Lilly in September 2014 and Lilly undertook not to infringe the SPC rights of Sanofi in France. Sanofi accepted the undertakings but then applied for interim measures that would enable Sanofi to monitor the use of insuline gargline in France to ensure it was for Bolar purposes. Among others, Sanofi requested information on the status of the stocks of the product, quantities transported through France, as well as documents justifying that the products were to be used for Bolar purposes. Sanofi acknowledged that Lilly is allowed to import, manufacture, use, export and hold any product of insulin gargline to perform the following acts:

- Send the product to a company in the UK preparing samples for potential clinical trials
- Performing works with the product necessary for the grant of the MA
- Manufacture and export the product in order to perform clinical trials in India
- Perform trials requested by the EMA
- Provide samples in amounts required by the regulatory authorities where an MA application is under examination
- Perform tests of temperature, stability and light impact, together with the studies on shipping conditions in order to complete marketing authorisations abroad
- Hold product as samples for clinical trials when required by regulatory authorities

The Paris Court found that Sanofi held no evidence that Lilly had infringed Sanofi's SPC rights or that there was imminent risk that it would do so. As a result, Sanofi had no grounds to request documents relating to the manufacturing process of one of its future direct competitors for this product and rejected Sanofi's request for interim measures.

This case confirms the broad interpretation of the Bolar exemption by the French courts. In particular, the decision states that Lilly France has the right to perform acts necessary to obtain marketing authorisations outside France. It moreover explains that the Bolar exemption applies to quantities of a patented product strictly necessary and required for the purposes of obtaining marketing authorisations in several countries. The French Court however did not go into the details of what quantities would be covered.

It is unclear whether other national courts would have taken a similar wide interpretation of the Bolar provision in similar cases in their countries.

3.1.4. Unitary Patent Protection

In 2012 the European Parliament and the Council of the European Union agreed on a package of regulations for the creation of a Unitary Patent Protection (UPP) and 25 Member States signed a Unified Patent Court Agreement for the establishment of a Unified Patent Court (UPC) that would have exclusive jurisdiction on litigation involving European patents with unitary effect or classical European patents validated in different

Member States. [125] The Unitary Patent Protection will give patent owners a unitary effect for a European patent in the EU Member States that are part of the legal instruments cited above with a single filing at the EPO. Patent holders now have a choice between i) national patent applications, ii) a 'classical' European patent application with subsequent validation in individual Member States, or iii) a Unitary Patent application. The Unitary Patent does not therefore replace the existing 'classical' European patent application. Holders of a 'classical' European patent can opt-out of the UPC as a forum during a transitory period of seven years. An innovator in deciding what route to follow to file a patent will need to make an assessment based on what geographic coverage he requires and the costs incurred under each route (validation costs, renewal fees, translation costs) and whether in case of a dispute the UPC or national courts are a better forum to hear the case.[126] According to the terms of the UPC Agreement the SPCs on Unitary Patents and the SPCs on European patents that have not opted out will also be decided by the UPC.

Article 27(d) of the UPC Agreement contains a Bolar exemption that references the wording of Article 10(6) of Directive 2001/83/EC as amended. In particular it notes that the rights conferred by a European patent with unitary effect shall not extend to:

> *"The acts allowed pursuant to Article 13(6) of Directive 2001/82/EC or Article 10(6) of Directive 2001/83/EC in respect of any patent covering the product within the meaning of either of those Directives"*[127]

There exists the risk therefore that the UPC may adopt a narrow interpretation of the Bolar when deciding on unitary and classical European patents that have not opted out. These legal uncertainties will remain unresolved until the UPC starts deciding on cases whereby the interpretation of the Directive by the Court will become clearer. Some commentators have suggested that an amendment to Directive 2001/83/EC (as amended in 2004) to adapt it to the more generous wording adopted by increasingly more Member States will resolve these uncertainties.

An additional uncertainty is whether the SPC on European patents with a unitary effect will be granted nationally or whether it will continue to be granted at the Member State level. If the SPC is granted centrally then the holders of a European patent with unitary effect will be able with one application to qualify for an SPC protection in all EU Member States that have ratified the agreement. If the SPC continues to be granted at the national level, unitary patent holders will still need to incur the transaction costs associated with a Member State by Member State application, which is one of the reasons for introducing the unitary patent in the first place. Unless a mutual recognition type procedure is adopted, then there could still be cases where the effective protection term of unitary patents differs across Member States, e.g. if the patent holder chooses not to file for an SPC in some EU countries. The most likely scenario according to legal commentators is that SPCs even for Unitary Patents will continue to be granted nationally at least in the

---

125 This legislative package contains two regulations creating a unitary patent with unitary effect and its language regime as well as an international agreement among Member States setting up a Unified Patent Court. (UPC). At the time of drafting this report, the UPC Agreement was still in phase of ratification by its signatory Member States. See http://ec.europa.eu/growth/industry/intellectual-property/patents/unitary-patent/index_en.htm

126 "An enhanced European Patent System", The Select Committee and The Preparatory Committee, available at http://www.unified-patent-court.org/images/documents/enhanced-european-patent-system.pdf

127 EU Agreement on a Unified Patent Court, Brussels 29 February 2013.

medium term, as a centralised granting would require more legislative changes and would take more time to implement.[128]

3.2. United States

According to the US Code 35 § 154, the term of a patent is 20 years from the date on which the patent application was filed.[129] The US patent law (US Code 35 § 156) provides for a patent term extension of five years to compensate for delays in the regulatory approval process.

The use of a patented compound or drug for purposes of obtaining a marketing approval or for submitting data required by the regulator, is exempted by the *Bolar* type provision as set out in US Code 35 § 271(e)(1), that states:

> *"It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products."*[130]

There has been controversy on what acts are covered by the provision. In *Merck KGaA v. Integra Life Sciences, Ltd.* the Supreme Court reversed the order of lower Courts and found that the provision applies to *any* preclinical studies that are appropriate for submission to the FDA irrespective of the phase of research in which they are developed and irrespective of the particular submission.[131] In particular this could include preclinical studies related to a drug's efficacy, mechanism of action, pharmacokinetics, and pharmacology. The Supreme Court further argued that even though in order to be covered by the provision scientific research must be performed with the *intent to develop* a particular drug, this does not preclude experiments on drugs or use of patented compounds in experiments that end up not being submitted to the FDA.[132]

In *Classen Immunotherapies, Inc v Biogen IDEC*, the Federal Circuit Court held that the provision did not extend to activities related to providing information to the regulator long after the marketing approval has been obtained.[133] This was interpreted as suggesting

---

128 "SPC and the UPC: Current Status", Bristows LLP, Laura Reynolds, 20 February 2015 (http://www.bristowsupc.com/commentary/spcs-and-the-upc/). "The effect of opt-out on SPCs", Taylor Wessing Synapse (http://united-kingdom.taylorwessing.com/synapse/spc_upc_optout_effect.html)

129 For patents that were in force on 8 June, 1995 or that were filed before this date, the patent term is the greater of either i) 20 years since the date of first filing, ii) 17 years since the patent was granted. See http://www.uspto.gov/web/offices/pac/mpep/s2701.html

130 As mentioned above, for biosimilars the abridged authorisation procedure was allowed via the Biologics Price Competition and Innovation (BPCI) Act that came into force in 2010.

131 *Merck KGAA v Integra Lifesciences I, Ltd.,* Supreme Court of the United States, 545 US 193. (2005) at 202.

132 *Ibid.* at 206.

133 *Classen Immunotherapies, Inc. v. Biogen IDEC*, 659 F.3d 1057 (Fed. Cir. 2011), cert. denied, 133 S. Ct. 973 (2013).

that the provision only applied to the use of a patented product at the pre-market approval stage. In a more recent case *Momenta Pharmaceuticals, Inc. v Amphastar Pharmaceuticals, Inc.*[134] the Federal Circuit Court ruled that the wording of the provision was sufficiently broad to cover not only pre-market approval submissions but any submissions required by the regulator either pre-market or post-market approval. Moreover the Court found that the provision covered not just submission of information to the FDA relating to a generic drug approval (Abbreviated New Drug Application) but was broader and covered any use "reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products". In particular, the Federal Circuit Court found:

> *"Although the Hatch–Waxman safe harbor provision was enacted in the context of the then-novel ANDA approval process, 35 U.S.C. § 271(e)(1) does not reference the portion of the Federal Food, Drug, and Cosmetic Act describing the ANDA requirements, e.g., 21 U.S.C. § 355(j). Instead, Congress used more flexible and expansive language to define the scope of § 271(e)(1), referring generally to "the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs." This broad language unambiguously applies to submissions under any federal law, providing that the law "regulates the manufacture, use, or sale of drugs." Limiting the scope of 35 U.S.C. § 271(e)(1) to just the submission of information pursuant to the Federal Food, Drug, and Cosmetic Act generally, or to the ANDA provision of the Federal Food, Drug, and Cosmetic Act in specific, would read words into the statute in violation of the express language chosen by Congress."*

The Court cases therefore suggest a relatively wide interpretation of the *Bolar* type exemption in the US. Moreover, the wording of the safe harbour suggests that it applies to any medicines, not just generics.

3.3. Canada

Canada introduced a Bolar type exemption (also called "early working" exemption) as well as a stockpiling exemption in 1993 through the introduction in its Patents Act of section 55.2, which stated:

> *"(1) It is not an infringement of a patent for any person to make, construct, use or sell the patented invention solely for uses reasonably related to the development and submission of information required under any law of Canada, a province or a country other than Canada that regulates the manufacture, construction, use or sale of any product.*
>
> *(2) It is not an infringement of a patent for any person who makes, constructs, uses or sells a patented invention in accordance with subsection (1) to make, construct or use the invention, during the applicable period provided for by the regulations, for the manufacture and storage of articles intended for sale after the date on which the term of the patent expires"*

134 *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.,* 686 F.3d 1348 (2012), US Court of Appeals, Federal Circuit.

The Manufacturing and Storage of Patented Medicines Regulations clarified that the applicable period for the stockpiling exemption was six months before the date of patent expiry.[135]

In 1997 the EU launched a complaint at the WTO arguing that Canada's patent exemptions (in particular section 55.2(1) and 55.2(2)) violated the TRIPS agreement. The WTO Panel in its report published in 2000 found that only the stockpiling exemption violated the TRIPS agreement and Canada subsequently repealed this provision.[136],[137]

The "early working" exemption is wide enough to cover any type of medicine and cover marketing authorisations in any country. Moreover, according to the submissions by Canada in the WTO proceedings, Section 55.2(1) of the Patents Act covers not only the manufacture or importation of the patented substance by the entity seeking marketing authorisation but also third parties supplying the patent protected API to an entity seeking marketing authorisation. In particular the Report of the Panel noted:

> *"Subsection 55.2(1) permitted a third party to use a patented invention without infringement liability only where the third party made, constructed, used or sold a patented invention solely for uses of the invention that were reasonably related to the development and submission of information required under any law that regulated the manufacture, construction, use or sale of a product to which the invention related. (The reference to selling the invention was necessitated by the fact that a generic drug manufacturer had to usually purchase the active ingredient for its product from a fine chemical producer. Other technical transfers made in the course of a regulatory review submission would include administration of the drug to test subjects and use outside the laboratory for priority testing"* (§ 4.14, emphasis added)

A footnote to this paragraph further explained:

> *"In response to a question from the Panel, Canada explained that, if the patentee claimed that a fine chemical manufacturer was infringing the patent….. the patentee would commence infringement proceedings under Sections 54 and 55 of the Patent Act. The manufacturer would then be obliged to prove that it would have been reasonable, objectively, for a party in its position to believe that the use made of its manufactured active ingredients related to the development and submission of information required by law. It would be common commercial*

---

135 WTO, Canada – Patent Protection of Pharmaceutical Products, a complaint by the European Committees and their Member States, (Canada – EU WTO dispute), Report of the Panel, March 2000, page 3. https://www.wto.org/english/tratop_e/dispu_e/7428d.pdf

136 *Ibid.*

137 Prior to the 1993 Bolar provisions Canada had a long history of compulsory licensing of pharmaceutical products in an effort to curb healthcare costs. Commentators suggest that it was only when the compulsory licensing of imports were allowed (in 1969) that the share of generics increased in the market, though prescription costs kept escalating. See Lexchin, Joel. "After compulsory licensing: coming issues in Canadian pharmaceutical policy and politics." Health Policy 40.1 (1997): 69-80. Atkinson Mary, "Patent protection for pharmaceuticals: a comparative study of the law in the United States and Canada." Pacific Rim Law & Policy Journal, 11.1 (2002). In 1987 Canada amended its Patents Act to: i) change the period of protection from 17 years from the date the patent was issued to 20 years from the date the patent was filed, effective from 1989; ii) allow the patenting of a chemical compound or medicine itself (up to then only the process to manufacture a pharmaceutical could be patented) and iii) introduce a period of protection from compulsory licensing of between 7 to 10 years. In 1993 compulsory licensing was completely abolished and the patent exemptions in section 55.2 were introduced. Cameron, M. Donald et al (2000), Cameron's Canadian Patent and Trade Secrets Law, Chapter 9. http://www.jurisdiction.com/patweb09.pdf

practice for the supply contract with the manufacturer to specify the purposes for which the chemicals were being manufactured and to provide an appropriate indemnity against infringement liability." (footnote 49)

Therefore, third party supply of patent protected APIs for purposes of obtaining marketing authorisation appears to be covered by the patent exemption provisions in Canada.

In 2006 Canada introduced a market protection period of eight years and a data protection period of six years. During the data protection period, a generic manufacturer cannot submit an application for marketing approval. This provision applies only to innovative drugs, i.e. drugs that do not contain ingredients previously approved in Canada. A key assessment on whether a drug is innovative is whether new and significant clinical trial data are submitted in support of its request for marketing authorisation.[138] This is longer than the 5 year data protection offered in the US but shorter than the 10 year market protection offered in Europe.

Another aspect of Canada's legislation is that Canada unlike many other developed countries does not have a provision that extends the patent protection period to compensate for delays in the marketing approval process. As part of the Comprehensive Economic and Trade Agreement (CETA) between Europe and Canada, Canada is to put in place a patent term restoration system along the lines of the Supplementary Protection Certificate system with a maximum period of 2 years.[139] The CETA agreement also allows for the possibility of exceptions during the SPC term for purposes of export to third countries.

3.4. Other countries

3.4.1. China

In China the patent protection term is for 20 years since patent application. The Chinese patent law does not include a patent term extension to compensate innovators for delays in the regulatory approval phase, which according to commentators can be long.[140]

The Chinese Law provides data protection only for innovative drugs containing new chemical ingredients. According to Article 35 of the Implementation Regulation of the Pharmaceutical Administration Law, the Chinese medicines agency will not approve a generic that used without the express consent of the patent holder, the undisclosed R&D and other data from the dossier of the reference product, for a period of 6 years since the date of marketing approval of the originator product. According to commentators, in practice this does not constrain generics to be approved during this period, as the Chinese medicine agency's requirements for generic approvals are very limited. Moreover, the data exclusivity is not clearly defined and may result in conflicts. A

138 http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/data_donnees_protection-eng.php

139 "CETA – Summary of the final negotiating results", September 2014. http://trade.ec.europa.eu/doclib/docs/2014/december/tradoc_152982.pdf

140 *Patent term extension and data exclusivity: a brief comparison of China and the United States*, Li Feng, PhD; Xin Liu, MD; Ningling Wang; and Chunhua Wu, American Intellectual Property Law Association, Biotech Buzz, International Subcommittee, February 2014. http://www.aipla.org/committees/committee_pages/Biotechnology/cl/Lists/Posts/Post.aspx?ID=7

consultation is currently taking place on issues of enforcement of the Pharmaceutical Administration Law that could result in changes to the provision.

3.4.2. India

Following the 2005 amendment of the Indian Patents and Designs Act of 1911, India to comply with the TRIPS agreement allowed a patent term of 20 years since patent application for products and processes.

India's patent system does not allow for a patent term extension to compensate innovators for delays in obtaining regulatory approvals. Moreover, there is no statutory protection for data exclusivity in India. Given the strong generic industry in India, there is a strong lobby against the inclusion of a data exclusivity period, arguing that it is not a TRIPS requirement and it would be to the detriment of the generic pharmaceutical industry and entry of generics in India.

India's Patent Act does not allow for the protection of inventions that are new forms of a known substance that do not result in increased efficiency of that substance. In a recent judgement on *Novartis vs Union of India*[141], the Indian Supreme Court, upheld the decisions by the Indian Patent Office and the Intellectual Property Appelate Board not to grant a patent to Novartis' Glivec on the basis that its product is simply a new form of imatinib and hence not patentable under section 3 (d) of the Patent Act.

3.4.3. Other countries

Information on the patent terms for third countries analysed in section 4.5 of our report is presented below:

- Russia: the patent term is for 20 years from the filing date of the invention. The term can be extended by the period elapsed between the filing date of the patent and the date of the first marketing authorisation, minus five years, similar to the SPC protection in Europe.[142]
- Brazil: the patent term is for 20 years from the filing date of the invention. No patent term extension is allowed to compensate for regulatory delays.[143]
- Australia: the patent term is 20 year from the filing date of the patent. A patent term extension of a maximum of 5 years is available to compensate for regulatory delays.[144]
- Japan: the patent term is 20 years form the filing date of the patent and a patent term extension of up to a maximum of 5 years is available to compensate for regulatory delays.[145]

---

141 'Novartis AG v. Union of India (UOI) and Ors.; Natco Pharma Ltd. v. Uol & Ors.; M/S Cancer Patients Aid Association v. Uol & Ors, April 2013.

142 http://www.wipo.int/wipolex/en/text.jsp?file_id=206380#LinkTarget_585

143 *Patent term extension in Brazil,* Leonor Galvão, American Intellectual Property Law Association, Biotech Buzz, International Subcommittee, February 2013. http://www.aipla.org/committees/committee_pages/Biotechnology/cl/Lists/Posts/Post.aspx?ID=7

144 Australia Patents Act 1990, No. 83 as amended, Chapter 6. https://www.comlaw.gov.au/Details/C2013C00151/Html/Text#_Toc355096042

145 https://www.epo.org/searching/asian/japan/faq.html#faq-445

4. ASSESSMENT

In this section we will analyse the impact of each potential change to the exemption provisions during the patent and SPC protection terms. First, in section 4.1 we describe the data we have relied on in our analysis. The following subsections present our assessment of the potential effects of each modification to the SPC term and the scope of the Bolar. In particular,

- In section 4.2 we assess the potential effects of changing the scope of the Bolar to cover all medicines, not only generic, hybrid or biosimilar medicines.
- In section 4.3 we assess the potential effect of changing the scope of the Bolar to cover marketing authorisations in any country, not only the EEA.
- In section 4.4 we assess the potential effect of changing the scope of the Bolar to allow the third party supply of APIs within the EU to generic companies wishing to obtain a marketing authorisation.
- Section 4.5 presents an assessment of the potential effects of allowing manufacturing during the SPC term in a domestic country for export to a third country (outside the EU) where there is no SPC or protection has expired.
- Section 4.6 presents an assessment of the potential effects of allowing manufacturing during the SPC term in a domestic country for export to another EU country where there is no protection or where the SPC has expired.
- Last, section 4.7 presents an assessment of the potential effects of allowing a 6 month stockpiling exemption during the SPC term in the domestic market to achieve timely entry upon SPC expiry.

In all these sub-sections, we start by describing the issues that arise from the current legislation, we put forward a testing hypothesis on the potential effects of changing the legislation, and we test it based on an analysis of the data described in section 4.1. Views on each of these potential measures and input on certain aspects was sought from the industry associations of innovative pharmaceuticals, EFPIA, and generics and biosimilars, EGA.

4.1. Data

In our analysis we have relied on the following data:

IMS data

We procured IMS Midas data on sales (at the manufacturer level in values and volumes[146]) of all pharmaceuticals at the package level for a number of EEA countries[147] plus Switzerland, Russia and Turkey. The data covered the period 2008Q1 to 2014Q3 and included the following information for each product (at the package level): country of

146 In Standard Units, where 1 SU is the smallest available dose, e.g. 1 tablet or 1 vial.

147 The following EEA countries are covered by the IMS Midas data: Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK.

sale, panel (hospital/retail), generic/branded, biological/non-biological, date of patent expiry, date of protection expiry.[148]

We separately also procured:

- IMS Health data on total pharmaceutical sales (in local currency at the manufacturer level and in Standard Units), broken down into biologic/non-biologic molecules and within biologic into biosimilar/biocomparable, branded, generic and other, and within non-biologic, into generic/branded/other for the following countries: Australia, Brazil, Canada, China, Japan and the USA. Data were provided annually for the period 2013-2014.

- IMS Midas data on the sales (in EUR sales at the manufacturer level and Standard Units) in third countries (Canada, US, Australia), of certain molecules whose SPC term in Europe expires later. The data were quarterly data for the period 2013Q1-2015Q2.

Country of manufacture of API and finished product

We obtained information from the EMA and national medicine agencies on the manufacturing location of the API and the finished product[149] for a sample of generic entrants following protection expiry during the period 2008Q1 to 2014Q3. To select the sample we used the following method. Using IMS Midas data, we identified first generic entrants during our sample period as those generic companies that entered first following protection expiry of the originator product (we excluded branded generics, i.e. generics introduced by the originator company). To arrive at a manageable sample, we selected the top 50% bestselling molecules based on 2013 EEA sales values. In order to take into account country-specific bestselling molecules that would not appear in the top 50% based on EEA sales (e.g. because they were sold in a smaller EEA country), we also included molecules that in any EEA country represented the top 10% of the country's 2013 total pharmaceutical sales values. This selection resulted in 46 molecules. We reviewed these and excluded molecules that based on our research only had patents on

148 Date of protection expiry is the latest of the expiry of the patent term, the SPC term and market and data exclusivities. Protection expiry dates were not available for biological molecules in the data, only patent expiry dates are available.

149 By finished product we refer to the stage of production of the bulk pharmaceutical, where the active ingredient is mixed with excipients, but before the packing/labelling or batch release.

indications, method of use etc.[150] This resulted in 35 molecules, with a total of 1688 observations at the country of sale/ corporation/ product level.[151]

A request was first sent to the EMA, who supplied information on the manufacturing location of the finished product and the API for products that had obtained a centralised marketing authorisation.[152] Only 8 of the 35 molecules followed a centralised procedure, therefore of the 1688 observations, information was provided for 176 observations.

For the remaining products that had obtained a marketing authorisation from national medicine agencies, we sent a request to each national medicine agency. A request was sent out to 18 national medicine agencies that were members of the CMDh ("*Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human*").[153] Eleven national medicine agencies responded to our request.[154]

The responses provided by the 11 national medicine agencies and the EMA resulted in data on API and manufacturing locations for 834 observations in total.[155]

CPA report on global API

We procured the 2015 Global API report produced by the Italian Chemical Pharmaceutical Association (CPA) that included information on the production and sale of APIs by region and by therapeutic class.[156] The report also provided CPA's estimates of a cost index for API producing countries as well as productivity of production by major API country.

---

150 For example our original list of molecules included acetylsalicylic acid, the API of aspirin. This arose in our selection as a company had a patent on an alternative indication for this API. Given that IMS does not provide sales data split by indication, when we selected the top selling molecules, this includes sales of the molecules across all indications. It is therefore difficult in these cases to identify genuine entry (it is not clear whether when we observe entry following the protection expiry on the new indication, the new company's product is also for the same indication or not).

151 The molecules were the following: atorvastatin, budesonide, candesartan cilexetil, carbidopa, clopidogrel, drospirenone, efavirenz, excitalopram, esomeprazole, fluticasone, formoterol, irbesatran, lamivudine, lansoprazole, leuprorelin, levetiracetam, levodopa, memantine, olanzapine, oxydocone, pantoprazole, perindropril, piperacillin, quetiapine, risperidone, rosuvastatin, salmeterol, sildenafil, tacrolimus, tamsulosin, tazobactam, telmisartan, timolol, tramadol, valsartan. Because the IMS database was quarterly, in the vast majority of cases there were several companies already selling in the first quarter post protection expiry. Each observation consists of a country of sale/corporation/product.

152 A pharmaceutical company that applies for an EMA marketing authorisation for a particular product, can then supply this product throughout the EEA.

153 Austria, Belgium, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Slovakia, Spain, Sweden and the UK.

154 Austria, Belgium, Czech Republic, Germany, Greece, Hungary, Poland, Portugal, Romania, Sweden and the UK.

155 For 2 observations, information was missing on the API manufacturing country but information was provided for the finished product manufacturing country.

156 CPA, "Competition in the world APIs market", 2015 Edition.

Comtrade data

We obtained Comtrade statistics on the imports of EEA pharmaceuticals into the following countries: Australia, Brazil, Canada, China, Japan, Russia, Turkey and the US. Data were downloaded for the following HS codes[157]:

- 3001 (Glands and other organs for organo-therapeutic uses, dried, whether or not powdered; extracts of glands or other organs or of their secretions for organo-therapeutic uses; heparin and its salts; other human or animal substances prepared for therapeutic or prophylactic uses, not elsewhere specified or included)
- 3002 (Human blood; animal blood prepared for therapeutic, prophylactic or diagnostic uses; antisera and other blood fractions and modified immunological products, whether or not obtained by means of biotechnological processes; vaccines, toxins, cultures of micro-organisms (excluding yeasts) and similar products)
- 3004 (Medicaments (excluding goods of heading 30.02, 30.05 or 30.06) consisting of mixed or unmixed products for therapeutic or prophylactic uses, put up in measured doses (including those in the form of transdermal administration systems) or in forms or packs for retail sale)

We categorised codes 3001, 3002 and sub-code 300431 (insulin) as biologics and the rest as non-biologic.[158] We used Comtrade data in combination with the IMS Health data to estimate the share that European innovative, generic and biosimilar achieve in pharmaceutical sales in third countries. This was used as an input in the analysis of the SPC export waiver (scenarios 4 and 5).

EMA data on clinical trials

EMA provided us with data on all clinical trials conducted in the European Union or the EEA for the period May 2004-2015 that EMA feed to the WHO International Clinical Trials Registry.[159] Clinical trials conducted outside the EEA are included if they form part of a paediatric investigational plan or if they are sponsored by a marketing authorisation

157 For a description of chapter 30 of the HS Codes see http://www.wcoomd.org/en/topics/nomenclature/instrument-and-tools/hs_nomenclature_older_edition/~/media/F67AF24140A44B939D54AC81BC9362FB.ashx

158 The most granular level of reporting is at a 6-digit HS code. In some cases based on our research a 6-digit HS code could contain both chemical and biological medications, e.g. codes 300432 – medicaments containing adrenal cortex hormones and 300439 – Medicaments containing other hormones, contain some chemically produced and some biological molecules, however we do not have a means to separate those out. As the sales of chemically produced molecules are generally higher compared to sales of biologicals, we allocate these codes to non-biological.

159 http://apps.who.int/trialsearch/

holder and involve the use of a medicine in the paediatric population as part of an EU marketing authorisation.[160]

The data provided included information on the date of the clinical trial registry, title of the trial, type of trial (controlled, and if so whether a medicinal product was used as a comparator, randomised, single blind, open etc), phase of the trial (phase I, phase II etc), name of the product used and INN, sponsor code, inclusion/exclusion criteria, countries where the trial was run. The data were processed to extract information on the countries where the clinical trial was run and date of first registration of the clinical trial and to identify clinical trials where a comparator medicine was used.

4.2. Scenario 1: Extending the scope of Bolar exemption to cover all medicines

4.2.1. Issue

As discussed in section 3, there are differences among Member States on how they have implemented Article 10.6 of the Directive 2001/83/EC, as amended. Some Member States have adopted a wider scope of the exemption that covers all medicines, while others have adopted a narrower scope of the exemption that closely resembles the literal wording of the Directive.

The wording of the Directive suggests that the exemption covers only those medicines that qualify for an abridged application procedure. It is therefore unclear whether innovative drugs that need to use a patent or SPC protected compound in tests or trials (e.g. a comparator in a clinical trial) in order to obtain regulatory approvals are covered by the Bolar exemption in countries with a narrow scope of the Bolar. In such countries, innovators that require to use protected compounds in order to carry out activities necessary for regulatory approvals, face legal uncertainly. This is particularly so in those countries in which the experimental use exemption, which usually covers innovative drugs, has been interpreted narrowly by national courts.[161]

---

160 The clinical trial database covers clinical trials recruiting in the following countries: Afghanistan, Albania, Algeria, Angola, Argentina, Armenia, Australia, Austria, Bahamas, Bahrain, Bangladesh, Belarus, Belgium, Benin, Bosnia and Herzegovina, Botswana, Brazil, Bulgaria, Burkina Faso, Cambodia, Cameroon, Canada, Chile, China, Colombia, Comoros, Congo, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, European Union, Finland, France, Gabon, Gambia, Georgia, Germany, Ghana, Greece, Greenland, Grenada, Guatemala, Honduras, Hong Kong, Hungary, Iceland, India, Indonesia, Iran, Iraq, Ireland, Israel, Italy, Ivory Coast, Jamaica, Japan, Jordan, Kazakhstan, Kenya, Kuwait, Latvia, Lebanon, Libya, Liechtenstein, Lithuania, Luxembourg, Macedonia, Malawi, Malaysia, Mali, Malta, Martinique, Mexico, Moldova, Monaco, Montenegro, Morocco, Mozambique, Myanmar, Netherlands, Netherlands Antilles, New Zealand, Nigeria, North Korea, Norway, Oman, Pakistan, Panama, Paraguay, Peru, Philippines, Pitcairn, Poland, Portugal, Puerto Rico, Qatar, Reunion, Romania, Russian Federation, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, South Africa, South Korea, Spain, Sri Lanka, Sudan, Swaziland, Sweden, Switzerland, Taiwan, Tanzania, Thailand, Trinidad and Tobago, Tunisia, Turkey, Uganda, Ukraine, United Arab Emirates, United Kingdom, United States, United States Minor Outlying Islands, Uruguay, Venezuela, Vietnam, Zambia, Zimbabwe.

161 A question arises as to whether the Bolar exemption should be modified to cover all medicines or whether the experimental use exemption in these countries should be extended. In the UK, it is the experimental use exemption that was amended in October 2014.

The responses to the UK IPO consultation on this subject suggest that this legal uncertainty has been considered to be problematic by both the innovative and the generic industry.[162] Both sides were in agreement that the wording of the legislation resulted in uncertainty as to what activities fall in its scope and that there was need of change.

According to respondents to the initial consultation, the UK legislation did not provide innovative firms the freedom to conduct clinical and field trials, as the generic industry. The generic industry considered that the narrow wording of the Bolar created uncertainty as to which acts fall within its scope, as e.g. it was not clear whether tests and trials requested by regulatory authorities for ethical rather than legislative reasons were covered. This legal uncertainty resulted in increased costs of doing business for innovators as well as generics and biosimilars running tests and clinical trials in the UK. Though limited information on the costs of doing business as a result of this uncertainty was provided, an R&D based firm noted the following costs incurred as a result of the narrow scope of the Bolar provision and experimental use exception in the UK[163]:

- Approximately 60% of molecules in clinical development have potential infringement issues with respect to clinical trials only;
- External costs associated with revocation or opposition of these patents is estimated to be greater than £5.6 million, while internal costs are estimated to be approximately £1.35 million;
- Internal legal costs from freedom-to-operate (FTO) analyses range from £90,000 to £135,000 per case depending on the priority of the case, whereas average EPO opposition costs range between £100,000-200,000.
- The company estimated total savings as a result of this change in regulation of almost £7 million.

Additionally stakeholders in that consultation noted that:

- Current legislation is a factor on the choice of the location of clinical trials, though it is not the only factor. It is particularly burdensome for smaller companies that have a limited budget for assessing infringement risk;
- Three companies indicated that they were advised or chose to run trials in another country due to infringement risk in the UK;

---

162 UK IPO, (2011) "The research and Bolar exemptions: an informal consultation on patent infringement in pharmaceutical clinical and field trials", http://webarchive.nationalarchives.gov.uk/20140603093549/http://www.ipo.gov.uk/response-2011-bolar.pdf
Respondents to the initial consultation included: the Association of the British Pharmaceutical Industry (ABPI), BioIndustry Association (BIA), Bird & Bird, Boehringer-Ingelheim, Cancer Research UK, Chartered Institute of Patent Attorneys (CIPA), CRO personnel, Eli Lilly, EGA, IP Federation, Interpat, Japan Intellectual Property Association (JIPA), Japan Pharmaceutical Manufacturers Association (JPMA), Johnson & Johnson, Merck, Novartis. Respondents to the final consultation included: the ABPI, BIA, the British Generic Manufacturers Association (BGMA), CIPA, Eli Lilly, Ethical Medicines Industry Group (EMIG), Fujifilm Diosynth Biotechnologies, GlaxoSmithKline, Intellectual Property Lawyers Association (IPLA), IP Federation, ISIS (University of Oxford Technology Transfer Company), JIPA, Licensing Executives Society (LES), Patent Judges, Pharmaceutical Life Cycle Management Solutions, Polpharma, PraxisUnico, personnel at pharmaceutical company, Wellcome Trust, Welsh Assembly Government.

163 The Research and Bolar Exception: Proposals to exempt clinical and field trials using innovative drugs from patent infringement, Government Response, February 2013.

- The delay of a trial and subsequent delay in getting a product to market has associated costs, though the exact figure depends on the case at hand.
- Pharmaceutical companies incur significant costs obtaining FTOs, estimated at tens of thousands of British pounds, licensing negotiations may be £10,000 to £15,000 per licence, costs of challenging the validity of patents or defending an infringement action are also significant, though difficult to quantify as they depend on the case at hand.
- The proposed changes may improve the commercialisation success rate as more safety data would be generated through others' use of a drug in a trial environment. This would have a public health benefit.
- Under the current legislation clinical research jobs in the UK are lost to other countries, as companies prefer to conduct tests and trials in countries where there is no risk of infringement.

Ireland also introduced a Bill in 2014 extending the scope of the Bolar provision to include *"all studies/tests/experiments/clinical and field trials and consequential practical requirements*" necessary to obtain a marketing authorisation for a new as well as a generic product and for marketing authorisations in any country. The stakeholder responses to the consultation did not provide details on the additional costs of running tests and trials in Ireland that arise due to the narrow scope of the Bolar. Some respondents maintained that the narrow scope resulted in a competitive disadvantage for Ireland in this area. Respondents suggested that it would be useful to clarify the existing exemption and extend it to cover studies/tests/experiments/clinical and field trials and consequential practical requirements necessary to obtain a marketing authorisation for a new as well as a generic product and for marketing authorisations in any country. No quantification of the benefits to employment and tax revenues was undertaken in the impact assessment nor was there a detailed discussion of the cost to stakeholders of the current narrow scope.[164]

To add to this evidence, we asked the innovative pharmaceutical industry association, EFPIA, whether their members had been at risk of infringement when conducting trials in countries with a narrower Bolar scope and to quantify if possible the additional costs of running trials in counties with a narrower Bolar scope.

EFPIA's response was that their members had been at risk of infringement when conducting trials in countries with a narrower Bolar scope, though no specific recent examples were provided. In relation to the question of quantification of costs to innovative firms of running tests/trials in countries with a narrow Bolar scope, EFPIA was unable to provide estimates, indicating that these could vary from case to case.

EGA also viewed a harmonised and broad interpretation of the EU Bolar as beneficial to the pharmaceutical industry as a whole, because firstly it would reduce legal costs for

164 The Irish Department of Jobs, Enterprise and Innovation in its Impact Analysis considered that the amendments would provide R&D companies with greater legal protection when carrying out experiments and trials for the purposes of obtaining regulatory approvals and would thus increase the attractiveness of Ireland as a location to undertake R&D, thereby increasing skilled jobs and exports of the pharmaceutical industry which is a significant contributor to the domestic economy (through jobs and tax revenues) and trade. Department of Jobs, Enterprise and Innovation, "Regulatory Impact Analysis: Review of the Research Exemption Provision", https://www.djei.ie/en/Legislation/Legislation-Files/Regulatory-Impact-Analysis-Review-of-the-Research-Exemption-Provision-Section-42g-of-the-Patents-Act-1992.pdf

companies and secondly it would streamline strategic planning within the EU. Currently, the different national frameworks existing in Europe result in burdensome legal advice for companies. Moreover, a harmonisation across the EU of a wide Bolar would simplify strategic planning as companies need not decide on e.g. the geographical scope of the product at such an early stage.

Both EFPIA and the EGA in their responses to our questionnaire agreed that the scope of the Bolar is one among a number of factors affecting the choice of location of a clinical trial. Additional factors according to EFPIA include for example where a particular patient population is found as well as access to large and diverse population centres within a reasonable radius. According to EGA, the choice of location of a clinical trial also depends on practical aspects such as: time lines of studies; expected recruitment rates; quality of centres; costs estimated; country-specific requirements for clinical trials that would require specific protocol amendments; strategic importance of a specific region for the marketing.

4.2.2. Testing hypothesis

The responses to the UK IPO consultation and EFPIA's and EGA's responses to our questionnaire suggest that innovative and, to a lesser extent, generic and biosimilar companies face additional costs in running tests and clinical trials in countries with a narrower Bolar scope. However, none of the responses (nor the impact assessment in Ireland) provided detailed data that would allow a quantification of the additional costs of running clinical trials and other tests in countries with a narrow Bolar scope. It is telling of the difficulty of measuring the financial impact that neither the UK nor the Irish impact assessment contained a quantification of the monetary benefits of amending their patent legislation. In particular, the UK IPO in its February 2013 report on the consultation explained:[165]

> *"Respondents indicate that deciding where to run trials is not straightforward and many factors need to be considered when choosing a location. This makes quantification of the costs directly associated with the current legislation very difficult, and consequently very little detailed evidence was provided. Stakeholders did indicate the following areas are those where costs are incurred: legal assessment of the infringement risk, freedom-to-operate analyses, obtaining validity opinions, opposition proceedings, infringement actions, licensing negotiations, and delays in getting a new product to market."*

The responses to the UK consultation and EFPIA's responses to our questionnaire suggest that while the scope of the Bolar exemption is one factor influencing the location of clinical trials, it is one among many factors. This suggests that it may be difficult to isolate and measure the effect of the Bolar scope on the innovative activity in a country (measured by the number of clinical trials run).

4.2.3. Assessment of potential effect on the innovative industry in Europe

To assess the potential effect of the proposed change on the innovative pharmaceutical industry, we first examine whether there is any evidence of fewer clinical trials being run in countries with a narrow Bolar scope compared to countries with a wide scope, while controlling for other factors affecting the choice of where to conduct a clinical trial.

---

165 The Research and Bolar Exception: Proposals to exempt clinical and field trials using innovative drugs from patent infringement, Government Response, February 2013.

We then use estimates of additional costs innovative companies face when carrying out trials in countries with a narrow Bolar, as identified in the UK consultation and provide an illustration of the savings that could result from the proposed change in a sample of countries that currently have a narrow Bolar scope. We focus on the costs of freedom-to-operate tests, as these costs can be expected to be among the common costs incurred when running clinical trials on innovative products, whereas other costs (e.g. costs of infringement actions, costs of revoking a patent and so on), though potentially significant in terms of magnitude, depend on a case by case basis.

Analysis of the effect of the scope of the Bolar on the number of clinical trials run

To assess whether the scope of the Bolar affects the number of clinical trials run in a country, we obtained data from the EMA on clinical trials conducted in the EEA over the period 2004-2015.[166] The clinical trial data included information on: the date of registration of the clinical trial, countries where the trial is or will be carried out, information on the type of trial (random, controlled etc.), whether another comparator medicine was used, as well as details on the product tested and scope of the trial.

Figure 4 below plots the number of controlled clinical trials where another comparator medicinal product was used, by country of recruitment and by year of first registration of the clinical trial. Countries with a narrow Bolar scope (Belgium, Ireland, the Netherlands, Sweden and the UK) are shown with a dashed line.[167] There is variation over time in the number of clinical trials run. There is also variation on the number of clinical trials run by country. Countries with the largest number of clinical trials over this period are: Germany (brown line), Italy (dark green line), UK (blue dashed line), Spain (peach line) and France (but only in the period 2007-2009). The black lines show the average number of clinical trials for countries with a wide Bolar (solid line) and countries with a narrow Bolar (dashed line). We observe that on average the countries with a wide Bolar scope have more clinical trials compared to countries with a narrow Bolar scope.

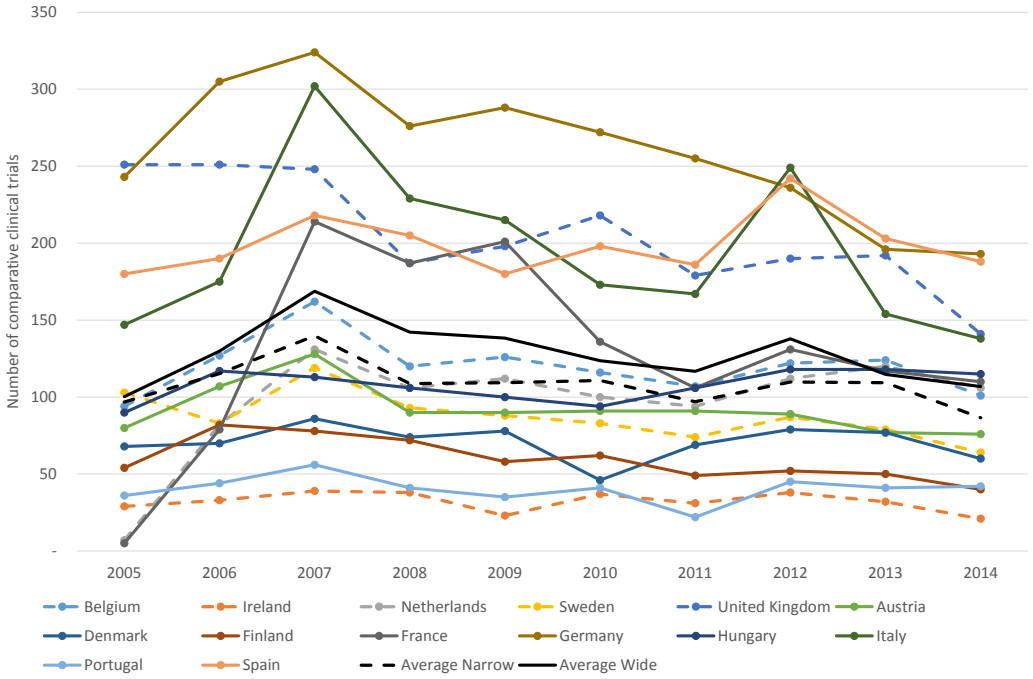
We cannot infer causality from this observation, as there could be other factors that result in a higher number of clinical trials in countries with a wider Bolar scope. One such factor is the size of the population in each country. According to EFPIA the size of the population is an important determinant of where to conduct clinical trials, as the larger is the population the more likely it is that eligible and diverse participants will be found for a clinical trial. Figure 5 below expresses the number of clinical trials by 1 million inhabitants.[168] Controlling for the size of the population, we observe that it is no longer the case that fewer clinical trials are run in countries with a narrow Bolar scope compared to countries with a wider scope. In fact, we observe that on average clinical trials per 1 million inhabitants are *lower* in countries with a wider Bolar scope (black solid line) compared to countries with a narrower Bolar scope (black dashed line), but the difference is relatively small.

166 The EMA clinical trial registry contains information for clinical trials that started in May 2004, therefore data for this year are partial.

167 Data for 2004 are not plotted as we have partial data for this year, as explained above.

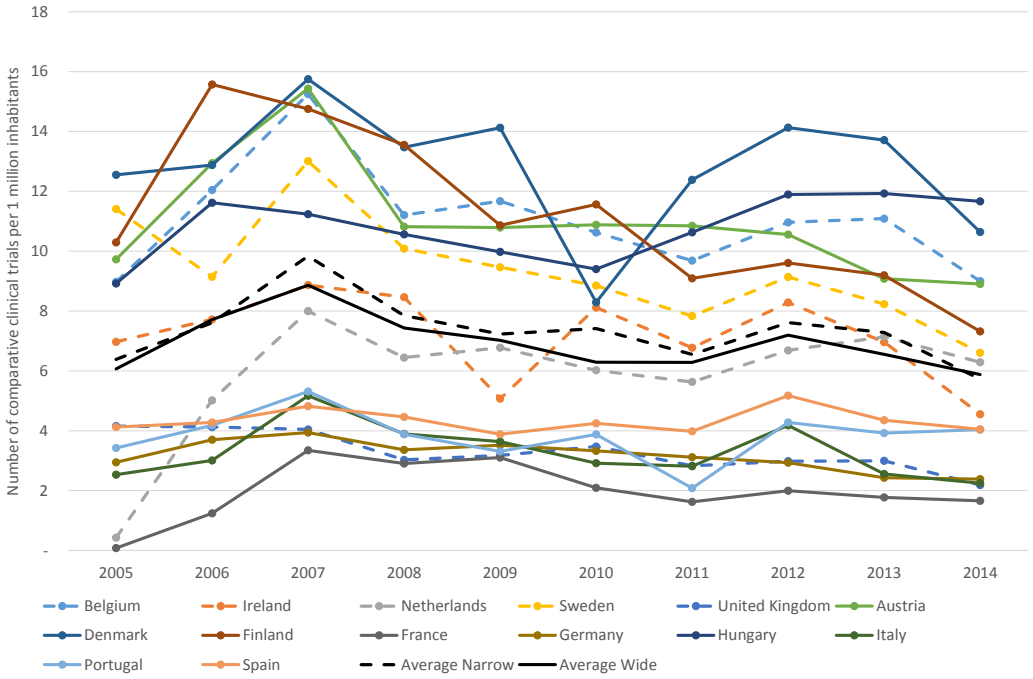
168 Information on the population of each EEA country was obtained from the World Bank (http://data.worldbank.org/indicator/SP.POP.TOTL)

Figure 4: Number of comparator clinical trials by European country, 2005-2014



Source: CRA analysis on EMA data

Figure 5: Number of comparator clinical trials per 1 million inhabitants by European country, 2005-2014



Source: CRA analysis on EMA data

Of course the size of the population is not the *only* factor affecting the choice of the location of clinical trials. For example, in the UK consultation the following additional factors were noted by respondents as influencing the choice of location of clinical trials: quality of academic and research facilities, healthcare infrastructure, medical expertise, financial incentives. Similar factors were also identified by EFPIA. The EGA mentioned

country-specific requirements for clinical trials that would require specific protocol amendments as well as strategic importance of a specific region for the marketing of a product as additional factors.

Regression analysis can be used to isolate the effect of each factor on a variable of interest, in this case the number of clinical trials run in a country. To help determine whether the scope of the Bolar has an effect on the number of clinical trials run in a country, while controlling for other factors, we regressed the number of clinical trials run by country on the following explanatory variables:

- **Population**: as discussed above the size of the population is an important determinant of the choice of location of clinical trials. This is also evidenced by the graphs above that show more clinical trials being run on average in larger sized countries (Germany, UK, Spain and France) compared to smaller ones. However we also observe a sizeable number of clinical trials in smaller countries (e.g. Belgium, the Netherlands) suggesting that the population may not be the only determining factor.
- **Hospital bed density**: data on hospital bed density for each of the 14 European countries analysed were obtained from the World Bank website.[169] Hospital bed density can act as a proxy of hospital infrastructure development and we would expect a positive relationship between the number of clinical trials run and number of beds per population.[170]
- **Physician density**: data on the number of licensed physicians per population were obtained from the OECD website.[171] We would expect a positive relationship between the number of physicians per population and the number of clinical trials run in a country, as physicians (and specialists) help in the selection and monitoring of patients during clinical trials. Of course it is the quality of the physicians and specialists that is more important rather than the number as such, but no data were available to be used as a proxy of the quality of physicians and specialists in a country.
- **Researchers in R&D density**: data were downloaded from the WHO website.[172] The number of researchers in R&D is used as a proxy for the quality of academic and research facilities in a country. We expect a positive relationship between the number of clinical trials run in a country and this proxy variable.
- **A Bolar dummy** that was equal to 1 for countries with a wide Bolar scope and 0 for countries with a narrow Bolar scope. A positive coefficient on this dummy variable would indicate that more clinical trials are run in countries with a wider Bolar scope compared to countries with a narrower scope.

---

169 World Bank data (http://data.worldbank.org/indicator/SH.MED.BEDS.ZS).

170 The number of specialist hospitals or hospital beds per population could also be used as a proxy but there were no data available for all the countries analysed. In any case, it is reasonable to expect a positive relationship between the number of hospital beds and number of specialised hospital beds.

171 OECD data (http://stats.oecd.org/Index.aspx?lang=en&SubSessionId=e9461bc0-5865-4fb2-8124-ec41c18a20af&themetreeid=-200). Other measures of physicians density (practising physicians, professionally active physicians) are not used as they are missing for countries with narrow Bolar scope (e.g. the Netherlands).

172 WHO Global Health Observatory Data Repository (http://apps.who.int/gho/data/node.main.506?lang=en).

Other control variables could have potentially been added. For instance, medical devices density would be expected to be positively correlated with the number of clinical trials as they are needed to conduct particular tests. However, there were missing data on these other candidates for control variables for key countries in assessing the effect of the scope of the Bolar exemption, such as the UK and Sweden.[173]

Moreover, there are other variables that according to the industry could affect the choice of where to conduct clinical trials, but due to data availability issues were not included. In particular, financial incentives provided for innovation, such as tax breaks or subsidies, can be expected to be positively associated with the number of clinical trials conducted in a country, however detailed data on this were not available over the period and the countries examined. For some clinical trials the strategic importance of certain countries for marketing of the product could be an important choice variable, however as this depends on a case by case, no data were available to enable us to quantify this factor. Some countries may require specific protocol amendments for clinical trials or have other requirements that are more onerous and could therefore be less preferred locations for clinical trials (cf. EGA's response). However we have no data to capture these country specific factors. Qualitative factors, such as reputation and quality of doctors are difficult to measure, e.g. a response to the UK consultation suggested that UK NHS consultants have a worldwide influence, which could affect the choice of location of clinical trials.

Further, the control variables we used in our regressions have missing values. As exhibited in the number of observations per model specification in Table 5, the more control variables are added, the fewer observations are used.[174] Lastly, as the data we use are typically an aggregate of national data compiled by international bodies, differences in measurement between countries might affect our estimations.

We estimated the effect of the scope of the Bolar on the number of clinical trials run in a country with several specifications that differ in the control variables used (see Table 4 below). All density variables are per million inhabitants and taken in logarithms, as is the number of clinical trials run.

173 We also experimented with additional specifications, adding as an explanatory variable the share of the population that was born outside the country, based on OECD statistics. Our expectation was that the coefficient on this variable would be positive, as population diversity is one of the factors identified by EFPIA that could increase the attractiveness of a country as a location for clinical trials. However, the coefficient on this variable was negative and statistically insignificant in all the specifications and did not materially change the results.

174 E.g. the *Physicians density* OECD data is missing for all countries from 2012 and always missing for France and Austria.

Table 4: Explanatory variables included in specifications of the econometric analysis of the effect of the scope of the Bolar on the number of comparator clinical trials run in a country

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Bolar Wide dummy	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Population	Yes	Yes	Yes	Yes	Yes	Yes	Yes
R&D researchers	-	-	Yes	Yes	Yes	Yes	Yes
Licensed physicians	-	-	-	Yes	Yes	Yes	Yes
Hospital beds	-	-	-	-	Yes	Yes	Yes
Year	-	-	-	-	-	Yes	-
Year dummies	-	-	-	-	-	-	Yes

We present the results of our estimation of the effect of the scope of the Bolar on the number of clinical trials run in a country in Table 5 below. The estimations are performed on available data, excluding year 2004 and 2014.[175]

The effect of the scope of the Bolar exemption is negative and not statistically significant in all specifications.

The population of a country seems to have a positive and statistically significant effect on the number of clinical trials run in a country. This effect is robust across all specifications and has a magnitude of about 0.5, meaning a 10% increase in population is associated with a 5% increase in the number of clinical trials run in a country.

The density of R&D researchers and licensed physicians density do not seem to have a statistically significant relationship to the number of clinical trials run in a country. However, hospital beds density is positively associated with the number of clinical trials run in a country; this relationship is significant in specification 5, not statistically significant in other specifications. A 10% increase in the number of hospitals beds per a million inhabitants is associated with a 5.1% increase in the number of clinical trials in that model.

The inclusion of a time trend or year dummies does not significantly change the results. Estimated coefficients in models 6 and 7 are similar to coefficients in model 5, although the coefficient associated with hospital beds density becomes not statistically significant. However, due to the missing data for control variables (especially hospital beds density), the inclusion of a time trend or year dummies might unintentionally capture country specific effects since countries on which the estimation is performed change over time.[176]

Our preferred specification is therefore model 5.

175 We have partial clinical trial data for 2004. The UK and Ireland changed from a narrow Bolar scope to a wide Bolar scope in 2014. As we do not have sufficient data after the change and since the change occurred at the end of 2014 for the UK, we exclude 2014 from the analysis.

176 For instance, hospital beds density is available for Hungary from 2007 to 2009 and from 2009 to 2012 for Belgium. For a given year, countries on which the estimation is performed would therefore differ significantly and this could be picked up by the time trend or year dummies.

Table 5: Econometric estimation of the effect of a Wide Bolar exemption on the number of clinical trials run in a country where another comparator medicinal product was used

Dependent variable	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Bolar Wide	-0.0008	0.0126	-0.0377	-0.0186	-0.1607	-0.1728	-0.1504
	(0.18819)	(0.19184)	(0.17815)	(0.17380)	(0.16421)	(0.17266)	(0.17849)
Population	0.4747***	0.4928***	0.5248***	0.5530***	0.5510***	0.5541***	0.5686***
	(0.09048)	(0.11051)	(0.05815)	(0.06771)	(0.08065)	(0.08333)	(0.08097)
R&D researchers		0.0704		0.1451	0.1171	0.1483	0.1289
		(0.18303)		(0.20514)	(0.14956)	(0.16757)	(0.16257)
Licensed physicians			0.8336*	0.8835*	0.7198*	0.7924*	0.7550*
			(0.42705)	(0.41283)	(0.35553)	(0.41337)	(0.41909)
Hospital beds					0.5143**	0.4953*	0.4771*
					(0.23284)	(0.23163)	(0.24438)
Year						-0.0218	
						(0.02214)	
Constant	-3.2997*	-4.1799	-11.0975**	-13.1691**	-15.7708**	27.2422	-16.2792**
	(1.53805)	(3.15823)	(3.97518)	(4.71477)	(5.34447)	(40.90250)	(5.84664)
Observations	126	111	107	96	65	65	65
R2	0.45	0.44	0.69	0.70	0.82	0.83	0.86
Adjusted R2	0.44	0.42	0.68	0.68	0.81	0.81	0.82

Source: CRA analysis on EMA data on clinical trials and WHO and OECD data

Notes: All density variables are per million inhabitants and taken in logarithms, as is the number of clinical trials run. The parameters are estimated using Ordinary Least Squares (OLS) regression. Standard errors reported in brackets. * p<0,1, ** p<0,05, *** p<0,01. Country-clustered standard errors are used. The coefficients for year dummies are not reported in Model 7

The results should not be interpreted as conclusive evidence that a widening of the Bolar scope will have *no effect* on the innovative pharmaceutical industry. If there was no effect, then it is unlikely that both the UK and Ireland would have amended their patent acts to broaden the scope of the Bolar or research exemptions recently. The lack of identification of an effect is consistent with responses from the industry suggesting that the scope of the Bolar is *one* among *many* factors influencing the location of clinical trials. While we have attempted to control for a number of these other factors, as explained above the proxies we have used (based on data availability) may not be exhaustive and may also be imperfect measures of the true underlying factors.

Moreover, a harmonisation of the Bolar with a wide scope across the EEA can also be seen as consistent with the new clinical trial regulation (that will replace Directive 2001/20/EC) that harmonises the carrying out of clinical trials in Europe.[177] According to a report by Deloitte commissioned by Janssen Pharmaceutica[178], the disparity across European Member States on the requirements for the conduct of clinical trials is a factor hampering investment in pharmaceutical R&D in Europe. The report notes that before the new clinical trials regulation, companies had to submit a separate application in each country where a trial was to be run. Applications were usually followed by discussion and amendments as required by the ethics committee of each country. This process was burdensome and introduced additional costs and delays to the development process of innovative products.

Another potential analysis would have been to examine the impact of widening the Bolar exemption in the UK and Ireland on the number of clinical trials run in these countries. However, as not enough time has elapsed since the change in the patent acts of these countries, it is not possible to identify an effect yet.

Illustration of cost savings that could result from widening the scope of the Bolar

The responses to the UK consultation, identified the following areas of cost savings as a result of the change to the legislation: savings from freedom-to-operate studies, validity opinions, opposition or revocation proceedings, arbitration cases, licensing negotiation costs etc. Respondents to the UK consultation provided some ranges of estimates of costs relating to the UK, which were presented in section 4.2.1. Of course, not all of these costs are borne in every case, as for example not all infringing patents are opposed, not all cases of potential infringement lead to arbitration, and trial sponsors do not always licence a compound for trial use, so may not need to incur costs during licencing negotiations.

As an *illustrative* example, we estimate the savings that could result from a wider scope of the Bolar for the countries in our sample that have a narrow Bolar (Belgium, Sweden and the Netherlands), with respect to one cost element, namely FTO studies. We assume that a clinical trial recruiting in one of these three countries that currently has a narrow Bolar scope will need to carry out an FTO study, whereas such studies will not be required for clinical trials carried out in countries with a wide Bolar.[179] We estimate the cost savings by multiplying: i) the average[180] number of controlled clinical trials per year that rely on another medicine as a comparator and that recruited in these three countries, by ii) the lower and upper bound of cost estimates for an FTO study: £90,000 to £135,000 or €110,970 to €166,455 using average 2012 GBP/EUR exchange rate. Table 6 shows the results. Using the lower bound, the cost savings to these three countries that have a

177 The new regulation that will be effective as of May 2016, postulates a centralised application procedure via an EU portal, where the applicant nominates one country as the Reporting Member State for an application. For details see http://ec.europa.eu/health/human-use/clinical-trials/regulation/index_en.htm

178 *Investing in European health R&D, a pathway to sustained innovation and stronger economies,* (2015) a report by Deloitte commissioned by Janssen Pharmaceutica N.V.

179 We base this assumption on the responses to the UK consultation where a R&D based company noted that *as a result of* the narrow Bolar scope in the UK, an additional cost incurred is the cost of running FTO studies. If companies would need to undertake FTO studies anyway (irrespective of the scope of the Bolar) then the savings identified below would not apply.

180 We use the average number of clinical trials over a three year period (2012-2014) to smooth out any variations.

narrow Bolar scope would be almost €23 million per year and using the upper bound, they would amount to €34.2 million per year.

Table 6: illustration of cost savings from FTO studies as a result of widening the scope of the Bolar to apply to any medicine for Belgium, Netherlands and Sweden

		Lower bound	Upper bound
FTO search cost per case	£	90,000	135,000
EUR/GBP		1.23	1.23
FTO search cost per case	€	110,970	166,455
Average* number of comparative clinical trials recruiting in BE, NL or SE per year		205	205
Cost savings in BE, NL, SE from FTO studies	€	22,785,840	34,178,760

Source: Cost of FTO study based on responses to the UK IPO consultation, "The Research and Bolar Exception: Proposals to exempt clinical and field trials using innovative drugs from patent infringement, Government Response, February 2013", number of comparative clinical trials that used another medicine as a comparator based on EMA data. EUR/GBP midpoint average 2012 exchange rate based on www.oanda.com

Notes: *) The average number of clinical trials per year is based on a three year period 2012-2014 to smooth out variations.

The following caveats apply to the illustrative cost savings presented above. Firstly, these estimates only measure the costs associated with one cost element, FTO studies, and therefore tend to underestimate the total cost savings. Secondly, these estimates refer only to the three countries in our sample that have a narrow Bolar scope. To the extent that other European countries than those listed in Table 3 have a narrow scope the cost savings are underestimated. Thirdly, the estimates are based on FTO study costs that apply in the UK and which could be different for the three countries considered. If they are lower on average in other EU Member States, the figures could result in an overestimation of the effect. Last, we assume that all comparator clinical trials undertake FTO studies. This could overestimate the overall cost of FTO studies as it is likely that not all comparative clinical trials that use another medicine as a comparator would carry out such an analysis, as in some cases the comparator may already be known not to be covered by a patent or SPC. Moreover, if FTO studies would be required anyway in some cases, the cost savings above could overstate the impact. To the extent that the latter two effects dominate, the estimates should be considered as upper bounds.

4.2.4. Assessment of wider impact of the proposed measure

An extension of the Bolar to apply to any medicines is likely to positively affect incentives to innovate for the EU-based innovative pharmaceutical sector as it will remove the legal uncertainty associated with running regulatory tests and other trials on medicines that do not follow the abridged marketing authorisation pathway. By reducing the regulatory burden, this measure will increase returns to innovation and therefore increase incentives to innovate for European R&D based pharmaceutical companies in countries that currently have a narrow Bolar scope, such as e.g. Belgium, the Netherlands and Sweden.

The results of our econometric analysis suggest that there is a positive and statistically significant relationship between physician density and the number of clinical trials per population run in a country, though we cannot infer causality or the order of causation

from these results. The UK consultation contains anecdotal evidence that companies have chosen to conduct clinical trials in countries other than the UK as a result of the risk of infringement in the UK.[181] On this basis, broadening the scope of the Bolar can be expected to increase the number of skilled jobs in a country that switches from a narrow to a wide scope of the Bolar. It is not possible for us to estimate exactly by how much the number of skilled jobs will increase. Factors to consider, include the man-hours of skilled personnel utilised in clinical trials as well as their capacity utilisation. For example, if additional trials can already largely be supported by existing doctors and other employees through an increase in their productivity, the impact on skilled jobs will be more limited, but the positive impact on the level of expertise and the economy as a result of an increase in productivity will remain.

Another consideration when examining the effect on the EU as a whole is the extent to which innovators when considering where to conduct clinical trials are more likely to choose another EU country with a wide Bolar scope as opposed to a country outside the EU. Some respondents in the UK consultation mentioned other EU countries with a wider scope (Germany, Italy, Spain) but also the US and China and India as preferable locations due to their more generous Bolar provisions.[182] According to a report published by the EMA, the share of patients recruited from the EU/EEA/EFTA in clinical trials referenced in dossiers in centralised marketing authorisation procedures in Europe, ranged between 28% (in 2008) to 44% (in 2006-2007) over the period 2005-2011.[183] The report showed an increase in the number of patients recruited from emerging countries from 20.3% in 2005 to 37% in 2011.[184] The increased share of emerging countries as recruitment grounds for clinical trials is the result of a number of factors, including the ability to reduce operational costs while recruiting a large number of patients in a timely manner, the lower cost of carrying out trials in these countries, the growth of contract research organisations that specialise in global clinical trials, the harmonisation of guidelines for clinical research.[185] These data suggest that in an environment where non-

---

181 The Research and Bolar Exception: Proposals to exempt clinical and field trials using innovative drugs from patent infringement, Government Response, February 2013, pages 16, 19. Relevant responses, include:

An example where the decision was made to run a trial abroad where an in-force third party patent existed was due to expire before the final product could be marketed: 200-500 patients would have been recruited in the UK if the infringement risk did not exist. This was for a disease which was more prevalent in the UK than other European countries.

Companies developing new products must be given the same level of protection from infringement as the generic industry. This will provide a supportive landscape for innovative clinical research and will bring economic benefits to the UK e.g. preservation of skills and expertise, downstream activities such as manufacturing, and from a public health perspective, UK patient participation in trials. This will allow UK-based companies to be more competitive in an increasingly global industry and will increase the UK's ability to generate increased export sales.

182 UK IPO, (2011) "The research and Bolar exemptions: an informal consultation on patent infringement in pharmaceutical clinical and field trials", pages 7-8.

183 "Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency", EMA, 11 December 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf

184 Africa, Middle East/Asia/Pacific, Australia/New Zealand, CIS, Eastern Europe-non-EU, Central and South America.

185 Fabio A. Thiers, Anthony J. Sinskey and Ernst R. Berndt (2008), *Trends in the globalisation of clinical trials,* Nature Reviews, Vol. 7 January 2008. http://web.mit.edu/biology/sinskey/www/Thiers08.pdf

EU countries are becoming more fertile ground for carrying out clinical trials, there is potentially more need to simplify the regulatory environment and provide freedom to operate to innovative companies in order to retain and enhance the attractiveness of Europe as a location to conduct clinical trials, which will in turn have corresponding beneficial effects on skilled jobs and expertise in Europe.

An additional benefit of widening the Bolar scope to cover any medicine is that it will reduce delays associated with assessing the legal risks when conducting studies and trials in countries with a narrow Bolar scope, including the time required to carry out FTO studies, the potential delays associated with infringement actions, licensing negotiations etc. This will result in more timely access to innovative medicines for patients. This positive impact was acknowledged by respondents to the UK consultation and also by EFPIA in its responses to our questionnaire.[186]

Last, if the measure leads to more clinical trials in countries with currently a narrow Bolar scope, this will benefit the country patient population, as it has been shown that a new medicine adoption is wider in countries where the clinical trial was run, due to information spillovers making physicians more likely to prescribe the new medication.[187]

4.2.5. Effect of introduction of Unitary Patent Protection and Unitary Patent Court

In this section we consider the impact of the introduction of the UPP and UPC on this measure. As discussed above, the UPC Agreement currently references Art. 10 (6) of Directive 2001/83/EC. The effect of the introduction of UPP and the UPC will depend on whether the UPC adopts a narrow or a wide interpretation of the Bolar.

If the UPC adopts a narrow definition of the Bolar scope, then the benefits discussed above on incentives to innovate, number of clinical trials, skilled jobs and expertise could be reversed. Moreover, a narrow interpretation by the UPC would result in additional legal costs for companies currently operating in Member States with a wide Bolar scope.

If the UPC adopts a narrow interpretation of Art. 10 (6) of Directive 2001/83/EC, this could create a divide between national patents and European 'classical' patents that opt out of the UPC on the one hand and European patents with a unitary effect and European 'classical' patents that do not opt out of the UPC, on the other hand. National and European 'classical' patents that opt out of the UPC will be litigated before national courts which, will have a broader interpretation of the Bolar exemption if the assumed harmonisation analysed in the previous section takes place, whereas European patents with unitary effect or those that do not opt out of the UPC will be litigated before the UPC which could have a narrower interpretation of the Bolar exemption. This will work against

---

186 The Research and Bolar Exception: Proposals to exempt clinical and field trials using innovative drugs from patent infringement, Government Response, February 2013, page 3, 7, 12.

"*Responses suggest that the costs to the UK economy of the current legislation include the loss of skills and expertise if a trial is run abroad, and* ***the public health costs of delays in new products entering the market****"*

"Creating a level playing field will reduce barriers to innovation and ***reduce delays in getting treatment to patients****".*

"The delay of a trial and subsequent delay in getting a product to market has associated costs; the exact amount depends on the specifics of the case".

187 For a discussion of the literature studying the information spillover effect see "Economic research into the environment for clinical research and development in the UK", a report prepared for Novartis by Europe Economics, 16 October 2012. http://www.novartis.co.uk/downloads/europe-economics-clinical-trials-report.pdf

the harmonisation of the implementation of the Bolar exemption across Member States and may result in innovators preferring the UPC as a forum as it would be more favourable to the incentives of the patentees.

As an illustration of the additional costs that could arise should the UPC adopt a narrow interpretation of the Bolar exemption, relative to a situation where the Bolar exemption was harmonised across all EU countries to have a wide scope (i.e. the proposed exemption), Table 7 estimates the additional costs from one cost element, namely FTO studies. We assume that if the UPC adopts a narrow definition of the Bolar then companies considering conducting clinical trials using other medicines will be more likely to require FTO studies as the risk of infringement will be higher. This may be the case not only for comparators covered by European patents or unitary patents but also for those covered by national patents in countries that have ratified the UPC agreement. We estimate the costs of the introduction of the UPP and UPC if it adopts a narrow interpretation and if the wording of the current Art. 10(6) becomes national law, by multiplying the upper and lower bounds of costs associated with freedom-to-operate studies (ranging from £90,000 to £135,000 or €110,970 to €166,455 using average 2012 GBP/EUR exchange rate)[188], referenced in the UK consultation, by the average number of comparator clinical trials conducted in the EEA per year over the period 2012-2014. Assuming that should the UPC adopt a narrow interpretation of the Bolar, all comparator trials that recruited in the EEA would require an FTO study, the costs of the introduction of a UPC, relative to Scenario 1 (i.e. broad harmonised Bolar across all Member States), would range between €62.4 million and €93.6 million.

Table 7: illustration of additional costs from FTO studies as a result of introducing UPP and UPC with a narrow interpretation of the Bolar relative to scenario 1 (harmonisation of a wide Bolar across the EU)

		Lower bound	Upper bound
FTO search cost per case	£	90,000	135,000
EUR/GBP		1.23	1.23
FTO search cost per case	€	110,970	166,455
Average* number of comparative clinical trials per year, EEA		562	562
Costs from FTO searches should UPC adopt a narrow interpretation of the Bolar exemption	€	62,402,130	93,603,195

Source: Cost of FTO study based on responses to the UK IPO consultation, "The Research and Bolar Exception: Proposals to exempt clinical and field trials using innovative drugs from patent infringement, Government Response, February 2013", number of comparative clinical trials that used another medicine as a comparator based on EMA data. EUR/GBP midpoint average 2012 exchange rate based on www.oanda.com

Notes: *) The average number of clinical trials per year is based on a three year period 2012-2014 to smooth out variations.

188 Exchange rate based on average mid-point over the period 1 January 2012 to 31 December 2012, as reported by www.oanda.com . We chose 2012 as our base year, as the FTO cost estimates were included in the February 2013 Government response to the IPO consultation.

These estimates are only illustrative and are based on a number of assumptions some of which would overestimate and some would underestimate the true effect. Firstly, only the cost of FTO studies is considered here. Since other costs were also identified in relation to the narrow Bolar scope such as costs related to e.g. opposition proceedings, infringement actions, licensing costs etc., the cost estimates reported above are partial. Secondly, the magnitude of FTO costs per case relate to the UK, but would be different in other EU countries. Thirdly, we assume that an FTO is carried out for each comparative study that uses another medicine as a comparator. This could overestimate the overall cost of FTO studies as it is likely that not all comparative clinical trials that use another medicine as a comparator would carry out such an analysis, as in some cases the comparator may already be known not to be covered by a patent or SPC. Moreover to the extent that FTO studies would need to be carried out anyway, the above estimates could overstate the impact. To the extent that the latter two effects dominate, the estimates should be considered as upper bounds.

If, on the other hand, the harmonisation of the Bolar exemption is implemented via an amendment of Directive 2001/83/EC (as amended in 2004) to explicitly cover any medicine, the UPC's interpretation of the Bolar will be consistent with the harmonisation analysed here. This is because, as explained above, the UPC Agreement cross-references the Directive. If the Directive explicitly covers all medicines and marketing authorisations in any country, then both national courts and the UPC will have a consistent treatment of patent infringement cases relating to the Bolar exemption. Therefore all the benefits and savings presented in the previous subsection would apply.

4.3. Scenario 2: Extending the scope of the Bolar exemption to obtain marketing approvals anywhere in the world

4.3.1. Issue

In countries with a narrow Bolar scope it is not clear whether the use of patent protected compounds to obtain marketing authorisations in a country outside the EEA is covered by the exemption, whereas countries with a wider Bolar scope explicitly cover the use of patent protected compounds for medicines seeking marketing approvals in any country. As discussed in section 2, increasingly clinical trials are becoming more globalised, therefore there is potentially demand for clinical trials conducted by originators and biosimilars producers and bioequivalence tests conducted by generics companies to be run in Europe with a view to obtain marketing authorisation in a country outside Europe.

With regards to innovative medicines, increasingly clinical trials are being run globally. As mentioned above, data show that a significant number of clinical trials are conducted outside the jurisdiction where marketing approval is sought[189], though some countries, e.g. Japan[190] require in certain cases local testing.

189 *Supra* footnote 67.

190 Junichi Nichino (Novartis), Overcoming regulatory hurdles in running clinical trials in Japan, 2nd Global Clinical Trials Outsourcing Summit, Seoul, May 20, 2013 http://www.globalengage.co.uk/gctos/6Nishino.pdf

With regards to generics, some countries, such as Brazil, explicitly require the reference product to have marketing authorisation and be sold in Brazil.[191] Other countries, such as Australia, Switzerland and Canada accept bioequivalence tests based on reference products approved and marketed outside their country, provided that they have been conducted in jurisdictions with similar strict assessment criteria, e.g. Europe, US, Australia, Japan or Canada.

With regards to biosimilars, some countries such as China and Japan require the reference product to have a marketing authorisation in their country.[192] Other countries such as the EU[193], US[194], Canada[195], Brazil[196], Australia[197] and others also accept results based on reference products that are approved in other jurisdictions provided that they conform to strict criteria and the onus is on the applicant to demonstrate that the chosen reference product is sufficiently similar to the one authorised in their jurisdiction.[198]

Within this environment, a measure that will extend the scope of the Bolar to cover clinical trials and tests required by innovative medicines as well as generics and biosimilars to obtain marketing authorisation in any country, is expected to make the EEA a more attractive location for carrying such tests and trials and will benefit the EU-based innovative, generic and biosimilar industry, e.g. by avoiding the costs of duplicating tests and trials. This view was also expressed by innovative and generic/biosimilar respondents to the UK and Irish consultations on the subject. In particular, the majority of respondents to the UK consultation were against an option that only covered marketing authorisations in the EEA or the EU, on the basis that such a geographical restriction would require the sponsor to decide on the geographical intentions for a product at a very early stage.[199] Other comments included "there is no reason not to encourage all trials regardless of their intended final market, e.g. drugs and vaccines for use in developing

---

191 Davit Barbara, Braddy April C., Conner Dale P., Yu Lawrence X., (2013) *International Guidelines for Bioequivalence of Systemically Available Orally Administered Generic Drug Products: A Survey of Similarities and Differences,* American Association of Pharmaceutical Scientists, 2013 Oct. 15(4): 974-990. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3787230/#CR29

192 Biosimilar development and regulation in Japan, Generics and Biosimilars Initiative Journal (GaBI Journal). 2013;2(4):207-8. http://gabi-journal.net/biosimilar-development-and-regulation-in-japan.html . Biosimilars are regulated differently in China, by Katherine Wang for Pharma DJ, a pharmaceutical publication covering the Chinese market.

https://www.ropesgray.com/~/media/Files/articles/2015/May/20150529-Biosimilars-Regulations-Wang.ashx.

193 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf

194 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm

195 http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/seb-pbu/seb-pbu_2010-eng.php

196 Dr. Thomas Kirchlechner (Sandoz), "Biosimilar regulatory overview", Anvisa biosimilars workshop, Brasilia, 25 June 2013. http://portal.anvisa.gov.br/wps/wcm/connect/d9517880410c414b93dd939cca79f4cf/Panorama+mundial+do+desenvolvimento+de+produtos+biotecnol%C3%B3gicos+-+Thomas+Kichlechner.pdf?MOD=AJPERES

197 https://www.tga.gov.au/publication/evaluation-biosimilars

198 "Global biosimilars guideline development – EGA's perspective", Gabi online Journal, posted 28-09-2009. http://www.gabionline.net/Guidelines/Global-biosimilars-guideline-development-EGA-s-perspective

199 UK IPO, "The Research and Bolar exception: proposals to exempt clinical and field trials using innovative drugs from patent infringement", Government Response, Feb 2013, page 9.

countries" and "the manufacture of compounds in the UK for use in trials anywhere should be included. The broader exception will facilitate the speed to market of innovative drugs, and provide clarity where acts are done for more than one purpose, e.g. data is generated for regulatory approval in one country and will support health technology assessment in another country".[200] A concern expressed by the EGA, was whether work done in the UK to obtain marketing authorisation outside of the EU was an act of infringement, suggesting that an extension of the Bolar scope to cover marketing authorisations in any country would be beneficial for the generic industry too.[201]

Some respondents to the Irish consultation noted that the narrow scope of the Bolar in Ireland resulted in a competitive disadvantage for Ireland in this area. There is no elaboration on these responses in the Impact Assessment, therefore it is not clear whether this view related to the geographical scope of the exemption or the product scope or both.[202]

As discussed above, EGA's response to our questionnaire was that the proposed measure would benefit the pharmaceutical industry as a whole by simplifying strategic planning, as companies would no longer need to decide where to launch first at such an early stage.

4.3.2. Testing hypotheses

We test the following two hypotheses:

1. The proposal is likely to make EU countries with a previously narrow scope of the Bolar more attractive locations to conduct clinical trials. It is also likely to reduce costs incurred by innovative companies by avoiding duplication of clinical trials in the EU as well as in 3rd countries (that allow results from clinical trials conducted on reference products not authorised in their jurisdiction).
2. The proposal is likely to make EU countries with a previously narrow scope of the Bolar, more attractive locations to conduct bioequivalence tests for generics and for clinical trials to prove biosimilarity for biosimilars, benefiting EU based CRO companies. It would also result in savings for EU-based generics and biosimilars producers as they would not be required to duplicate such tests and trials to obtain authorisation in the EU and outside the EU. This benefit would apply for those jurisdictions that do not require the reference product to be locally authorised and sold.

4.3.3. Assessment of potential effect on the innovative pharmaceutical industry in Europe

One way to test the first hypothesis is to examine whether more clinical trials are run in countries with a narrower Bolar scope compared to countries with a wider Bolar scope, using EMA data on clinical trials run by country. It is not clear a priori whether the EMA data allow a separate identification of the potential effects of extending the geographical

200 *Ibid.,* page 11.

201 UK IPO, (2011) "The research and Bolar exemptions: an informal consultation on patent infringement in pharmaceutical clinical and field trials", page 7.

202 Department of Jobs, Enterprise and Innovation, "Regulatory Impact Analysis: Review of the Research Exemption Provision", Annex 2. https://www.djei.ie/en/Legislation/Legislation-Files/Regulatory-Impact-Analysis-Review-of-the-Research-Exemption-Provision-Section-42g-of-the-Patents-Act-1992.pdf

scope of the Bolar, as countries that have a wide scope of the Bolar in terms of product coverage, also have a wide scope in terms of geographic coverage (see Table 3). Furthermore, the results in section 4.2 above suggest that it is difficult to identify an effect of extending the scope of the Bolar on the number of clinical trials carried out, due to potentially omitted variables as well as the possibility that the control variables we used do not accurately measure the true underlying factors. The same problems are likely to apply here too.

Secondly, we discuss potential cost savings from widening the scope of the Bolar due to reduction in duplication of clinical trials studies, reduction in delays due to being able to recruit in more countries and other savings.

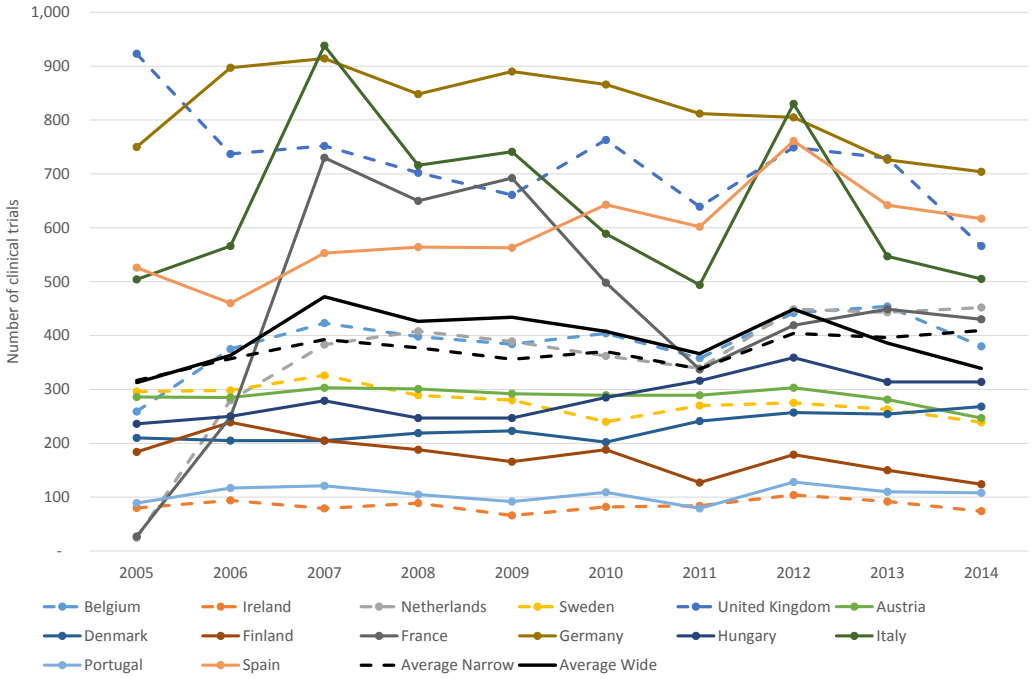
Effect of widening the scope of the Bolar to cover marketing authorisations in any country on the number of clinical trials run in a country

Figure 6 below plots the number of clinical trials by country of recruitment and by year of first registration of the clinical trial. For this analysis we do not limit the sample to comparative clinical trials but we include all clinical trials. Countries with a narrow Bolar scope (Belgium, Ireland, the Netherlands, Sweden and the UK) are shown with a dashed line.[203] The figure is similar to Figure 4 above. There is variation over time and across countries in the number of clinical trials run. Countries with the largest number of clinical trials over this period are: Germany (brown line), Italy (dark green line), UK (blue dashed line), Spain (peach line) and France (but only in the period 2007-2009). The black lines show the average number of clinical trials for countries with a wide Bolar (solid line) and countries with a narrow Bolar (dashed line). As before, we observe that on average the countries with a wide Bolar scope have more clinical trials compared to countries with a narrow Bolar scope.

Figure 7 below expresses the number of clinical trials by 1 million inhabitants. Controlling for the size of the population, we observe that it is no longer the case that fewer clinical trials are run in countries with a narrow Bolar scope compared to countries with a wider scope. In fact, we observe that on average clinical trials per 1 million inhabitants are *lower* in countries with a wider Bolar scope (black solid line) compared to countries with a narrower Bolar scope (black dashed line).

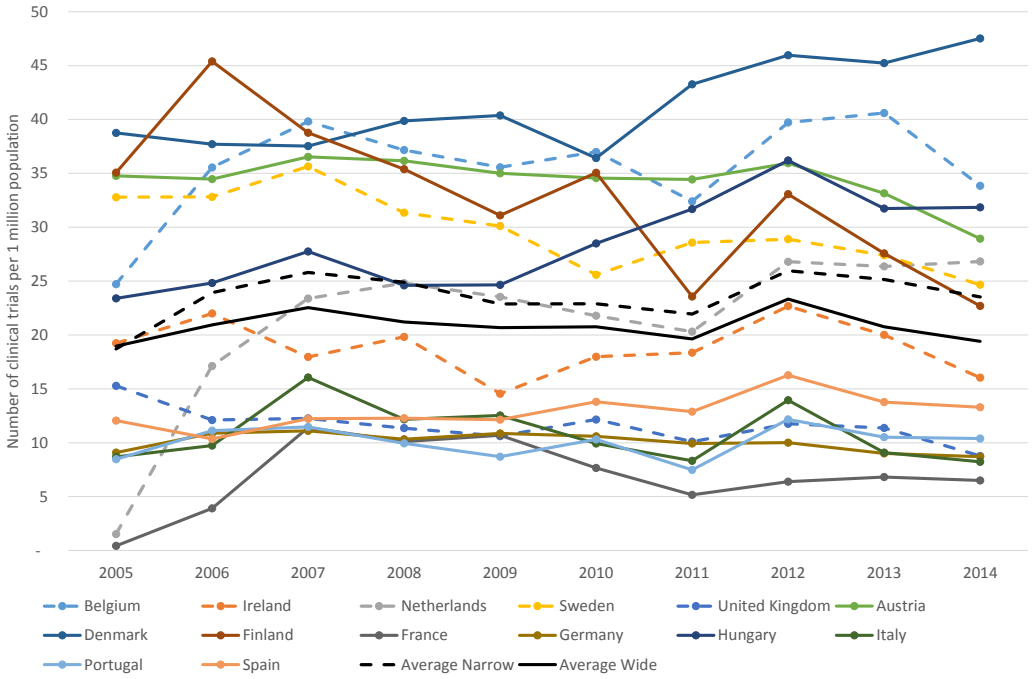
203 Data for 2004 are not plotted as we have partial data for that year.

Figure 6: Number of clinical trials by European country, 2005-2014



Source: CRA analysis on EMA data

Figure 7: Number of clinical trials per 1 million inhabitants by European country, 2005-2014



Source: CRA analysis on EMA data

In Appendix B we present the results of the regression analysis of the number of clinical trials on the same control variables as used in section 4.2 and a dummy for the Bolar. In our preferred specification (Model 5), the fact that a country has a wide Bolar scope is statistically insignificant in all specifications. Population and licensed physicians density are significant at the 5% level and have a positive coefficient, while hospital beds density

and R&D researchers' density coefficients are not significant. The strongest effect is associated with licensed physicians: a 10% increase of the number of licensed physicians is associated with a 9% increase in the number of clinical trials run in a country.

As discussed above, these results should not be interpreted as conclusive evidence that a widening of the Bolar scope will have *no effect* on the innovative or generic and biosimilar pharmaceutical industry. Instead, they are consistent with the view expressed by industry responses that the Bolar is *one* among *a number* of factors affecting the choice of where to run clinical trials. Failure to identify an effect may also be because the proxies we used (based on data availability) were not exhaustive and that other factors that are difficult to measure could affect the choice of clinical trials, such as e.g. financial incentives provided for research, reputation of specialists and doctors etc. Moreover it could be that the control variables we used were imperfect measures of the true underlying factors.

Cost savings that could result from widening the scope of the Bolar to cover marketing authorisations in any country

The measure is expected to reduce costs to innovative firms of running clinical trials for a number of reasons:

- By increasing the number of countries from which patients can be recruited to support marketing authorisations in any country, it is likely to reduce clinical trial delays associated with patient recruitment. For example, figures referenced in a cost-benefit study of the Electronic Health Records for Clinical Research European Project, suggest that almost half of trial delays are caused by participant recruitment problems.[204] By increasing the number of EU Member States where trials can be conducted to obtain marketing authorisation outside the EEA, this measure contributes to a reduction in costs, as the more countries are available for recruitment purposes the higher the probability of recruiting the targeted number of patients and the lower the chances of clinical trial delays. For a blockbuster drug these delays could amount to $2.7 million (or €2.4 million using 2015 average USD/EUR exchange rate) per day in lost sales worldwide.[205]
- It is likely to reduce the need to duplicate clinical trials to support marketing authorisations in non-EU countries. The costs of carrying out clinical trials are significant. A 2012 study by Europe Economics prepared on behalf of Novartis provides estimates of per patient costs of clinical trials for 5 EU countries (Germany, Italy, Poland, Spain and the UK) ranging from €5,679 for Poland to €9,758 for the UK.[206] The average number of patients per country of recruitment for a Phase III clinical trial is 114 based on EMA clinical trial data.[207] Table 8

204 http://www.ehr4cr.eu/files/flyers/EHR4CR%20CBA%20POSTER_4Nov2014.pdf

205 In line with industry norm, we define a blockbuster drug as one that generates sales of at least $1 billion annually, which corresponds to $2.7 million on a daily basis.

206 Economic research into the environment for clinical research and development in the UK, a report prepared for Novartis by Europe Economics, 16 October 2012. http://www.novartis.co.uk/downloads/europe-economics-clinical-trials-report.pdf

207 We estimated the average number of participants by EU country for Phase III clinical trials, by dividing the target size per clinical trial by the number of countries of recruitment and then taking an average across the EU28 countries.

indicates the cost savings from not having to run a clinical trial in 1, 2, 3 and 4 additional countries as a result of this measure. The cost savings of not having to run a clinical trial in one additional country as a result of this measure could be €647,406 to €1.1 million, depending on the per patient cost of the clinical trial. The cost savings of not having to run a clinical trial in four additional countries as a result of this measure could be €2.6 million to €4.4 million, depending on the per patient cost of the clinical trial. These savings are indicative and are for a single clinical trial only and are based on EU per patient costs of clinical trials. These cost savings make the simplifying assumption that the cost of clinical trials in non-EU countries is similar to the cost in the EU.

Table 8: Indicative cost savings from not having to run clinical trials in additional countries as a result of widening the scope of the Bolar, EUR

Clinical trial costs per patient	€5,679	€9,758
Average number of patients per Phase III trial	114	114
Cost of running trial in 1 additional country	€647,406	€1,112,412
Cost of running trial in 2 additional countries	€1,294,812	€2,224,824
Cost of running trial in 3 additional countries	€1,942,218	€3,337,236
Cost of running trial in 4 additional countries	€2,589,624	€4,449,648

Source: clinical trial cost per patient (Novartis, low figure refers to Poland, high figure refers to the UK); average number of clinical trials per country of recruitment (EMA clinical trial data)

- It will reduce the need to make early decisions about where to launch first. While we cannot monetise the savings associated with this, it is likely to benefit innovative companies, as by delaying the decision of where to launch first, the companies can benefit from additional information that could become available that affects the perceived profitability of launching in that market. In fact, the option value of waiting has been analysed in a number of economic papers that have found a value of waiting to invest when there is uncertainty regarding the benefits and costs of an investment and when an investment is irreversible.[208]

Effect on the generic and biosimilar industry

With regards to the second hypothesis, namely the effect of extending the Bolar to cover marketing authorisations anywhere in the world, the EMA data on clinical trials only contain a very small number of bioequivalence tests and clinical trials on biosimilarity.[209] It is therefore not possible to draw robust conclusions from these data.

As in the case of innovative pharmaceuticals, this proposal is likely to result in cost savings for both the generic and biosimilar industry and benefit EU based CRO companies for the following reasons:

208 The seminal paper on this was by Robert McDonald, Daniel Siegel, *The value of waiting to invest*, The Quarterly Journal of Economics (1986) 101 (4): 707-727

209 We searched for the terms “generic”, “bioequivalence” or “biosimilar” in the EMA clinical trial dataset and in each case fewer than 100 observations (over a total of more approximately 63 thousand) were found. In this case one observation was a clinical trial/country of recruitment combination.

- It will reduce the need to run additional bioequivalence tests to obtain marketing authorisation in other countries. As there are already a number of European countries with a wide Bolar scope, EU based generic companies wishing to use results from studies to support marketing authorisations outside the EU are likely to choose these countries to run their bioequivalence tests. The savings from extending the number of EU countries where bioequivalence tests may be carried out to support marketing authorisations outside the EU, may therefore not be significant. A study by Best Practices LLP based on survey of 18 generic companies found that less than 25% of respondents relied on CROs in less regulated markets for their bioequivalence studies. However, the majority of respondents expect to increase or not change their use of CROs in less regulated regions, such as India, China, Russia and Eastern Europe, while another study based on a survey of 26 CROs suggest that 57% conduct bioequivalence studies in India, 22% in Eastern Europe, 13% in Russia and the same in other less regulated markets and 4% in China.[210] These figures indicate that at least for bioequivalence tests where the enrolment and design criteria are not as strict or complex as they are for clinical trials, there could already be more choice of locations to conduct such tests.
- It will reduce the legal risk and need to obtain different legal advice by EU country on what acts are covered by the Bolar in each Member State. We have no estimates of these costs that would enable us to quantify this saving, but it has been identified as a cost under the current legislation by the EGA. These cost savings would apply to innovative as well as generics and biosimilar producers.
- The measure could result in cost savings for biosimilars. This is because biosimilars need to conduct trials to prove biosimilarity which are more costly than running bioequivalence tests on healthy volunteers. Although they are run on fewer individuals (EMA guidelines suggest approximately 100 patients), clinical trials for biosimilars are costly, for two main reasons. Firstly, the cost of obtaining the reference product is significant. This cost is incurred both at the pre-clinical phase where biosimilar producers need samples from different batches of the reference product and at the clinical trial phase. At the phase III clinical trial phase required volumes could range between 2,000 to 10,000 vials or syringes over a two to four year period. By way of example, a 150 mg vial of Herceptin in the UK costs £407.4 according to NICE. A clinical trial for a biosimilar of Herceptin could therefore cost between £814,800 (2,000 times £407.4) and £4.07 million (10,000 times £407.4 million), only considering the costs of the reference medicine. As expiration dates are short and trial recruitment varies, care should be taken to organise the purchasing to ensure that enough product is available so as not to delay the trial but also to ensure that the product that has been acquired will be used in time.[211] Secondly, as with clinical trials for innovative products,

210 Best Practices LLC describes itself as a research, consulting and publishing firm that provides best practive benchmarking in the field of pharmaceutical, biotech, medical device, healthcare technology and other innovative industries. http://www.best-in-class.com/ The study referenced is entitled “Pharma Bioequivalence Strategies: performance metrics, processes and trends”.

211 Michael Cohen, Sourcing innovator products in the age of biosimilar research, posted 01 June 2015 on GaBi online. http://www.gabionline.net/Sponsored-Articles/Sourcing-innovator-products-in-the-age-of-biosimilar-research

patient recruitment can be difficult as patients may be reluctant to participate in a study knowing that only some of them will receive the reference medicine and some will receive the biosimilar that does not have yet proven efficacy.[212] For these reasons, the costs of having to duplicate clinical trials is likely to be significant for biosimilars. Therefore a measure that enables the results of biosimilar clinical trials to be used for marketing authorisations in any country are expected to benefit European biosimilar producers. The availability of more countries from which to be able to recruit patients is an additional benefit, particularly in light of the difficulty of recruiting patients for biosimilar clinical research cited above.

4.3.4. Assessment of wider impact of the proposed measure

An extension of the Bolar to cover tests and trials for purposes of obtaining marketing authorisation in any country is expected to positively affect incentives to innovate in the EU by increasing the attractiveness of EU Member States as a location to run clinical trials for originators and biosimilars.

The survey by Best Practices LLP mentioned above suggests that the 18 generic companies surveyed rely on CROs in less regulated markets (mainly India, but also Eastern Europe, Russia and others) for 25% of their bioequivalence tests, and the majority expect the number of bioequivalence studies conducted in these regions to increase or remain the same in the future. The proposed measure is likely to increase the attractiveness of Europe as a location to conduct these studies, therefore benefiting CROs located in European countries with a narrow Bolar scope, which currently may not be preferred as using the results of trials and bioequivalence tests for marketing authorisations outside Europe may be found to be infringing the patent(s) of the reference medicine.

As discussed above, our econometric analysis also indicates a positive and statistically significant relationship between the number of clinical trials run in a country and the number of physicians per population, though we cannot infer causation or the order of causation from these results. It can be expected though that an increase in the number of clinical trials for innovative medicines or biosimilars in Europe will result in an increase in skilled jobs in this sector. The magnitude of the effect will depend on whether the additional trials and tests can be supported by existing skilled workers through an increase in their productivity or whether additional skilled jobs would be required. In either case the effect is likely to be beneficial for the European economy.

The proposed measure is also likely to benefit the patient population by reducing delays in clinical trials for originators and biosimilars due to patient recruitment problems. Moreover, as discussed above, running a clinical trial in a specific country benefits the patient population in that country as it makes physicians that worked on the study more likely to prescribe and patients more likely to accept the new medicine.[213]

---

212 Erwin A. Blackstone and P. Fuhr Joseph, (2013) *The economics of biosimilars,* American Health and Drug Benefits 2013 Sep-Oct; 6(8). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031732/

213 A summary of the literature on the information spillover effect is available in "Economic research into the environment for clinical research and development in the UK", a report prepared for Novartis by Europe Economics, 16 October 2012. http://www.novartis.co.uk/downloads/europe-economics-clinical-trials-report.pdf

4.3.5. Effect of Unitary Patent Protection and Unitary Patent Court

In this section we consider the impact of the introduction of the UPP and UPC on this measure. As discussed above, the UPC Agreement currently references Art. 10 (6) of Directive 2001/83/EC. If the UPC adopts a narrow definition of the Bolar scope, then the benefits and cost savings to the innovative, generic and biosimilar industry could be reversed. As explained above, a narrow interpretation of the Bolar by the UPC and the adoption of the current wording of Art. 10 (6) of the Directive as national law by the countries that have ratified the UPC agreement will work against the harmonisation of the implementation of the Bolar exemption across Member States.

Innovative companies wishing to use results from clinical trials to support marketing authorisations outside Europe, would need to incur additional legal costs, as before deciding where to run clinical trials they would need know whether the comparator medicine is covered by a patent and if so whether in case of arbitration it would be decided by the UPC or national court. In case of a unitary patent or European patent that had not been opted out, undertaking clinical trials or bioequivalence tests in the EEA to obtain marketing authorisation outside the EEA could be found to infringe the patent as they are not explicitly covered by the current wording of the Bolar.

As we do not know how many clinical trials are conducted with a view to gaining marketing approvals outside the EEA we cannot estimate additional legal costs that would arise should the UPC adopt a narrow interpretation of the Bolar. However the costs for innovative companies are likely not to be additional to those identified in section 4.2.5 as e.g. a single FTO study would be needed for each case irrespective of whether a marketing authorisation within the EEA only or also outside the EEA was sought.

Biosimilar companies wishing to use results of clinical trials for marketing authorisations outside Europe as well as generic companies wishing to use the results of bioequivalence tests for the same purposes would however potentially incur additional legal costs to determine whether the reference medicine is covered by a unitary, European or national patent. As we do not know how many bioequivalence tests or clinical trials by biosimilars are carried out in the EEA with a view to gaining marketing authorisations outside the EEA, we cannot quantify the additional cost for generics and biosimilars.

Furthermore, a narrow interpretation by the UPC could result in the need to duplicate results of clinical trials for innovative medicines and biosimilars to support marketing authorisations outside Europe, resulting in higher costs of development. As mentioned above, the average per patient cost of a clinical trial for an innovative product was estimated to be in the range of €5,679 for Poland to €9,758 for the UK.[214] Assuming similar costs outside Europe and assuming that a phase III clinical trial would need to be carried out on an additional 500[215] patients for an innovative product as a result of this measure, it would result in additional costs of €2.8 million to €4.9 million for one product only. In the case of biosimilars, as mentioned above, the costs relating to the purchase of the reference product only for purposes of the clinical trial could be several million per case.

---

214 Economic research into the environment for clinical research and development in the UK, a report prepared for Novartis by Europe Economics, 16 October 2012. http://www.novartis.co.uk/downloads/europe-economics-clinical-trials-report.pdf

215 As explained in section 2.1.2 a Phase III trial is conducted on several hundred to several thousand patients.

For EU-based generics, such a change is likely to result in Europe becoming a less attractive location to conduct bioequivalence tests and more bioequivalence tests being conducted outside the EEA through e.g. outsourcing to CROs. As discussed above, based on a survey of 18 generic companies a quarter of their bioequivalence studies is outsourced to CROs is less regulated markets. This share would be expected to increase for companies wishing to use the results of such tests to support marketing authorisations outside the EEA. This could negatively affect generic companies that wish to retain some steps of the bioequivalence process internal to control quality. Such a measure would also negatively impact the EU-based CRO industry as they would not be covered for carrying out bioequivalence tests for supporting marketing authorisations outside the EEA.

If the harmonisation of the Bolar exemption is implemented via an amendment of Directive 2001/83/EC (as amended in 2004) to explicitly cover marketing authorisations in any country, the interpretation by the UPC of the Bolar will be consistent with the harmonisation discussed above. This is because, as explained above, the UPC Agreement cross-references the Directive. If the Directive explicitly covers all medicines and marketing authorisations in any country, then both national courts and the UPC will have a consistent treatment of patent infringement cases relating to the Bolar exemption. Therefore all the benefits discussed in the previous subsection would apply.

4.4. Scenario 3: Extending the scope of the Bolar exemption to allow the supply of APIs within the EU

4.4.1. Issue

The current wording of Article 10(6) of Directive 2001/83/EC as amended and its implementation in individual Member States results in legal uncertainty for European API suppliers wishing to supply APIs to generic firms conducting tests and trials necessary to obtain marketing authorisations. In particular it is not clear whether the Bolar extends to the manufacture and sale by third party API suppliers of protected APIs to European generic producers for purposes of conducting the necessary tests and trials to obtain marketing authorisation. The recent Astellas v Polpharma case discussed in section 3.1.3 is evidence of this legal uncertainty.

This negatively affects both European generic suppliers and European API manufacturers. It negatively affects the European API manufacturers as it precludes the supply of protected APIs for Bolar purposes in those countries where the compound is protected. As explained by the EGA, there are switching costs of changing API supplier from the testing phase to the advanced production phase, as changing supplier can result in additional regulatory approvals and potential delays. Therefore, if generics producers are forced to consider API suppliers from unprotected markets (outside Europe) to supply them with the APIs needed during the development phase, given the switching costs involved, they will likely remain with the same suppliers at the commercial manufacturing phase. European API suppliers will therefore be unable to compete for this business, resulting in lower sales and potentially a loss of jobs in Europe.[216]

216 Extending the Bolar to allow the supply of APIs within Europe during the development phase, absent a stockpiling exemption, would still not cover the supply of APIs in large quantities required for preparing for 'day 1' launch.

The legal uncertainty regarding third party API supply also negatively affects European generics producers as it reduces supply options available to them. Most generic producers are unable to produce all the APIs they require in house. According to EGA, large generic companies supply products based on 300 different APIs. [217] It is therefore impossible even for larger generic producers to produce in-house all their API requirements. Third party supply is also important for smaller generic producers, many of whom do not have in-house API production capabilities.

4.4.2. Background on the global and European API industry

According to the 2015 CPA report, the global generic API industry for supply to the merchant market amounted to $25 billion in 2014 (€18.8 billion). Table 9 shows the breakdown by geographic area/country. As can be seen from the table, Asia/Pacific and in particular China and India account for 65% of world production, followed by Western Europe (mainly Spain and Italy) with 21%, Africa and the Middle East with 4% and Eastern Europe, North America (mainly US), Latin America with 3% each.

217 Prof. Dr. Dres h.c. Joseph Strauss, 'Legal opinion on the The Interpretation of Art. 10 Para. 6 of the Directive 2001/83/EC of the European Parliament and of the Council of November 6, 2001, on the Community Code Relating to Medicinal Products for Human Use (OJ, EU No. L311/67 of 28.11.2001) as Amended by the Council Directive 2004/27/EC of the European Parliament and the Council of March 31, 2004 (OJ, EU No. L136/34 of 30.4.2004)", 31 March 2014, para 7.2.2-7.2.3.

Table 9: Production of generic APIs for the merchant market by geographic region/major countries, 2014

	USD million	EUR million[3]	Share
North America [1]	**770**	**580**	**3%**
Latin America	**760**	**573**	**3%**
Europe	**6,015**	**4,531**	**24%**
- Italy	3,500	2,637	14%
- Spain	1,180	889	5%
- Poland	350	264	1%
- Hungary	320	241	1%
- other countries[2]	665	501	3%
CIS	**130**	**98**	**1%**
Asia/Pacific	**16,365**	**12,328**	**65%**
- China	9,260	6,976	37%
- India	6,620	4,987	26%
- other countries	485	365	2%
Africa & Middle East	**960**	**723**	**4%**
Total	**25,000**	**18,833**	**100%**

Source: CPA, Competition in the world APIs market, 2015 Edition

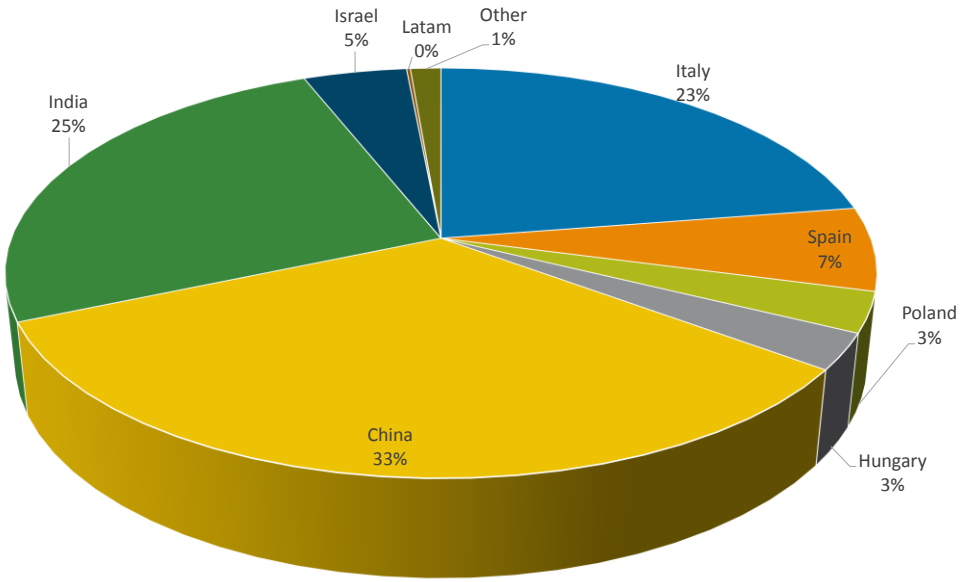
Notes: 1) Mostly US, 2) Mostly Portugal, Slovakia and the Czech Republic, 3) Converted to EUR using the average USD/EUR exchange rate for the year 2014 (www.oanda.com).

Focusing on the European API industry, as can be seen from Table 9 it is significant in terms of revenue generated, amounting to approximately $6 billion (€4.5 billion) in 2014, of which approximately 70% was exported outside Europe. Within Europe, the largest generic API producing countries are Italy and Spain (accounting for 78% of European production value), followed by Poland and Hungary (each accounting for about 5-6% of European production). Smaller generic API producing countries include the Czech Republic, Slovakia, Slovenia, Croatia and Romania.

The majority of Italy's and Spain's exports are destined to heavily regulated markets outside the EEA (US, Japan). These countries have experienced a high growth in the sale of more complex APIs used in oncology and central nervous system (CNS).

Figure 8 below presents the share of sales of generic APIs to Europe accounted for by each API producing country. China accounts for 33%, followed by India (25%), Italy (23%), Spain (7%), Israel (5%) and Poland and Hungary with 3% each. API supplies from a European country accounted for 35% of generic API sales in Europe.

Figure 8: Penetration in generic API sales, merchant market, Europe



Source: CPA

In the US, there are only a few generic API manufacturers, which means that about 84% of generic API requirements are imported.[218] Italian API suppliers account for 32.8% of generic API merchant sales in the US, followed by India (22.2%), US (15%), Spain and China with 11.7% each. The situation is similar in Canada, where again the number of domestic generic API suppliers is limited.[219]

The Chinese API industry is highly fragmented with approximately 1,300-1,500 registered API manufacturing companies in the country. Of these, CPA's research suggests that approximately only 55 have experience in supplying regulated markets (US, Canada, Japan, Europe)[220] and the innovation rate in the industry is relatively low (compared to Western API manufacturers but also compared to Indian API producers).

The Indian API industry comprises approximately 620 API manufacturers. According to the CPA, the role of Indian API suppliers has changed over time as they have moved up the supply chain from supplying only intermediate products to supplying finished dosage forms to pharmaceutical companies. Compared to the Chinese API suppliers, Indian API suppliers have a consolidated know-how in chemical synthesis and engineering and boast a large number of skilled scientists with Western education. CPA estimates that

218 The main characteristics of the US API industry is a focus on innovation, advanced know how in the production of highly potent and cytotoxic APIs, innovative manufacturing technologies, supply of equipment, process control systems, data management products and laboratory scale up to commercial production. Additionally there are many innovative companies that produce their API needs in house (not included in the figures presented in Table 9).

219 The CPA report does not provide details on production and sales of generic APIs in Canada.

220 According to a 2014 article, as of late 2013 438 sites in China were supplying APIs to Europe and 496 in India. *Evolution of a dynamic healthcare market*, Emily Kimball, Pharmaceutical Research Analyst, Thomson Reuters http://www.chemanager-online.com/en/topics/economy-business/evolution-dynamic-healthcare-market

there are approximately 70 Indian API companies with experience in supplying regulated markets.

4.4.3. Assessment of potential effect on the European API manufacturing industry

Testing hypothesis

An extension of the scope of the Bolar exemption to cover the supply of APIs within Europe for Bolar purposes could result in a higher share of APIs used by European generics producers to be sourced from European API suppliers rather than imports. The hypothesis is based on the following:

- As discussed above, there is uncertainty about the legality of offering, manufacturing and supplying patented APIs for Bolar purposes within Europe. This suggests that other things equal (cost, quality, API physical attributes etc), if European API supply for development purposes was explicitly covered by the Bolar exemption, this could result in a higher share of APIs supplied to European generics manufacturers for development purposes from Europe as opposed to imports.
- According to the EGA once a generic producer chooses API suppliers[221], it is unusual to switch when the commercial production starts. This is because API from a different supplier could have a different stability profile, which could lead to the need for new stability batches, new analytical studies on impurities and so on. Moreover, medicine agencies request documentation for any change in the manufacturing process (including change of API supplier), which could make the process of changing expensive. EGA estimates that for more complex APIs, the cost of switching API suppliers could reach €4 million. This suggests that once an API supplier is chosen at the development and pilot batch stage it is unlikely to be changed.

Moreover, should an SPC export waiver be implemented (see scenarios 4 and 5), the beneficial effect of an extension of the Bolar on the EU based API industry would be augmented. The additional EU based generic export sales that would result from an SPC export waiver, would require APIs as inputs. An extension of the Bolar to cover third party API supply within Europe would result in a higher share of the third party API requirements to be sourced from EU based API producers as opposed to imports.

Evidence on API sourcing of first generic entrants following protection expiry

To help evaluate whether generics producers sourcing their APIs outside Europe are more likely to be the first to enter following protection expiry in Europe, we used data obtained from the EMA and national medicine agencies on the manufacturing location of APIs and finished products, for a sample of first generic entrants following protection expiry.

Table 10 presents the location of API manufacturing for first generic entrants distinguishing between generics manufactured in Europe versus generics manufactured

221 According to the EGA response some companies choose a two suppliers to ensure supply availability.

outside Europe.[222] The information received from the EMA and national Medicine Agencies does not distinguish between in-house versus third party API supply. The first column presents the country of API manufacture, the second column presents the number of observations (country of sale/corporation/product) that source their APIs from that particular country. As mentioned before, for a number of reasons (e.g. to ensure reliability of supply) a generic company will have more than one (usually) two API suppliers. This is observed in the data where for the majority of products, more than one API manufacturing countries are listed for a particular product. This means that summing column 2 across the rows results in a higher number of observations than the total observations in our sample and summing column 3 across the rows results in a share greater than 100%.[223]

As Table 10 indicates, for the vast majority of first entrants following protection expiry during our sample period, the API was sourced from India and China. Focusing on generics produced in Europe, the vast majority (73%) sourced APIs from India, followed by China (36%). API sourcing from European countries accounted for 43% of observations[224] for which the final dosage form was also produced in a European country. Among European API manufacturing countries, Slovenia was the most common (19% of observations), followed by Spain (10%) and Italy (7%). It should be noted that the majority of observations where the API country is Slovenia and Israel relate to in-house API supply.[225] Moreover, as explained in section 3.1.1, in Spain pharmaceutical products were not patentable until 1992, only processes were patentable. This may have benefited the local API industry by giving local producers the freedom to produce compounds that were protected in other European countries if the process used did not infringe the national patent. Additionally, in Spain, Portugal and Greece, SPC regulation became effective in 1998 (later compared to other Western European countries). Moreover, countries that joined Europe in 2004 only then introduced SPC protection, with a retroactive effect that in cases was limited to products having received a marketing authorisation close to the accession period. This could also explain the higher incidence of APIs produced in counties such as e.g. Poland and Malta.

Of the observations with a European API manufacturing country, the majority also had a non-European country as an alternative supplier. Only 14% of observations sourced APIs exclusively from Europe.

For generics manufactured outside Europe, the majority sourced their API requirements from India (79%), followed by Israel (26%) and China (16%). API sourced from a European country (among others) accounted for 11% of observations of generics manufactured outside Europe.

---

222 Generics manufactured in Europe include those products that entered first across Europe and for which the manufacturing facilities include at least one European country. Generics manufactured outside Europe include those products that entered first in Europe following protection expiry and which are manufactured exclusively outside Europe.

223 Since our unit of observation is country of sale/corporation/product, and since an EMA marketing authorisation holder will sell in more than one EEA countries, the API sourcing of products sold in more EEA countries is given more weight compared to the API sourcing of products sold in fewer EEA countries.

224 One observation is a country of sale/molecule/corporation/product.

225 The large representation of these countries is driven by the presence of certain large generic producers that have API manufacturing facilities in these two countries and are very active in being among the first to enter upon protection expiry.

Table 10: Manufacturing location of API of first generic entrants following protection expiry

	Generics manufactured in Europe		Generics manufactured outside Europe	
Country of API manufacture	**First entrants across the EEA sourcing API from the particular country**	**Share of total observations**	**First entrants across the EEA sourcing API from the particular country**	**Share of total observations**
India	489	73%	124	78%
China	245	36%	26	16%
Slovenia	128	19%	5	3%
Israel	88	13%	42	27%
Spain	65	10%	9	6%
Italy	44	7%	4	3%
Argentina	30	4%	1	1%
Poland	27	4%		
Malta	22	3%	1	1%
Korea	17	3%		
Netherlands	16	2%		
Turkey	11	2%	1	1%
Puerto Rico	3	0%	8	5%
Hungary	9	1%		
Canada	3	0%	5	3%
France	8	1%		
Czech Republic	3	0%		
Ireland	4	1%		
UK	4	1%		
Finland	1	0%	2	1%
Germany	2	0%	1	1%
Mexico			2	1%
Switzerland	2	0%		

	Generics manufactured in Europe		Generics manufactured outside Europe	
Country of API manufacture	**First entrants across the EEA sourcing API from the particular country**	**Share of total observations**	**First entrants across the EEA sourcing API from the particular country**	**Share of total observations**
Austria			1	1%
Latvia	1	0%		
Scotland	1	0%		
Slovakia	1	0%		
Total observations	**673**		**158**	

Source: CRA analysis on EMA and national medicine agency data

In summary the following conclusions can be drawn from the above analysis:

- There is a high reliance on imported APIs from India and China even for European manufactured generics entering first following protection expiry. Though it is difficult to infer causality, this confirms that the majority of first entrants chose to source APIs from countries with weaker protection rules.
- For 43% of observations[226] of first entrants for which the final dosage form was manufactured in an EU country, at least one of the API sourcing countries was a European country. However a significant number of these observations (most observations where the API country is Slovenia) relate to in-house supply which is already covered by the Bolar and the vast majority have at least one additional API supplier outside Europe.[227] Only 14% of first generic entrants that manufactured the final dosage form in Europe, sourced their APIs exclusively from Europe. The high representation of some countries in this table (e.g. Spain as well as Eastern European countries that joined the EU later) could be explained by weaker historical patent and SPC protection rules. As explained in section 3.1.1, in Spain pharmaceutical products were not patentable until 1992, only processes were patentable. Moreover, SPC protection only became effective in Spain, Greece and Portugal from January 1998. This may have benefited the local API industry. Moreover, as explained in section 3.1.2, countries that joined Europe in the 2004 enlargement, such as Poland, Slovenia and Malta only then

226 One observation is a country of sale/molecule/corporation/product.

227 This could be relevant for the analysis of the export waiver and the stockpiling exemption during the SPC discussed later. Generic producers that select two API suppliers (one in Europe and one outside) may use the API supplier outside Europe in cases where timely entry is sought following expiry of the SPC term, as producing and supplying API within Europe in quantities above what is strictly required for trials and testing would not be covered by the Bolar even under a wider interpretation.

adopted the EU regulations, including SPC protection and in some cases the retroactive effect of the SPC was limited.

In the next section we assess the impact of extending the scope of the Bolar on the European API industry. We first discuss the impact if the measure was implemented on a standalone basis. We subsequently discuss the impact on the EU-based API industry of an extension of the Bolar in combination with an SPC export waiver.

Assessment of potential effect on the API industry

The choice of API supplier depends on a number of factors, including price, quality, security of supply, supplier relationships, and reputation. The current legal uncertainty regarding third party API supply also contributes to the choice of API supplier. However, it is difficult if not impossible to get reliable estimates on the contribution of each factor to the choice of API supplier in order to isolate the effect of the legal uncertainty created by the current Bolar.[228]

Despite this, the following considerations should be taken into account:

- According to CPA, manufacturing costs in China have been increasing and will continue to increase. Combined with lower productivity, this is expected to result in China losing its competitive advantage vis-à-vis Western Europe.[229]
- Chinese API suppliers in the late 2010s were hit by a series of episodes involving quality problems with their APIs, which has resulted in stricter regulations on API imports into the Western world (including the Falsified Medicines Directive (FMD) that entered into force in January 2013 in Europe).[230]

Although no supply problems were reported in Europe following the implementation of FMD, generic companies in Europe and the US were reported to be thinking about re-shoring their API supplies.[231] This suggests that factors that were favouring imports in the past may no longer be as supportive in the future. In this context, the beneficial impact to the European API industry of a change in the scope of the Bolar to clarify the legality of

---

228 We are not aware of any evidence, e.g. survey, which allows the quantification of the relative importance of each factor on the choice of API supplier.

229 CPA estimates a cost index that includes labour costs, energy costs, environmental costs, R&D costs, other costs (shipping and transportation costs, depreciation costs of equipment that are lower in China and India compared to Western Europe), other factors (such as the country's orientation towards exports, country's productivity and country's policy towards attracting foreign investments).

230 The most publicised of these was the Heparin scandal that reportedly resulted in 81 deaths in the US and a large number of serious injuries. https://en.wikipedia.org/wiki/2008_Chinese_heparin_adulteration As a result of this and other episodes, the US and EU competent authorities introduced stricter rules on the importation of APIs to be used in domestically authorised medicines, including written confirmation from competent authorities in the importing country that the facility producing the API is GMP compliant.
http://www.pharmafile.com/news/181764/api-imports-eu-gauging-fmd-s-impact

The Falsified Medicines Directive was implemented in January 2013 and was enforced by 2 July 2013 in the EU
http://ec.europa.eu/health/human-use/falsified_medicines/index_en.htm

231 API Supply Lines: examining the impact of the EU Falsified Medicines Directive and Global GMP Certifications, 29 May 2014, by Shannon Bennett, Pharmaceutical research analyst, Thomson Reuters.
http://connect.dcat.org/blogs/value-chain-insights/2014/05/29/api-supply-lines-examining-the-impact-of-the-eu-falsified-medicines-directive-and-global-gmp-certifications#.VebqxrvosaU

third party API supply within Europe, could be magnified compared to a situation where imports were on other grounds (cost, quality) superior to domestic supply.

Below we develop the methodology used to assess the effect of extending the Bolar scope to cover third party API supply on the European API industry and discuss our findings.

Methodology to assess the effect of extending the scope of the Bolar as a standalone measure

Assuming that the Bolar exemption is extended to allow the supply of protected APIs within Europe, generic companies will be able to obtain APIs for purposes of gaining marketing approval from three sources: 1) in-house production, 2) imports from outside Europe, and 3) supply from a European API manufacturer.

In order to assess the impact of the measure on European API manufacturing, we estimated the market size (in API sales volumes and final dosage form sales values) of products that would be in development by generics producers over the next 10 years and we then estimated the share that European API suppliers could capture of this market under various scenarios. The notes below provide details on the methodology.

First, to estimate the total market size of products that would be in development over the next 10 year period we used the following steps. Using IMS data we identified non-biologic molecules whose protection expires in any of the top 10 European pharmaceutical manufacturing countries[232] between 2018[233] and 2027. For each product satisfying these criteria, we retained the last 12 months of sales, expressed in API volumes (kg) and finished product sales values (EUR) in the top 10 European pharmaceutical manufacturing countries. We identified 158 molecules satisfying these criteria, with a total (pre- loss of exclusivity "LoE") sales value in the top 10 European pharmaceutical producing countries of €11.3 billion and total volume of API of 452 tonnes.

Secondly, we made an assumption about the share of the market that would be captured by European generics suppliers. As IMS does not provide data on the manufacturing location of generic suppliers, we relied on data on manufacturing locations of the finished products provided by the EMA. For a sample of countries and molecules for which the coverage of the manufacturing location data was relatively complete, we estimated the average share of European generics (in sales of finished dosage forms and in kg of API) 1, 2, 3 and 4 years following protection expiry.[234] Table 11 presents the results. The average share of sales values that European generics captured 1 year following protection expiry was 18% and increased to 41% by year 4. The average share of API volumes captured by European generic suppliers one year following protection expiry was

232 The top 10 European pharmaceutical manufacturing countries (Germany, Italy, France, Ireland, UK, Spain, Denmark, Belgium, Sweden and the Netherlands) accounted for 91% of European pharmaceutical production in 2013. EFPIA "The pharmaceutical industry in figures", 2015 edition. As the IMS Midas data did not cover Denmark, in the analysis we substitute Denmark with Poland, the next largest pharmaceutical manufacturing country in Europe.

233 We understand from the industry that the development stage of generics is approximately 3 years. Since the sourcing of APIs will be required at the development stage, we examine molecules whose protection expiry in Europe will occur 3 years from now (2015).

234 The sample consisted of 18 countries and 46 molecules with a total number of country/molecule combinations of 129.

26% and reached 52% 4 years following protection expiry.[235] We assume that the European generic share remains flat following 4 years of protection expiry.

Table 11: Average share of European based generic manufacturers following protection expiry

Years following protection expiry of reference product	Share of total sales value (finished dosage form) captured by European based generic manufacturers (%)	Share of API volumes captured by European based generic manufacturers (%)
1	18	26
2	32	44
3	35	48
4	41	52

Source: CRA analysis on IMS Midas and EMA data

Thirdly, we deducted the share of API sales that would be supplied by in-house production. CPA estimates that 37.5% of European generic API demand is satisfied by in-house supply. We therefore multiplied the resulting API sales volumes captured by European generics manufacturers (estimated in the step above) by 62.5% (100%-37.5%) to arrive at an estimate of API volumes that could be supplied to European generics producers by third party API suppliers.

Fourthly, estimated the share that European API suppliers could achieve in this market, using the actual 2014 share of European merchant generic API sales captured by European API suppliers, which according to CPA was 35%, i.e. assuming no change. [236] We then run three scenarios on the increase in share of European API suppliers as a result of the change in the Bolar:

- Case 1: 2.5 pct point increase in the share of European API suppliers in European generic API sales (37.5%)
- Case 2: 5 pct point increase in the share of European API suppliers in European generic API sales (40%)
- Case 3: 10 pct point increase in the share of European API suppliers in European generic API sales (45%)

Table 12 shows the annual estimated volumes of API that European API suppliers could capture in the European generic API merchant market for molecules coming off patent during the period 2018-2027 in the top 10 European pharmaceutical producing countries. The table also reports the additional annual API volumes assuming the change in the Bolar increases European API suppliers' share of the European API sales market by 2.5 pct points, 5 pct points and 10 pct points. It should be noted that the volumes below refer to API volumes required for *advanced manufacturing*, rather than testing for Bolar

235 These shares are very similar to the shares calculated on the basis of volumes of finished dosage form (IMS Standard Units).

236 The 35% presented in the CPA report is an average share that includes supply of unprotected/ no-longer protected APIs.

purposes[237], on the assumption that generics producers will remain with the same API supplier at the advanced manufacturing stage due to the costs of changing API suppliers from development/approval to advanced manufacturing.

Table 12: Annual API sales volumes (in kg) that European merchant generic API suppliers could capture for molecules coming off patent during the period 2018-2027 under various scenarios, cumulative (based on a sample)

		Additional API sales volumes (kg) under various scenarios		
Year of protection expiry	**No impact on share of European API suppliers**	**Case 1: (2.5 pct point increase in share of European API suppliers)**	**Case 2: (5 pct point increase in share of European API suppliers)**	**Case 3: (10 pct point increase in share of European API suppliers)**
2018	1,251	89	179	357
2019	5,993	428	856	1,712
2020	22,931	1,638	3,276	6,552
2021	26,778	1,913	3,825	7,651
2022	42,523	3,037	6,075	12,150
2023	45,445	3,246	6,492	12,984
2024	46,444	3,317	6,635	13,270
2025	46,584	3,327	6,655	13,310
2026	46,917	3,351	6,702	13,405
2027	47,040	3,360	6,720	13,440
Total 2018-2027	**331,907**	**23,708**	**47,415**	**94,831**

Source: IMS Midas data.

Notes: The years refer to the year of protection expiry in the top 10 European manufacturing countries. The volumes shown in each year include annual sales volumes that European generic API merchant suppliers could capture of molecules expiring in that year and of molecules having expired in previous years (for years 2019 onwards). So the volumes shown in year 2018 include annual volumes that European generic API merchant suppliers could capture for molecules expiring in that year only. The volumes shown in year 2019 include the annual volumes that European generic API suppliers could capture for molecules expiring in 2019 plus molecules expiring in 2018 and so on.

The table indicates that, over the period 2018-2027, European merchant API manufacturers could capture in total 332 tonnes of generic API volumes of the sample of molecules coming off patent during this period, assuming they achieve the same share of European generic API sales as that reported by CPA. If the extension of the Bolar to cover third party API suppliers resulted in an increase in European API suppliers' share of

237 We do not have data on the volumes used for testing purposes by generics during development, but we understand that they are small relative to advanced manufacturing volumes.

2.5 pct points, an additional 23.7 tonnes would be supplied over the 10 year period (7% increase). If the Bolar extension increased their share by 5 pct points, the additional API volumes over the period 2018-2027 would be 47.4 tonnes (14% increase), if it increased their share by 10 pct points the additional volumes would be 94.8 tonnes (29% increase).

The tables above make no adjustment for the formulation yield, i.e. how much raw API is needed to produce the final dosage form, taking into account scrap. Assuming an 80% yield would result in a 25% increase in the estimated volumes across the board.

Since volumes of APIs are not very meaningful given that the price of an API can vary from a few $ per kg to a few million $ per kg, e.g. for an oncology product, it is interesting to see how these volumes translate to sales values of APIs.[238] There are no public data on API prices nor are API prices tracked by data providers such as IMS Health or Evaluate Pharma. CPA's rough estimate is that the price of the API represents 10% of the final price of the finished dosage product.[239] Using this rough estimate, Table 13 calculates the annual API sales values that could result under each scenario, by multiplying the IMS sales values of the molecules identified (after adjusting for the share of European generics, the share of merchant API supplies and the share of European API suppliers under each scenario) by 10%. The table shows that, over the period 2018-2027, the total sales that European merchant generic API suppliers could capture of molecules coming off patent, assuming the same share as reported by CPA, is €632.6 million. If the Bolar extension results in a 2.5 pct point increase in European merchant API suppliers' share, the additional sales over this period would amount to €45.2 million (7% increase relative to no impact) which increases to €90.4 million (14% increase) with a 5 pct point increase in European merchant API suppliers' share and to €180.8 million (29% increase relative to no impact) with a 10 pct point increase in European merchant API suppliers' share.

238 This range is based on discussions with CPA.

239 Based on our discussion with CPA.

Table 13: Estimated annual API sales (in thousand EUR) that European generic API merchant suppliers could capture for molecules coming off patent during the period 2018-2027 under various scenarios, cumulative (based on a sample)

		Additional API sales (EUR thousand) under various scenarios		
Year of protection expiry	**No impact on share of European API suppliers**	**Case 1: (2.5 pct point increase in share of European API suppliers)**	**Case 2: (5 pct point increase in share of European API suppliers)**	**Case 3: (10 pct point increase in share of European API suppliers)**
2018	6,564	469	938	1,875
2019	20,054	1,432	2,865	5,730
2020	27,289	1,949	3,898	7,797
2021	53,767	3,840	7,681	15,362
2022	79,826	5,702	11,404	22,807
2023	81,454	5,818	11,636	23,272
2024	84,934	6,067	12,133	24,267
2025	88,092	6,292	12,585	25,169
2026	94,324	6,737	13,475	26,950
2027	96,330	6,881	13,761	27,523
Total 2018-2027	**632,633**	**45,188**	**90,376**	**180,752**

Source: IMS Midas data.

Notes: The years refer to the year of protection expiry in the top 10 European manufacturing countries. The sales values shown in each year include annual sales that European generic API merchant suppliers could capture of molecules expiring in that year and of molecules having expired in previous years (for years 2019 onwards). So the sales values shown in year 2018 include annual sales that European generic API merchant suppliers could capture for molecules expiring in that year only. The sales values shown in year 2019 include the annual sales values that European generic API suppliers could capture for molecules expiring in 2019 plus the sales values of API relating to molecules expiring in 2018 and so on.

Assessment of effect on EU-based API industry of extending the scope of the Bolar to cover third party API supply within Europe in combination with an SPC export waiver

In sections 4.5 and 4.6 we estimate the additional EU based generic export sales that could arise from an SPC export waiver. These additional generic sales would require APIs. In this section we estimate the additional sales that EU based API producers could achieve on those export sales as a result of the combination of the SPC export waiver with an extension of the Bolar to cover third party API supply within the EU.

Following a similar methodology as the one described above, we estimate the additional sales (in EUR terms)[240] that EU based API producers can achieve on generic export sales that would arise from an SPC export waiver. We do so by firstly multiplying the additional generic sales identified in Table 20 and Table 41 by 10% (the share of the value of the final dosage form accounted for by the API). This gives an estimate of the value of APIs required for the additional EU generic export sales for the sample of molecules analysed (including in-house and third party supply).[241] We then multiply the resulting figure by 62.5% (100%-37.5%) to arrive at the value of API sales that will be sourced from *third party* supply. Last, we multiply by 35% (the average share of EU generic API sales captured by EU based API producers) to arrive at an estimate of the additional sales that will accrue to EU API suppliers as a result of the SPC export waiver. These adjustments are shown in one step in column [4] of Table 14. The SPC export waiver is expected to result in additional API sales by EU based API suppliers of €172.3 million by 2025 and €197.8 million by 2030. Columns [5] to [7] of Table 14 indicate the additional sales that could result by a combination of the SPC export waiver and the extension of the Bolar to cover the third party API supply within Europe, depending on the scenario. Assuming that the share of EU-based API producers increases from 35% to 37.5% (column 5) the estimated additional EU-based generic API sales amount to €211.9 million by 2030 and go up to €254.3 million if we assume the share of EU API suppliers increases by 10 percentage points (column 7). These figures are based on a sample of molecules.

240 We do not have data on the volume of APIs for all the molecules in the sample used to estimate the SPC export waiver, therefore this analysis is only carried out on EUR sales.

241 To assess the impact on API supply of scenario 4 we use the additional export sales by EU based generics *before* adjusting for the loss of sales by the EU based innovators. This is because EU based innovators are more likely to rely on in-house API supply, therefore the potential loss of sales is unlikely to affect EU based third party API supply. For scenario 5, we use the additional export sales by EU based generics *after* adjusting for cannibalisation of other EU based generic and innovative suppliers, as we are not able to split out the loss of sales by EU based generics vs EU based innovators. The impact on EU based API supply is therefore conservative.

Table 14: Additional EU API sales (in EUR thousand) resulting from the combination of an extension of the Bolar to allow third party API supply and an SPC export waiver (based on a sample)

	Total additional sales due to the SPC export waiver to third countries	Total additional sales due to the SPC export waiver within Europe*	Total additional sales due to the SPC export waiver	Third party API sales captured by EU based API suppliers			
	[1]	[2]	[3]=[1]+[2]	[4]=[3]*10%*62.5%*35%	[5]=[3]*10%*62.5%*37.5%	[6]=[3]*10%*62.5%*40%	[7]=[3]*10%*62.5%*45%
2016	2,130,592	7,680	2,138,272	46,775	50,116	53,457	60,139
2017	3,312,134	23,520	3,335,654	72,967	78,179	83,391	93,815
2018	4,624,716	45,960	4,670,676	102,171	109,469	116,767	131,363
2019	5,336,348	75,360	5,411,708	118,381	126,837	135,293	152,204
2020	5,781,445	111,060	5,892,505	128,899	138,106	147,313	165,727
2021	6,219,238	151,200	6,370,438	139,353	149,307	159,261	179,169
2022	6,634,548	198,420	6,832,968	149,471	160,148	170,824	192,177
2023	7,025,585	241,800	7,267,385	158,974	170,329	181,685	204,395
2024	7,341,574	279,660	7,621,234	166,714	178,623	190,531	214,347
2025	7,565,375	311,880	7,877,255	172,315	184,623	196,931	221,548
2026	7,791,830	344,040	8,135,870	177,972	190,684	203,397	228,821
2027	8,058,430	370,440	8,428,870	184,382	197,552	210,722	237,062
2028	8,341,579	387,360	8,728,939	190,946	204,585	218,223	245,501
2029	8,582,936	387,360	8,970,296	196,225	210,241	224,257	252,290
2030	8,652,958	387,360	9,040,318	197,757	211,882	226,008	254,259

Source: CRA calculations based on Table 20; Table 41

Notes: In Table 41 we estimate the additional generic export sales that would arise from an SPC export waiver within Europe under three scenarios regarding the extent of cannibalisation of sales by other EU based producers. For simplicity in the table above, we only present the middle scenario (that assumes that 40% of additional generic export sales are at the expense of other EU pharmaceutical producers).

Assessment of impact on EU API manufacturing employment

To translate these figures into additional jobs, we relied on data on API worker productivity reported by the CPA for three European countries that are the largest API producers: Italy, Spain and Poland. According to the CPA the 2014 average output per worker in was $315,000 in Italy, $272,000 in Spain and $142,000 in Poland. We

converted these to EUR using the 2014 annual exchange rate and then created an average for the three countries weighted by their API production value.

Table 16 estimates the additional jobs that would arise from the implementation of a wide Bolar scope to cover the third party API supply within Europe as a standalone measure. We estimate the additional jobs that could be created as a result of this measure to range between 205 and 820. Even though there are no official figures of employment in the API industry in Europe, these figures are small even in absolute terms, suggesting a modest impact on employment, as presumably at least part of the additional sales could be accommodated by an increase in productivity of the existing workforce.

Table 17 estimates the additional jobs in EU API manufacturing taking into account both the extension of the Bolar to cover third party supply of APIs within Europe and the SPC export waiver. We estimate that depending on the scenario regarding the effect of the extension of the Bolar on European API suppliers' share, the combined measures could result in approximately 960 to 1,150 jobs.

The total impact on European API manufacturing employment would range from 1,166 in Case 1 to 1,973 in Case 3.

Table 15: Estimate of API worker productivity, weighted average Italy, Spain, Poland, 2014

		Yearly average output (USD per worker)	**API production (USD million)**
Italy	USD	315,000	3,500
Spain	USD	272,000	1,180
Poland	USD	142,000	350
Weighted average	*USD*	*292,875*	
USD/EUR exchange rate		1.3285	
Weighted average	***EUR***	***220,455***	

Source: CPA report, ECB exchange rates

Table 16: Estimate of additional jobs in the European API industry that could result from the proposed measure assuming no change in productivity (based on a sample)

	Case 1	**Case 2**	**Case 3**
Additional sales (EUR thousand) by 2027	45,188	90,376	180,752
Average worker productivity (EUR per worker)	220,455	220,455	220,455
Additional jobs by 2027	205	410	820

Source: CRA estimates based on inputs from Table 13 and Table 15

Table 17: Estimate of additional jobs in the European API industry that could result from the combination of an SPC export waiver and an extension of the Bolar to cover third party supply of APIs within the EU, assuming no change in productivity (based on a sample)

	Case 1	Case 2	Case 3
Additional sales (EUR thousand) by 2030	211,882	226,008	254,259
Average worker productivity (EUR per worker)	220,455	220,455	220,455
Additional jobs by 2030	961	1,025	1,153

Source: CRA estimates based on inputs from Table 14 and Table 15

Caveats

The following caveats apply to the above analysis:

- The estimated API sales volumes that European API third party suppliers could capture, are based on aggregate data on the share of in-house versus third party generic API sales and on the share of total European generic API sales captured by European API producers. These shares could differ on a molecule by molecule basis, however no disaggregated information is available. Moreover, the latter shares, as reported by CPA, are based on API sales values but we apply them to volumes (kg of APIs), as only volumes of APIs are reported by IMS Midas data. If, on average, higher value APIs are supplied by European API suppliers compared to non-European ones, the share of total generic API volumes supplied by European API suppliers could be lower than the 35% reported by CPA. However, given that the molecules coming off patent during the period 2018-2027 that we have identified are mostly high potency/ high value molecules (e.g. CNS and oncology), which as discussed above are less likely to be supplied from China and other importing countries, the share of supply from European API manufacturers could be higher than the aggregate reported by CPA, which includes all generic APIs. It is a priori not possible to estimate which way the bias would go.
- In estimating API sales values that European API third party suppliers could capture under the various scenarios, we rely on a rough estimate of the share of API price in the price of the final dosage form product. Given the lack of data on API prices for the molecules in our sample, we believe that this estimate is preferable to using some arbitrary average API price across all molecules.
- Given the lack of data on the relative importance of each factor (including the Bolar exemption) on the choice of API supplier, it is not possible to predict with any degree of accuracy by how much the change in the Bolar exemption will increase the share of generic European APIs sales captured by European API suppliers. We have therefore run some scenarios to illustrate the magnitude of the effect under different assumptions on the impact. However we cannot express an opinion as to which scenario is the most or least likely one.

4.4.4. Assessment of potential effect on the generic industry

Generic penetration and speed of entry depend on a number of factors, including expected profitability and market specific factors (demand and supply side policies favouring generic penetration). A number of empirical papers have examined the factors affecting generic penetration and speed of entry. A summary of recent papers is provided in Appendix E. One common finding among these papers is that expected profitability positively affects speed of entry and generic penetration.

Factors that lower the costs of supply can be expected to increase the profits that generic suppliers anticipate to make in a market and in turn increase generic penetration and speed of entry.

The cost of procuring raw materials (APIs) at the development and advance manufacturing phase is an important cost for generics. Clarifying and extending the scope of the Bolar exemption to cover the third party supply of APIs within Europe, is likely to lead to lower costs of supply for European generics, by:

- Reducing transport costs as well as customs clearance and other delays associated with imports[242]
- Increasing effective competition in the supply of APIs.

Arguably for some products the effect could be more pronounced than for others. European generic manufacturers of more specialised products such as oncology and central nervous system (CNS) products for which API production requires more specialisation than that available to many Chinese API producers would benefit from a greater availability of specialised API suppliers such as those in Europe. The impact is likely to be larger for smaller generic companies who need to rely on third party APIs for most or all of their requirements and for which importing may be an inferior option, e.g. due to scale.

Even though we do not have data to quantify the effect on the cost of supply of APIs, the considerations above suggest that such a change could be beneficial to generic penetration by European suppliers particularly in more complex to produce products.

4.4.5. Assessment of potential costs of this measure

If this measure resulted in the supply of protected APIs for commercial purposes, it would result in costs to the innovative pharmaceutical industry in the form of lost sales during the period of protection. However, for a number of reasons, this risk is unlikely to be significant. Firstly, it can be expected that the risk of infringement would dissuade EU-based API suppliers from engaging in such activities. It could be argued that since API suppliers would not know the intended use of the API by their customers (generic manufacturers), they could not mitigate the risk of commercial supply of the protected product by a generic producer. However, it is reasonable to expect that API suppliers can know with some degree of certainty whether the API supplied was for development or advance manufacture purposes, based on the ordered volumes and their knowledge of the generic manufacturer requesting the API (see also the decision by the Dusseldorf Court of Appeals on the Astellas vs Polpharma case). Moreover, generic manufacturers

242 According to a report by FTI, importing APIs adds 14 weeks to the development phase of a pharmaceutical. FTI report, “A narrow interpretation of the Bolar exemption in the EU pharmaceutical industry”, April 2014, paragraph 5.11.

wishing to enter a market at risk (i.e. during the period of protection), could already do so without this exemption, by procuring the API from less protected markets. Specifying appropriate conditions subject to which the API supply within Europe is covered by the Bolar, is likely to reduce these risks.

4.4.6. Effect of Unitary Patent Protection and Unitary Patent Court

In this section we will discuss the impact on the proposed measure of the introduction of the UPP and UPC. If the UPC adopts a narrow interpretation of the Bolar, then the positive impact on the European API and generic industry could be reversed. If the UPC adopts the view that third party API supply is not covered by the Bolar, similar to the Polish Supreme Court finding in the Polpharma vs Astellas case, European generic producers may be unable to source APIs from European API producers during the testing phase. Given the costs of switching suppliers between the development and advanced manufacturing phase, this is likely to reduce sales by European API producers going forward, as these products move to the advanced manufacturing phase.

Relative to a world where a harmonised wide Bolar provision applied in all EU Member States that explicitly covered third party API supply within Europe for Bolar purposes, the introduction of a UPC with a narrow interpretation could result in the European API industry losing the additional estimated sales presented in Table 13 and part of the additional sales presented in Table 14 and the corresponding additional jobs. A narrow interpretation by the UPC could therefore, at worst, cost the European API manufacturers between almost €45.2 million and €180.8 million in additional sales for molecules whose protection expires during the period 2018-2027. Moreover, it would result in a loss of sales between €14-56 million from API sales destined for the export market.[243] There would be a corresponding loss of jobs between 269 and 1,076. These costs represent an upper bound.

A narrow implementation of the Bolar provision by the UPC could result in additional costs of supply for EU based generics as it would reduce their available options for API supply during the testing phase to those that can be imported. Even though most APIs are currently imported from outside Europe (mainly India and China), as discussed above for some more complex compounds the available third party API supplier options may be more limited.

4.5. Scenario 4: Allowing manufacturing of SPC protected medicines in protected (domestic) markets for purposes of exporting to third countries where the corresponding patent or SPC has expired

4.5.1. Issue

As discussed in section 3 above, currently the SPC confers to the holder the same rights as conferred by the basic patent and is subject to the same limitations and same obligations. As a result, during the SPC term, not only can generics not be marketed but the manufacturing of the protected compound or medicine for export or stockpiling in the domestic market is also prohibited.[244] In this section we focus on the assessment of the

243 This is calculated by subtracting the figures in each of the columns [5] - [7] from the figures in column [4] of Table 14.

244 Regulation EEC No 469/2009, Art 5, Effects of the certificate.

effects of allowing manufacturing of SPC protected products in the domestic country for export to unprotected or no longer protected third countries (outside the EEA).

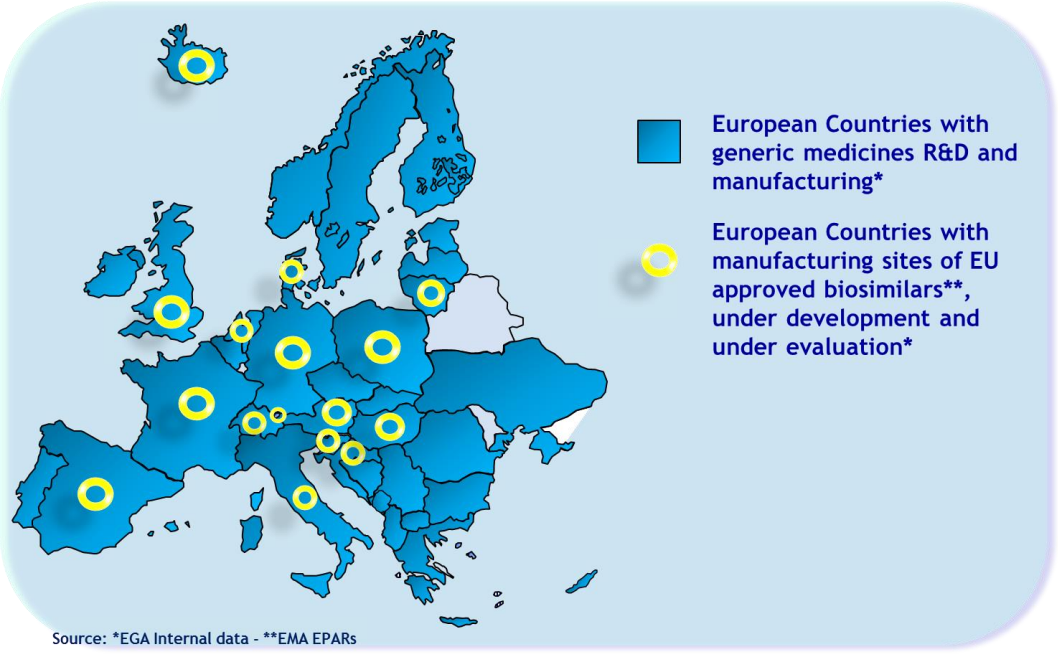
From our discussions with the EGA we understand that the European generic and biosimilar industry are concerned because their inability to manufacture during the SPC term in the domestic market for export to unprotected or no longer protected markets puts them at a disadvantage relative to manufacturers located in countries without SPC protection. In particular, the inability to manufacture for export during the SPC term in the domestic market harms the EU based generic and biosimilar industry for the following reasons:

- EU-based generic/biosimilar manufacturers are forced to enter with delay (sometimes significant considering the maximum 5 year SPC term) in foreign unprotected or no longer protected markets, with potentially a detrimental impact on their probability of success in these markets.
- Larger generic/biosimilar producers with global manufacturing facilities may prefer to locate production outside Europe in order to be able to supply unprotected markets, negatively affecting employment and manufacturing in Europe.

  In the case of generics, large multinational producers may prefer to have either a single or (to ensure stability of supply) a small number of locations for the manufacturing of a product to benefit from economies of scale in production. The regulatory freedom to supply a number of markets from that location is an important factor affecting the choice of where to locate advanced manufacturing. Smaller generic producers without a global network of manufacturing facilities, in order to be able to enter timely in markets where protection has expired, might have to contract out the manufacturing of these products to CMOs located outside Europe. According to the EGA, due to the investments that CMOs need to make, they usually require long term agreements. As a result, it is likely that the manufacturing of the product will remain outside Europe even following the SPC expiry term in Europe. In some cases, the costs of contracting out production make the financials look less promising, thus generic producers may prefer not to enter those markets at all.

  In the case of biosimilars, due to the advanced regulatory framework in Europe for the placing on the market of biosimilars, a number of biosimilar manufacturers have invested in biosimilar R&D and manufacturing facilities in Europe. The map below provided by the EGA shows the location of biosimilar R&D and manufacturing facilities in Europe. Because of the close link between product development and advance manufacture of biological and biosimilar products, once a decision has been made about the location of production it is very difficult to relocate. As discussed in section 2 above, according to EGA, the minimum cost of relocating the production of a single biological product is €10 million and 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 is not affected, the costs easily multiply. The current SPC regime is placing these producers at a disadvantage as they cannot compete on a level playing field with manufacturers located outside Europe for the supply to markets where the protection has expired.

Figure 9: Map of European countries with R&D and manufacturing facilities for generics and biosimilars



On the other hand, from our discussions with EFPIA, we understand that the EU based innovative pharmaceutical industry is concerned that allowing manufacturing for export during the SPC term would create a risk of products destined for export markets to be leaked into the protected market resulting in infringement.

Below we present our assessment of the potential impact of an SPC export waiver to third countries on the European generic, biosimilar and innovative pharmaceutical industry. We first begin by summarising evidence from empirical papers on the importance of speed of entry in generic product success and we subsequently examine whether manufacturers located in countries without SPC terms (or where SPC has expired) are more likely to be first to enter following protection expiry in Europe.

In subsections 4.5.3 and 4.5.4 we assess the effect of an SPC export waiver on the European pharmaceutical industry, in subsection 4.5.5 we consider the wider effects on employment, incentives to invest and speed of entry of generics, while in subsection 4.5.6 we consider the effect on the proposed measure of the coming into force of the UPP and UPC.

4.5.2. Importance of speed of entry in generic product success

In pharmaceutical markets, the speed of entry following protection expiry is an important determinant of the success of the product in terms of market share and profitability. Therefore if European generic entrants are forced, as a result of the SPC, to enter with a delay in unprotected or no longer protected markets, this may severely impact the probability of their success in that market. A number of empirical studies have confirmed the first mover advantage in generic entry.

Shajarizadeh et al (2015)[245] examine the effects of market entry timing on firms' share of the Canadian generic pharmaceutical market using IMS Health Canada data from 2001 to 2011 for 40 molecules that experienced entry between 2003 and 2007. They find that the first entrant enjoys a first mover advantage over the share that would be expected (1/number of firms) of approximately 29% that declines by about 1.3% per quarter, i.e. in their set up the first mover advantage disappears after 6 years which represents a durable advantage. Second entrants also enjoy a 10% first mover advantage, though this result is based on a few observations and may not be robust. They hypothesise that factors contributing to the first mover advantage of first entrants include pharmacy and patient inertia to switching generic suppliers.

Yu and Gupta (2008)[246], examine 49 molecules that lost exclusivity in the US over the period 1992-2000. They find that early generic entrants have a substantial first mover advantage over later entrants in the retail market, after controlling for prices and marketing activities. They do not find such strong evidence for the hospital market. The authors interpret these findings as the result of the difference between hospitals and retail pharmacies in sourcing generics. Hospitals' decisions on which generics to source are largely based on price (especially in tenders), whereas retail pharmacies once they've started sourcing one product may be slower to switch to another or add another generic. Moreover, consistent with past literature they find that the order of market entry moderates the effects of marketing. Demand is more sensitive to price and less sensitive to advertising for later entrants.

Hollis (2002)[247] examines the effect of the timing of entry on the market share of generics in Canada and finds that the first generic entrant can expect a long-term advantage of approximately 20-35 percentage points in its market share compared to later entrants.

Caves et al (1991) [248] also examine the first mover advantage in generic entry and find that the price of generics to the branded product decreases sharply as the number of generic entrants increases implying a profit advantage for the first generic entrant.

Feedback from EGA also confirms that there is a first mover advantage for generic and biosimilar producers. As discussed in section 2, a number of European countries have a sliding scale of reimbursement prices for generic medicines with the prices of later entrants declining significantly. Even without sliding reimbursement scale, prices generally fall with the number of entrants in a market. As a result, profits are higher during the first months following launch and decline thereafter. Generics companies thus race to be the first to enter. Additionally, in some Member States hospitals or insurers conduct tenders immediately following protection expiry. If a generic is delayed in entering the market following protection expiry it cannot participate in these tenders. This is particularly problematic for large tenders that cover a substantial part of the market and may last for

245 Ali Shajarizadeh, Paul Grootendorst & Aidan Hollis (2015) Newton's First Law as Applied to Pharmacies: Why Entry Order Matters for Generics, International Journal of the Economics of Business, 22:2, 201-217.

246 Yu, Yu and Gupta, Sachin (2008), Pioneering Advantage in Generic Drug Competition. International Journal of Pharmaceutical and Healthcare Marketing 01/2014; 8(2).

247 Hollis, Aidan (2002), "The Importance of being First: Evidence from Canadian Generic Pharmaceuticals," Health Economics, 11 (8), 723 – 34.

248 Caves, Richard E., Michael D. Whinston, Mark A. Hurwitz, Ariel Pakes, and Peter Temin (1991), "Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry," Brookings Papers on Economic Activity, 1-48.

up to 2 years. Delayed entrants could remain out of a substantial part of the market for a long period of time, making the investment in developing the product less attractive. Kanavos (2012) discusses this point in the context of the sickness funds and insurer tenders in Germany and the Netherlands.[249]

For biosimilar products the decline in prices is not as steep as in the case of generics. Even in this market however there is a race to launch first as later entrants have difficulty in gaining market share without further declines in prices.

We have also examined the market share disadvantage of later entrants compared to first entrants based on protection expiry and subsequent generic entry events during the period 2008Q1 to 2014Q3 on average across the EU5 as well as in Russia and Turkey.[250] The details of this analysis are presented in Appendix C. Table 18 presents the results of our analysis. The table shows the ratio of the share of the later entrant (coming in 1 and 2 years after the first generic entrant) to the share of the first entrant, calculated one and two years after the entry of the later entrant for the EU5, Russia and Turkey. As can be seen below, in the EU5 the share of a generic entrant coming in 1 year after the first entrant calculated one year *following* the later entrant's entry is 11% that of the first entrant while it is 20% when calculated two years following the later entrant's entry.[251] In Russia and Turkey we see that first entrants have a first mover advantage but it is lower compared to the EU5, and it tends to decay faster compared to the EU5, but is still present 2 years following entry of the later entrant. Our results are generally consistent with the findings of the papers discussed above, that indicate a durable first mover advantage of first generic entrants over time.[252]

249 Kanavos (2012), *Tender systems for outpatient pharmaceuticals in the European Union: evidence from the Netherlands and Germany,* prepared for the European Commission.

250 We chose the EU5 as these are the largest and most developed in terms of generic development European markets that could be closer proxies to the third countries considered compared to taking an average across all EEA countries available in our database. We do not have detailed IMS data that would enable us to undertake a similar analysis for the other third countries considered here, namely US, Canada, Brazil, China and Australia.

251 We chose a two year horizon as there were not enough generic entry events during our sample period to reliably estimate the market share disadvantage 3 or more years after the entry of the later entrant, for entrants coming in 1 and 2 years after the first generic entrant.

252 The magnitudes of our calculations are not directly comparable, as we compare the average share of first entrants to that of entrants coming 1 year later or 2 years later, irrespective of how many have entered in the interim period. Hollis for example in his 2015 paper examines the first mover advantage of the first entrant relative to the expected share which they define as 1/ number of generics in period t.

Table 18: Market share disadvantage of later generic entrants

		Ratio of the share of later generic entrant to first generic entrant, calculated at time:	
		T_1 = 12 months after entry of later entrant	T_2= 24 months after entry of later entrant
Generic firm entering 1 year *after* entry of first generic entrant	EU5	11%	20%
	Russia	17%	66%
	Turkey	27%	36%
Generic firm entering 2 year *after* entry of first generic entrant	EU5	6%	12%
	Russia	11%	22%
	Turkey	8%	24%

Source: CRA analysis on IMS Midas data

4.5.3. Assessment of potential effect on European generic and biosimilar manufacturing

Testing hypothesis

We expect an SPC export waiver to third countries to result in increased manufacturing of generics and biosimilars in Europe. Below we explain the methodology used to estimate the effect.

Assessment of the effect on the European generic and biosimilar manufacturing

The following diagram describes graphically the method used to estimate the effect of the SPC export waiver to third countries on the European generic and biosimilar manufacturing industry.

If an SPC export waiver to third countries is implemented, European generics producers will be able to start selling earlier into markets where the protection has expired earlier (time T1 in the diagram below). Under the status quo, European generics producers can only start selling into markets where the protection has expired earlier, once the SPC expires in Europe (time T2 in the diagram below).[253] In addition, as explained earlier, there is a market share disadvantage associated with the delay in entering a market, so that under the status quo, European generics producers can expect to achieve a lower share in third countries due to the delay in entering those markets.

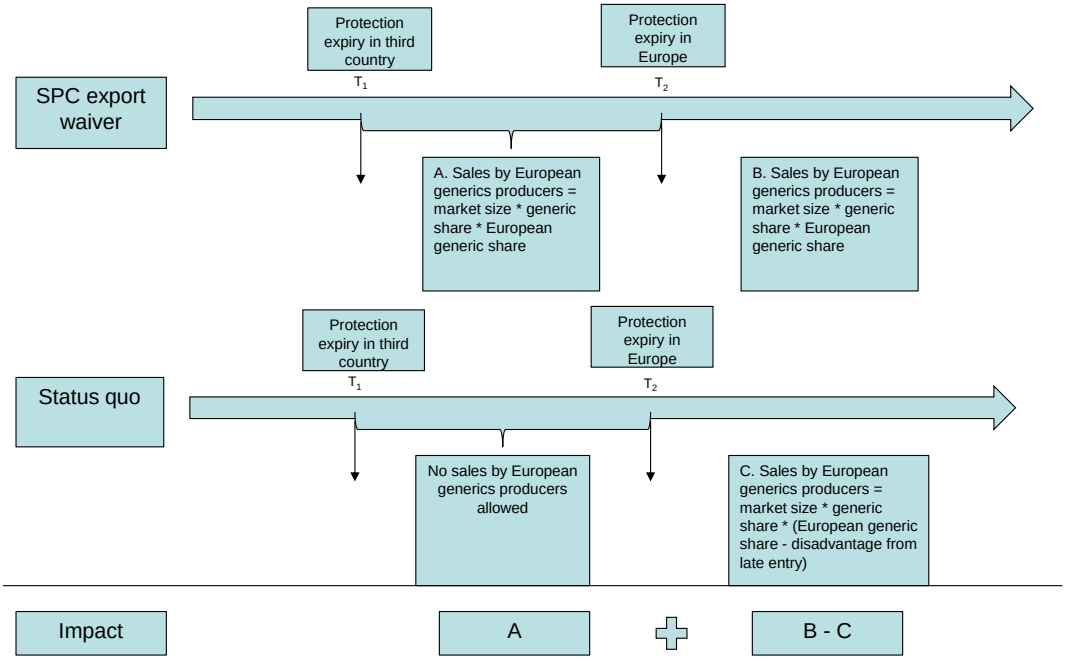
To estimate the impact of the SPC export waiver to third countries we deduct the estimated sales achieved by European generics producers in third countries under the status quo (block C in the diagram below) from the sales achieved under an SPC export waiver (blocks A plus B in the diagram below). This simplifies to the sum of lost sales

253 We ignore any delays associated with e.g. stockpiling or other regulatory delays to prepare for commercial production in the third country.

during the SPC term in Europe (period T1-T2), plus the first mover advantage from earlier entry under the export waiver.

Of course there could be factors other than the delay related to the SPC term that affect the time to entry into an export market, such as e.g. delays in preparing the dossier and receiving regulatory approvals, delays associated with pricing and reimbursement to the extent that these apply in third countries, among others. However, these factors can be expected to be common across all generic entrants irrespective of their origin of manufacture and are unlikely to be affected by the SPC export waiver. If these factors result in a delay in market entry of e.g. 6 months, this 6 month delay would mean that under the status quo European generic/biosimilar manufacturers could enter 6 months following the SPC term expiry in Europe, whereas under the SPC export waiver they would enter 6 months following the protection expiry in the export market. Even under these conditions to estimate the effect of an SPC export waiver, the relevant period to examine would be the difference between the SPC term in Europe and the protection expiry term in the export market.

Figure 10: Methodology for assessing effect of SPC export waiver to third countries



Below we explain in more detail the method and data used in each step.

1. We first identified molecules whose SPC expiry term in Europe occurred later compared to other third countries. We relied on two sources to collect a sample of such molecules. The first source was the IMS Midas dataset that allowed us to identify products with European SPC expiries over the next 15 years (2016-2030) occurring at least a year later compared to Russia and Turkey.[254] The second

254 We focused on molecules expiring later in the EU5 compared to Russia and Turkey, as these are the largest European pharmaceutical markets and therefore the markets where SPC protection is most likely to be sought by innovative pharmaceutical producers. Moreover IMS data do not cover the protection expiry of molecules in a number of countries, e.g. Bulgaria, Croatia, Estonia, Latvia, Lithuania, Luxemburg and Slovenia, and in other countries some but not all molecules were covered.

source was data from EGA and confidential data from a generic producer on a sample of molecules with SPC expiries over the next 15 years in Europe and earlier protection expiry in US, Canada, China, Brazil, Australia and Japan.[255] These 8 countries accounted for 60% of European pharmaceutical exports (excluding intra-EEA trade) in 2014.[256] For each of these molecules we obtained the 2014 sales value (in EUR) and volume (in standard units) in the export market, based on IMS Midas data.[257]

2. Secondly, for each molecule and third country in our sample we estimated the sales lost by European generics manufacturers during the SPC term, as follows:

    a. We estimated the market size that would be available to all generics producers once the molecules became off patent in the relevant third countries. We used country specific data on generic penetration and price evolution of generics since protection expiry obtained from empirical papers and public IMS Health reports.[258] For Russia and Turkey these figures were calculated directly from the available IMS Midas data.

    b. We applied to the resulting figures the share that European generics producers could achieve in these markets if they entered during the first year of protection expiry, i.e. under the SPC export waiver. As a proxy for the share that European generics and biosimilars could achieve in

---

255 As the data were provided on a confidential basis they are only presented in aggregated form in this report. Only two molecules were identified with earlier protection in Australia. This is probably the result of the sample of molecules used and is not necessarily representative of the relative expiration dates of all protected molecules between Europe and Australia.

256 Based on United Nations Trade Statistics, Comtrade, SITC 54.

257 For the products identified on the basis of the available IMS Midas database, the sales value refers to the 12 months ending Q3 2014 as this is the end period of our dataset.

258 Data on the share of generic volumes in unprotected sales for the US, Canada, Australia and Japan was obtained from the IMS Institute for Healthcare Informatics November 2013 report on *The Global Use of Medicines: Outlook through 2017*.

Data on the share of generic volumes in unprotected sales for Brazil was obtained from the IMS report "Generic medicines: essential contributors to the long term health of society", by Alan Sheppard, Thought leadership Brussels, March 2010.

Data on the development of generic prices since protection expiry for the US, Canada, Japan and Australia was obtained from the NBER Working Paper by Patricia Danzon and Michael Furukawa, *Cross-national evidence on generic pharmaceuticals: pharmacy vs physician driven markets*, NBER WP 17226, July 2011. For Brazil we assumed that generics are priced at a 35% discount to originators, which is the statutory pricing of generics adopted by CMED, the Brazilian national medicine authority since 2004. See Eduardo E.P. Fiuza and Barbara Cabarello (January 2015), *Estimations of generic drug entry in Brazil using count versus ordered models,* IPEA DP 186. For China we did not find any public data on price decay and we assumed that the price of generics is 50% below the price of originators. Assuming a 30% discount to originators, the impact of the SPC would be 1% *higher* and assuming a 70% discount to originators would result in a 1% *lower* impact.

For Russia and Turkey, using available IMS Midas data we estimated the average share that generics achieve on sales following protection expiry.

The IMS Midas data available to us do not separate out branded from unbranded generics, therefore we have included both branded and unbranded in the calculation of generic penetration in Russia and Turkey. For the remaining export countries the source documents from which generic penetration/generic price decay data were obtained did not specify whether branded generics were also included.

sales in the third countries we used the ratio of imports of generics/biosimilar pharmaceuticals in that country from the EEA (obtained from trade statistics) divided by pharmaceutical sales in that country (based on IMS data).[259]

3. Thirdly, we estimated additional sales that European generics producers could achieve under the SPC export waiver to third countries*, for two* years following the SPC expiry in Europe due to the first mover advantage of earlier generic entry compared to export sales that could be achieved by European generics producers if they entered the third market in the year of protection expiry in Europe. This was calculated as:

$$EEA\ generic\ share\ in\ third\ market \times generic\ market\ size\ in\ third\ market \times (1 - market\ share\ disadvantage)$$

Where the estimated EEA generic share in the third market is that calculated under point 2.b. above, and the market share disadvantage is that presented in Table 18.[260]

4. The last step involved adding 2 and 3 to arrive at the full impact.

We present the results of this analysis first for generics and then for biosimilars.

Generics

Table 19 presents some descriptive statistics for the sample of molecules used in our analysis. Of the sample of 117 molecules examined, the protection of 76 (65%) molecules expired earlier in Canada, 74 (63%) in China, 72 (62%) in the US, 70 (60%) in Brazil and in Russia, 44 (38%) in Japan, 33 (28%) in Turkey and 2 (2%) in Australia. The average delay in number of years between the protection expiry in a third country and Europe ranged between 2.23 (for the US) and 3.85 years (for Canada).

259 There are no reliable data on the share that European generic and biosimilars achieve in sales in third countries. For this reason we relied on a comparison of trade statistics with IMS sales in these countries. To avoid the inclusion of raw and intermediate products imported from the EEA and further processed in these countries we only examined HS codes that related to products packed for retail sale (HS 3001, 3002, 3004). Trade statistics do not separate out generics/biosimilars from originator products. To estimate imports of generic/biosimilars from the EEA in each third country, we assumed that the ratio of imported generics/biosimilars to originator products was the same as the ratio of generic pharmaceutical sales to originator sales in the importing country (calculated on the basis of IMS data). For some countries: Australia, Canada, Russia and Turkey, this method resulted in very high shares that European generics could achieve in exports (>50%). For these countries we assumed that the share would be equal to the average share of the remaining countries (US: 16%, Brazil: 21%, China: 32%, Japan: 24%), namely 23%. This assumption could potentially underestimate the share that European generics can achieve in adjacent third countries such as Russia and Turkey. IMS did not report biosimilar sales for China, Russia and Turkey. Moreover for Brazil, the estimated share of biosimilars resulted in an unreasonably high share (>100%). For these countries we assumed that the share that European biosimilars could achieve in these markets was the lowest among the remaining countries (25% for the US).

260 For delays of 2 years or more we applied the market share disadvantage of entrants coming in 2 years after the first generic entrant, whereas for delays less than 2 years we applied the market share disadvantage of entrants coming in 1 year after the first generic entrant. We used the average EU5 figure for the third countries for which we did not have data to calculate the market share disadvantage (Canada, China, US, Brazil, Japan, Australia).

Table 19: Descriptive statistics for a sample of non-biological molecules used in analysing the impact of an SPC export waiver

Country	Number of molecules in our sample	Number of molecules examined with later SPC expiry date in Europe	Share of molecules in the sample	Average number of years of delay
Canada	117	76	65%	3.85
China	117	74	63%	3.47
US	117	72	62%	2.23
Brazil	117	70	60%	3.42
Russia	117	70	60%	2.75
Japan	117	44	38%	3.44
Turkey	117	33	28%	3.81
Australia	117	2	2%	0.54

Source: CRA analysis on IMS, EGA and Comtrade data

Table 20 presents our estimates of the additional export sales (based on data from Table 19 and the inputs described in footnote 259) that European generics could capture under an SPC export waiver compared to the status quo. The year refers to the year of protection expiry in the third country and the sales are shown cumulatively.[261] As can be seen from the table, total generic sales during the period between the protection expiry in the third country and the SPC expiry in Europe, in the 8 third countries and sample of molecules analysed, amount to € 23.5 billion by 2025 and €26.2 billion by 2030. We estimate additional export sales by European generics during the SPC term at €4.4 billion by 2025 going up to €4.9 billion by 2030, a share of approximately 19%. The additional sales that European generics could achieve in the export market two years following the SPC expiry in Europe due to the first mover advantage relative to the status quo are estimated to reach €3.1 billion by 2025 and €3.8 billion by 2030.[262] The total additional sales taking into account the lost sales during the SPC protection period and the additional sales that European generics can achieve due to the first mover advantage of earlier entry, two years following SPC expiry in Europe are estimated to reach €7.6 billion by 2025 and €8.7 billion by 2030. It should be emphasised that these results are based

261 As we examine molecules whose SPC term expires in Europe between 2016 and 2030, the figures for 2016 include sales of molecules that expired before 2016 in third countries.

262 In Table 20 the additional sales due to the first mover advantage are shown by year of protection expiry in Europe. So for year 2016, column [1] presents the market available to all generic producers in export markets for molecules expiring in that year (or earlier) in that market and that have a later protection expiry date in Europe. Column [2] shows the share of this market that can be captured by European generics, while column [3] shows the additional sales that European generics producers can achieve of molecules expiring in that year (or a year before) in Europe. Column [4] shows the total estimated additional export sales by year by adding the export sales that can be achieved during the SPC term as a result of the waiver and the export sales that can be achieved after the SPC term due to the first mover advantage of early generic entrants. Therefore it is not appropriate to express [3] or [4] as a share of [1] as the mix of products is different.

on a sample of molecules and countries[263], and does not reflect the full potential impact if all export countries and molecules were considered.

For comparison, total EEA exports of non-biological molecules to the third countries considered[264] amounted to €40 billion in 2014.[265] Based on figures in Table 19, the average delay (weighted by number of molecules by export country) in our sample of molecules/countries was 3.2 years. Therefore the €7.6 billion in additional sales represent annual sales of €2.3 billion, a 6% increase on total export sales. Note that since our findings are based on a sample of molecules and countries, the 6% represents a lower bound. Our sample of molecules represents 32% of all molecules (by count) whose protection expires in Europe during the period 2016-2030, therefore the impact on export sales could be up to 18% (3 times 6%).

263 Based on IMS Midas data the protection of 370 non-biological molecules expires in the EU during the period 2016-2030, therefore our sample of 117 molecules represents 32% of all molecules expiring in the EU during this period.

264 Excluding Australia, as from our sample of 117 molecules, only 2 molecules had earlier expiry in Australia.

265 Includes innovative and generics.

Table 20: Additional export sales to third countries by European generics manufacturers under an SPC export waiver, cumulatively in EUR thousand (based on a sample)

Year of protection expiry in third country	Estimated generic sales during the period between protection expiry in the third country and SPC protection period in Europe	Additional export sales during period between protection expiry in third country and SPC expiry in Europe	Additional export sales during period between protection expiry in third country and SPC expiry in Europe (% of generic market in third countries)	Additional sales post SPC expiry in Europe due to first mover advantage relative to status quo (calculated 2 years since protection expiry)	Total additional sales due to the SPC export waiver
	[1]	[2]	[3] = [2]/[1]	[4]	[5] = [2]+[4]
2016	10,167,794	2,099,007	21%	31,585	2,130,592
2017	13,500,783	2,684,931	20%	627,203	3,312,134
2018	15,284,998	2,994,918	20%	1,629,798	4,624,716
2019	16,655,978	3,230,435	19%	2,105,913	5,336,348
2020	17,789,759	3,427,505	19%	2,353,941	5,781,445
2021	19,710,447	3,753,299	19%	2,465,938	6,219,238
2022	21,314,494	4,029,365	19%	2,605,183	6,634,548
2023	22,390,048	4,217,257	19%	2,808,328	7,025,585
2024	22,963,980	4,323,249	19%	3,018,325	7,341,574
2025	23,453,529	4,412,205	19%	3,153,170	7,565,375
2026	24,298,828	4,557,317	19%	3,234,513	7,791,830
2027	25,484,228	4,753,232	19%	3,305,198	8,058,430
2028	26,118,004	4,862,125	19%	3,479,453	8,341,579
2029	26,222,112	4,878,552	19%	3,704,384	8,582,936
2030	26,222,112	4,878,552	19%	3,774,406	8,652,958

Source: CRA analysis on IMS Midas data, Comtrade data and data from EGA

Notes: The years refer to the year of protection expiry for the sample of molecules examined in the following countries: Australia, Brazil, Canada, China, Japan, Russia, Turkey and the US. The sales values shown are *cumulative.* For example, in column [1] the value shown under year 2016 refers to total estimated generic sales for molecules expiring in third countries in 2016 (or earlier if the SPC expiry date in Europe was after 2015) that are still under protection in Europe. The value under year 2017 refers to total estimated generic sales for molecules expiring in third countries in 2016 and 2017 and that are still under SPC protection in Europe, and so on. Similarly the values in column [2] refer to the sales that EEA generics can achieve in these third countries. In column [3] the sales refer to the additional sales due to the first mover advantage of EEA generics if they enter third countries earlier, from the date of SPC expiry in Europe. Therefore, under year 2016 column [3] shows the

additional sales that EEA generics suppliers can achieve in third countries for molecules whose SPC term expires in Europe in that year. Under year 2017 column [3] shows the additional sales that EEA generics suppliers can achieve in third countries for molecules whose SPC term expires in Europe in that year (2017) and in earlier years (2016). The additional sales are only computed up to 2 years following the date of SPC expiry in Europe.

Table 21 and Table 22 break down the additional sales by destination, grouping countries into those that have patent extension terms (Australia, Japan, Russia, US) that are mostly developed markets, with the exception of Russia, and those that do not (Brazil, Canada, China, Turkey) that are mostly emerging markets with the exception of Canada. Additional sales to third country markets that have patent extension terms amount to €5.3 billion by 2025 (including additional sales due to the first mover advantage), whereas additional sales to countries without a patent extension term amount to €2.2 billion by 2025 (including additional sales due to the first mover advantage).

Table 21: Additional export sales to third countries with patent extension terms (Australia, Japan, Russia, US) by European generics manufacturers under an SPC export waiver, cumulatively in EUR thousand (based on a sample)

Year	Market size available to generics producers during the period between protection expiry in the third country and SPC protection period in Europe	Additional export sales during period between protection expiry in third country and SPC expiry in Europe	Additional export sales during period between protection expiry in third country and SPC expiry in Europe (% of generic market in third countries)	Additional sales post SPC expiry in Europe due to first mover advantage relative to status quo (calculated 2 years since protection expiry)	Total additional sales due to the SPC export waiver
	[1]	[2]	[3]=[2]/[1]	[4]	[5] = [2] + [4]
2016	5,855,542	943,185	16%	13,133	956,318
2017	8,608,624	1,389,275	16%	443,445	1,832,719
2018	10,126,621	1,636,382	16%	1,223,420	2,859,802
2019	11,325,164	1,831,206	16%	1,618,908	3,450,114
2020	12,296,357	1,989,939	16%	1,831,148	3,821,087
2021	14,010,408	2,266,839	16%	1,919,323	4,186,163
2022	15,431,904	2,500,191	16%	2,034,303	4,534,494
2023	16,373,652	2,656,886	16%	2,212,653	4,869,539
2024	16,845,042	2,739,363	16%	2,394,430	5,133,793
2025	17,254,131	2,810,087	16%	2,512,079	5,322,166
2026	18,034,438	2,940,391	16%	2,581,536	5,521,927
2027	19,170,396	3,124,972	16%	2,643,368	5,768,341
2028	19,753,259	3,222,076	16%	2,807,026	6,029,101
2029	19,857,200	3,238,463	16%	3,012,303	6,250,766
2030	19,857,200	3,238,463	16%	3,071,349	6,309,813

Source: Table 20

Table 22: Additional export sales to third countries without patent extension terms (Canada, Brazil, China, Turkey) by European generics manufacturers under an SPC export waiver, cumulatively in EUR thousand (based on a sample)

Year	Market size available to generics producers during the period between protection expiry in the third country and SPC protection period in Europe	Additional export sales during period between protection expiry in third country and SPC expiry in Europe	Additional export sales during period between protection expiry in third country and SPC expiry in Europe (% of generic market in third countries)	Additional sales post SPC expiry in Europe due to first mover advantage relative to status quo (calculated 2 years since protection expiry)	Total additional sales due to the SPC export waiver
	[1]	[2]	[3]=[2]/[1]	[4]	[5] = [2] + [4]
2016	4,312,252	1,155,822	27%	18,452	1,174,274
2017	4,892,160	1,295,656	26%	183,758	1,479,415
2018	5,158,377	1,358,535	26%	406,378	1,764,914
2019	5,330,815	1,399,229	26%	487,005	1,886,234
2020	5,493,402	1,437,565	26%	522,793	1,960,358
2021	5,700,039	1,486,460	26%	546,615	2,033,075
2022	5,882,590	1,529,175	26%	570,880	2,100,054
2023	6,016,396	1,560,371	26%	595,675	2,156,046
2024	6,118,938	1,583,886	26%	623,895	2,207,781
2025	6,199,398	1,602,118	26%	641,091	2,243,209
2026	6,264,390	1,616,926	26%	652,977	2,269,903
2027	6,313,832	1,628,260	26%	661,830	2,290,090
2028	6,364,745	1,640,049	26%	672,428	2,312,477
2029	6,364,912	1,640,088	26%	692,081	2,332,170
2030	6,364,912	1,640,088	26%	703,057	2,343,145

Source: Table 20

It may be argued that the share that Europe based generics can achieve in emerging markets is more uncertain due to their higher cost relative to cheaper domestically produced generics, which could make it harder for these products to enter the positive reimbursement lists.[266] To address this point we also run a sensitivity where we assumed that the share that European generics could achieve in generic sales in emerging markets (Brazil, China, Russia and Turkey) was only 10%. The effect was to reduce additional sales during the SPC protection term from €4.4 billion to €3.8 billion, a 14% reduction (corresponding to a 16% share by European generics of the generic market in third countries) by 2025, and total additional sales (including first mover advantage) from €7.5 billion to €6.7 billion by 2025 (a 12% reduction).

It may also be argued that the market share disadvantage estimates that we used to estimate the additional sales due to earlier entry in the period after the SPC expires in Europe, may not be directly applicable to emerging markets such as Brazil and China, as the estimates for these two countries are based on market share disadvantage figures calculated from IMS Midas data on the EU5 countries.[267] The additional sales due to the first mover advantage for China and Brazil amount to approximately €363 million or almost 5% of the total additional sales (first mover advantage plus sales during the SPC term) calculated for all countries in our sample. Therefore, even if the estimates we used were not applicable to these two countries the effect on the total estimated additional export sales due to the SPC export waiver is likely to be small.

266 China regulatory and market access pharmaceutical report, 2014, Pacific Bridge Medical, page 8 and 53-54. http://www.pacificbridgemedical.com/wp-content/uploads/2015/04/China-Regulatory-and-Market-Access-Pharmaceutical-Report-2014.pdf

267 For Russia and Turkey we were able to estimate this effect directly as we had IMS Midas data for these two countries.

Table 23: Additional export sales to third countries by European generics manufacturers under an SPC export waiver assuming a lower share by European generics in emerging markets as a sensitivity, cumulatively in EUR thousand (based on a sample)

Year of protection expiry in third country	Estimated generic sales during the period between protection expiry in the third country and SPC protection period in Europe	Additional export sales during period between protection expiry in third country and SPC expiry in Europe	Additional export sales during period between protection expiry in third country and SPC expiry in Europe (% of generic market in third countries)	Additional sales post SPC expiry in Europe due to first mover advantage relative to status quo (calculated 2 years since protection expiry)	Total additional sales due to the SPC export waiver
	[1]	[2]	[3] = [2]/[1]	[4]	[5] = [2]+[4]
2016	10,167,794	1,574,252	15%	19,304	1,593,556
2017	13,500,783	2,121,697	16%	527,364	2,649,060
2018	15,284,998	2,418,784	16%	1,433,441	3,852,225
2019	16,655,978	2,646,954	16%	1,890,025	4,536,979
2020	17,789,759	2,836,829	16%	2,128,961	4,965,790
2021	19,710,447	3,153,463	16%	2,234,738	5,388,200
2022	21,314,494	3,422,163	16%	2,367,849	5,790,012
2023	22,390,048	3,604,387	16%	2,565,525	6,169,912
2024	22,963,980	3,706,960	16%	2,769,796	6,476,756
2025	23,453,529	3,793,539	16%	2,901,262	6,694,801
2026	24,298,828	3,937,210	16%	2,980,708	6,917,918
2027	25,484,228	4,132,383	16%	3,049,868	7,182,250
2028	26,118,004	4,241,234	16%	3,222,958	7,464,191
2029	26,222,112	4,257,660	16%	3,447,229	7,704,889
2030	26,222,112	4,257,660	16%	3,517,277	7,774,937

Source: Table 20, assuming a 10% share by European generics in emerging markets.

It should be noted that we have made no adjustments for growth in sales in export markets, therefore our estimates presented in Table 20 are likely to understate the impact of an SPC export waiver. One of the main attractions of emerging markets in particular for pharmaceutical companies, is their demographic profile as well as the increasing

prevalence of chronic and Western type diseases such as cancer and cardiovascular diseases. In fact, the pharmaceutical markets in emerging economies such as China, Brazil, India, South Korea, Mexico and Turkey have experienced sustained growth of over 20% CAGR since the early 2000s according to a recent report and are expected to continue to grow at double digit growth rates. In particular China is expected to grow at 12% per year over the period 2013-2020, resulting in an almost doubling of sales over a seven year period.[268] Our estimates above do not factor in any growth and therefore underestimate the impact of an SPC export waiver.

Biosimilars

There are a number of differences between chemically synthesised and biological medicines. Due to their complexity and the resulting additional data required to obtain marketing approvals, there is a longer delay between protection expiry of a biological product and the launch of a biosimilar, compared to chemically synthesised products. Examining the delay between patent expiry[269] in the EU5 countries and marketing authorisation for biosimilar products of 5 out of the 6 biological molecules authorised during our sample period[270], we find that the delay has reduced from about 8-9 years for follitropin alfa to 1.5 years for infliximab. Of course, one reason for the observed delays is that we do not have information on the data and market exclusivity periods or SPC periods for these biological molecules, so it is likely that large part of the observed delay from patent expiry to marketing authorisation or to market entry is due to the existence of an SPC protection or data or market exclusivity after the patent expiry. For example, insulin glargine only lost its SPC protection in France in May 2015 and Eli Lilly received a marketing authorisation for a biosimilar in August 2014, almost a year before.[271] Therefore if data on the SPC expiry of the molecules in Table 24 were available, we may have observed significantly reduced delays.

268 *Ibid.* pages 5-6.

269 IMS Midas data only report patent expiry dates for biological molecules but not protection expiry dates (i.e. including SPC, data and marketing exclusivity periods). As a result our analysis in the table is based on patent expiry dates, which could explain the long observed delays.

270 Biosimilars have been authorised for the following molecules: epoetin, filgrastim, follitorpin alfa, somatropin, infliximab and insulin glargine. However for somatropin the marketing authorisation date as well as first entry in the EU5 was before the beginning of out IMS data, so we cannot calculate delay in entry for biosimilars of this molecule.

271 See discussion of Sanofi/Eli Lilly case in France in section 3.1.3.

Table 24: Delay between patent expiry and marketing authorisation and first sales of biosimilars, EU5

Molecule(s)	Date of national patent expiry in EU5	Delay in years to marketing authorisation	Average delay in years to first sales in EU5
Follitropin Alfa	Oct-04	8.9	9.6
	Jan-06	7.7	8.6
Epoetin Alfa	Dec-04	2.7	2.7
	Feb-08	-	1.0
Epoetin Zeta	Dec-04	3.0	4.3
	Feb-08	-	1.0
Filgrastim	Aug-06	2.1	2.5
Insulin Glargine	Jul-07	7.2	-
	Feb-08	6.6	-
	Nov-09	4.8	-
Infliximab	Mar-12	1.5	-

Source: CRA analysis on IMS Midas data

Note: Blanks are shown where either the national patent expiry was *after* the marketing authorisation date or where no sales are shown in our data for the approved biosimilar.

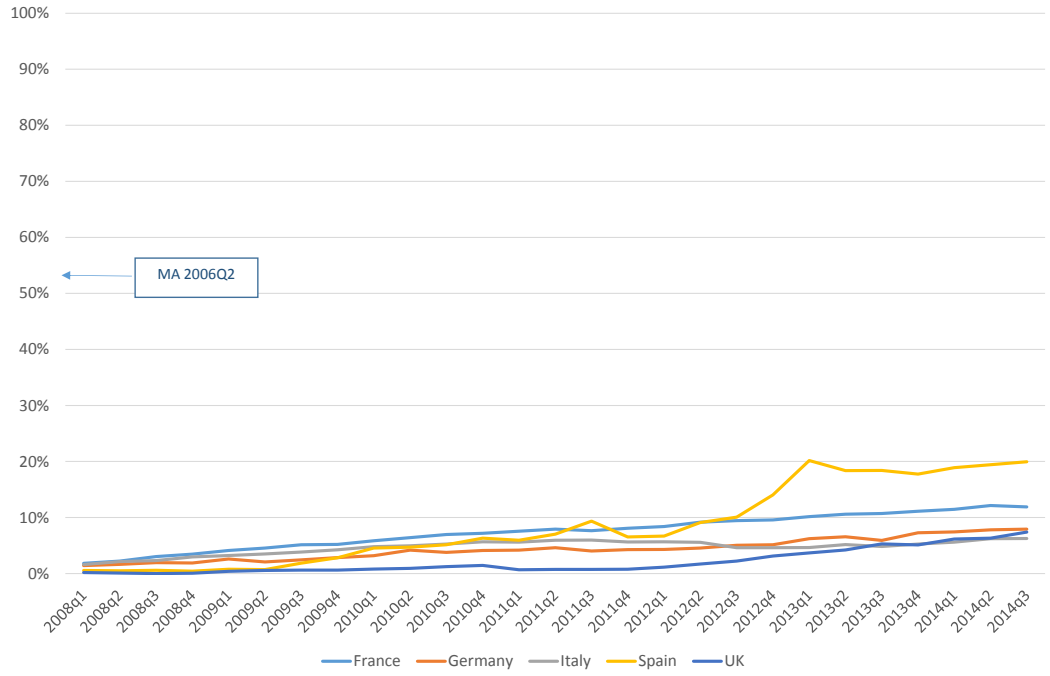
We also observe variation in the penetration of biosimilars, by molecule and by EU5 country (we focus on the EU5 as these are the largest European countries by pharmaceutical sales). The next figures show the development of biosimilar penetration (measured as the share of biosimilar EUR sales to total molecule sales, including non-reference products) for filgrastim, epoetin and somatropin. We focus on these three molecules as they are the ones that have sales in the EU5 countries during our sample period.[272]

As the figures show, in the case of filgrastim, biosimilars achieved a high penetration soon after the marketing authorisation date and reached very high levels (76% on average across the EU5) by the end of our sample period (5 years since the European marketing approval date). Biosimilars of somatropin and epoetin, on the other hand, have achieved lower penetration. In the case of epoetin, with the exception of Germany where biosimilars entered first and by 2008 had already achieved a high penetration, biosimilar entry and penetration in the other EU5 countries has been very slow. For somatropin, penetration has been very low (less than 10% for most countries during our sample period) despite the product receiving marketing authorisation in 2006. The penetration rates are also closely related to the number of marketing authorisation holders of biosimilars for each molecule. Whereas there are 8 biosimilar marketing authorisation holders for filgrastim, there is only one biosimilar marketing authorisation holder for

272 Biosimilars of infliximab and follitropin only have sales in the last quarter of our dataset, whereas no sales of biosimilar insulin glargine are reported by IMS during our sample period.

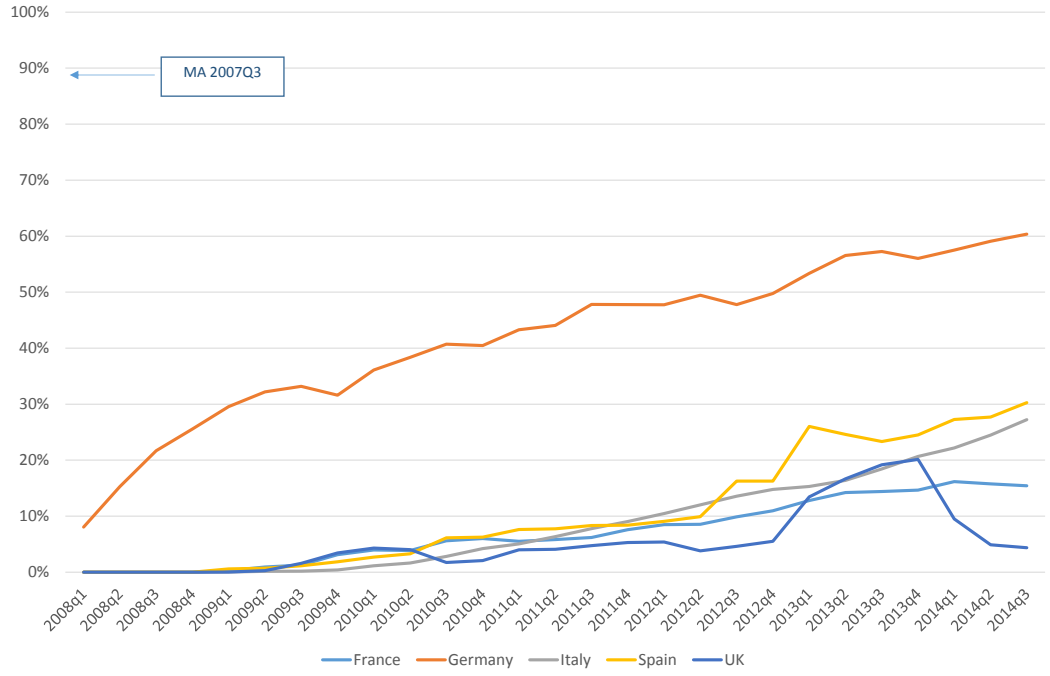
somatropin (Sandoz) and five biosimilars for epoetin, despite their earlier protection expiry in Europe.

Figure 11: Market share development of biosimilar somatropin in EU5, EUR 2008Q1 to 2014Q3



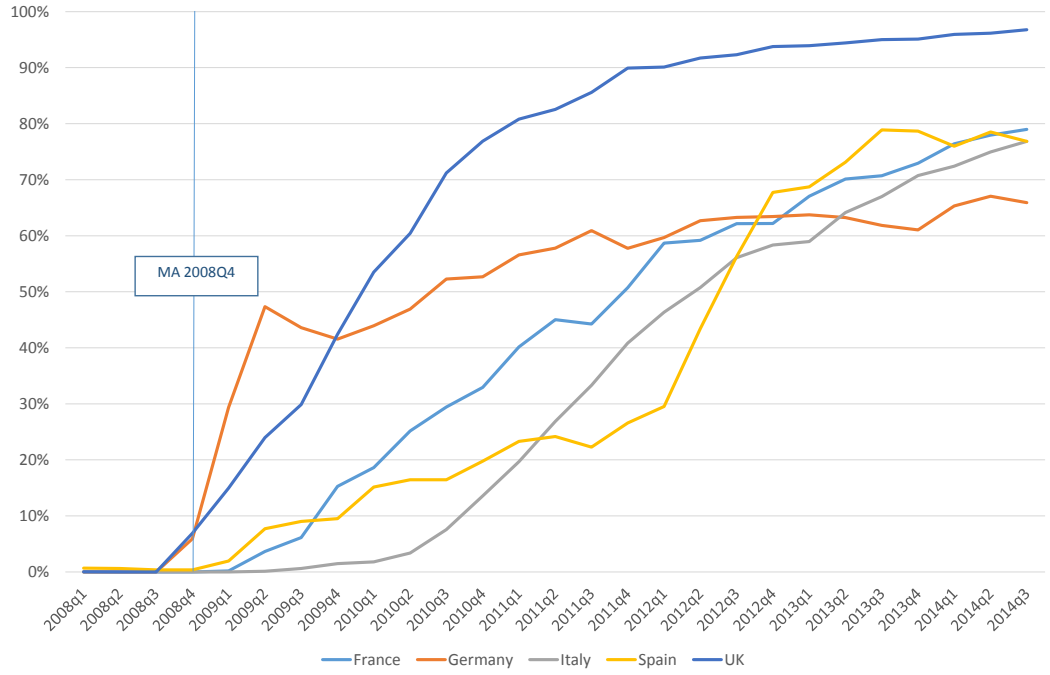
Source: CRA analysis on IMS Midas data

Figure 12: Market share development of biosimilar epoetin in EU5, EUR 2008Q1 to 2014Q3



Source: CRA analysis on IMS Midas data

Figure 13: Market share development of biosimilar filgrastim in EU5, EUR 2008Q1 to 2014Q3



Source: CRA analysis on IMS Midas data

Methodology

Using a similar method to the one described above for generics we identified a sample of biological molecules, whose SPC term expires in Europe later compared to at least one of the 8 third countries studied.[273] Table 25 presents some descriptive statistics for the sample of molecules used in our analysis. Of the 17 molecules examined, the protection of 9 (53%) expired earlier in the US, 8 (47%) in Canada, 7 (41%) in Russia, 6 (35%) in China, 5 (29%) in Brazil and Japan and 1 (6%) in Turkey. The average delay in number of years between the protection expiry in a third country and Europe ranged between 1.4 years (for the US) and 6 years (for Brazil).

273 We did not identify any biologic molecules whose protection expired earlier in Australia.

Table 25: Descriptive statistics for the sample of biological molecules used in analysing the impact of an SPC export waiver

Country	Number of molecules in our sample	Number of molecules with later SPC expiry date in Europe	Share of molecules in the sample	Average number of years of delay
US	17	9	53%	1.37
Canada	17	8	47%	3.42
Russia	17	7	41%	2.86
China	17	6	35%	3.16
Brazil	17	5	29%	6.06
Japan	17	5	29%	2.46
Turkey	17	1	6%	2.00

Source: CRA analysis on IMS and EGA data

Table 27 presents our estimates of the additional export sales that European biosimilars could capture under an SPC export waiver during the period of SPC protection in Europe. There are a few differences between the method used in the case of generics and the method used here. These are detailed below.

Firstly, due to lack of data on biosimilar penetration in the third countries examined, we need to rely on data on biosimilar penetration in Europe. As we have seen above, based on the few molecules for which we have enough data on biosimilar sales during our sample period, there is significant variability in biosimilar penetration across molecules and within molecules across the EU5 countries. This suggests that it is not straightforward to use an average of these data as a proxy for the share that biosimilars can achieve in molecules coming off patent in third countries before the SPC expiry date in Europe. [274] We have therefore run two scenarios:

1. 'Fast penetration' scenario we assume that biosimilars in third countries would achieve the average penetration achieved by biosimilars of filgrastim in the EU5.
2. 'Slow penetration' scenario we assumed that biosimilars in third countries would achieve the average penetration of somatropin and epoetin (weighed by sales in the EU5 countries).

Table 26 presents the average penetration in years following the marketing authorisation in the fast and slow penetration scenarios. For example in the 'fast penetration' scenario we assumed that the market for biosimilars in the third countries would be 22% times the 2014 sales value of the biological molecule whose protection expired earlier in the third

274 Given the observed variability in penetration rates across countries, we considered whether a subset of the EU5 would be better comparators to some third countries compared to others. However, lack of data on the penetration of biosimilars in these third countries precluded us from making any such assumptions and we used the average EU5 penetration rate for each third country, which is a simplification.

countries compared to Europe, during the first year after protection expiry in the third country, 40% times the 2014 sales value of the candidate biological molecules in the second year following protection expiry and so on.

Table 26: EU5 biosimilar penetration in years following protection expiry

	EUR share of biosimilars (%)				
	1 year after MA	**2 year after MA**	**3 year after MA**	**4 year after MA**	**5 year after MA**
Fast penetration	22%	40%	53%	69%	76%
Slow penetration	4%	5%	8%	10%	13%

Source: CRA analysis on IMS Midas data and EMA data on dates of marketing authorisation

Note: In calculating the share of biosimilars we have included in the relevant market the reference, biosimilar as well as non-reference products.

Secondly, due to lack of enough data to calculate the market share disadvantage of later entry (as there aren't many biosimilar producers for a given molecule), we only calculate the impact of the SPC export waiver based on the lost sales between the date of protection expiry in the third country and the date of protection expiry in Europe.

Thirdly, we also assume that even under an SPC export waiver, entry in the third market by *any* biosimilar producer would occur one year following SPC expiry in the third country. This assumption reflects the finding above that there is a longer delay in entry of biosimilars relative to the date of protection expiry of the reference product compared to generics.[275] It can be expected that over time this delay will reduce.

Finally for China, Russia and Turkey IMS Midas data do not split out sales of biosimilars, therefore we cannot use the same methodology to proxy the share that European biosimilars can achieve in these markets.[276] Moreover for Brazil, the methodology we use results in shares greater than 100%. For these four countries therefore we assume that the share that European biosimilars could achieve in domestic biosimilar sales is equal to the lowest share that we estimate for the remaining third countries (US, Canada, Japan). The lowest is for the US, where we estimate that European biosimilars could achieve 25% of the US biosimilar market.[277]

The findings are presented in Table 27. In the fast penetration scenario, the market size available to all biosimilar producers during the period between the protection expiry in the third country and the SPC expiry in Europe amounts to € 10.4 billion by 2025 (based on data from Table 25), of which we estimate (based on data described in footnote 259) that European biosimilars producers could capture €2.97 billion by 2025, a share of 29%. In the slow penetration scenario, the market size available to all biosimilar producers during

275 Data on the speed of entry of generics in Europe are presented in section 4.7.4.

276 *Supra.* Footnote 259.

277 We use the lowest share among the remaining countries to take into account the possibility that it may be more difficult for European biosimilars to significantly increase sales in emerging markets due to their higher price relative to locally produced bio-comparable products. See also later discussion.

the period between the protection expiry in the third country and the SPC expiry in Europe amounts to €1.63 billion by 2025, of which we estimate European biosimilars producers could capture €463 million by 2025, a share of 28%. These results are based on a *sample* of molecules and third countries and do not represent the full effect of an SPC export waiver on European biosimilar producers. The sample of molecules is smaller than the sample used to estimate the effect for generics, which partly explains the lower absolute size of the estimated biosimilar market size in third countries and additional sales to EU-based biosimilar producers. If all molecules and all third countries were considered then the impact would be correspondingly higher. E.g. if considering all potential molecules and third countries resulted in a market size of €20 billion for biosimilars by 2025, the corresponding impact could be €5.7 billion (29% of €20 billion).[278]

Table 27: Additional export sales to third countries by European biosimilar manufacturers under an SPC export waiver, cumulatively in EUR million (based on a sample)

Year	Market size of biosimilar sales in third countries during SPC protection		Additional export sales by European biosimilars to third countries during SPC protection		Share of European biosimilars in biosimilar market in third countries	
	Fast penetration	Slow penetration	Fast penetration	Slow penetration	Fast penetration	Slow penetration
2016	3,779,127	595,799	1,133,655	176,747	30%	30%
2017	4,963,581	789,328	1,465,233	230,163	30%	29%
2018	7,492,709	1,204,575	2,154,827	343,709	29%	29%
2019	9,580,553	1,490,346	2,737,226	424,299	29%	28%
2020	9,832,801	1,535,605	2,805,399	436,288	29%	28%
2021	10,067,051	1,578,485	2,866,626	447,358	28%	28%
2022	10,068,367	1,578,743	2,867,022	447,435	28%	28%
2023	10,122,978	1,589,095	2,882,289	450,318	28%	28%
2024	10,263,823	1,609,382	2,924,086	456,448	28%	28%
2025	10,404,118	1,629,409	2,970,237	462,938	29%	28%
2026	10,676,498	1,673,446	3,046,632	475,139	29%	28%
2027	10,727,396	1,680,914	3,059,492	477,030	29%	28%

Source: CRA analysis on IMS Midas data, Comtrade data and data from EGA

Notes: The years refer to the year of protection expiry for the sample of molecules examined in the following countries: Brazil, Canada, China, Japan, Russia, Turkey and the US. The sales values shown are *cumulative.* For example, the value shown under year 2016 refers to total estimated biosimilar sales for molecules expiring

278 Considering more third countries could change the weighted average share that EU based biosimilars can achieve in export markets (given that the 29% is based on the 8 third countries considered). The purpose of the above illustration is to show that the effect would be correspondingly higher if we had a fuller dataset rather than a sample.

in third countries in 2016 (or earlier if the SPC expiry date in Europe was after 2015) that are still under protection in Europe. The value under year 2017 refers to total estimated biosimilar sales for molecules expiring in third countries in 2016 and 2017 and that are still under SPC protection in Europe, and so on.

The tables below break down the additional sales by destination, grouping countries into those that have patent extension terms, which as discussed above are mostly developed countries, with the exception of Russia, and those that do not, which as discussed above are mostly emerging countries, with the exception of Canada. Additional sales by European biosimilar producers as a result of an SPC export waiver to third country markets that have patent extension terms amount to approximately €2 billion by 2025 in the fast penetration scenario and almost €320 million in the slow penetration scenario, whereas additional sales to countries without an SPC amount to almost €908 million by 2025 in the fast penetration scenario and €143 million in the slow penetration scenario.

Table 28: Additional export sales to third countries with patent extension terms (Japan, Russia, US) by European biosimilar manufacturers under an SPC export waiver, cumulatively in EUR million (based on a sample)

Year	Market size of biosimilar sales in third countries during SPC protection		Additional export sales by European biosimilars to third countries during SPC protection		Share of European biosimilars in biosimilar market in third countries	
	Fast penetration	Slow penetration	Fast penetration	Slow penetration	Fast penetration	Slow penetration
2016	2,319,558	380,005	589,639	96,597	25%	25%
2017	3,258,028	534,651	837,498	136,989	26%	26%
2018	5,463,177	889,311	1,407,904	228,526	26%	26%
2019	7,277,524	1,116,603	1,879,819	288,200	26%	26%
2020	7,490,274	1,156,595	1,932,888	298,175	26%	26%
2021	7,703,129	1,196,604	1,985,983	308,155	26%	26%
2022	7,703,599	1,196,673	1,986,100	308,172	26%	26%
2023	7,749,201	1,205,234	1,997,475	310,308	26%	26%
2024	7,868,365	1,222,401	2,029,927	315,104	26%	26%
2025	7,976,998	1,237,959	2,062,437	319,685	26%	26%
2026	8,226,273	1,278,500	2,128,859	330,393	26%	26%
2027	8,276,382	1,285,794	2,141,358	332,212	26%	26%

Source: Table 27

Table 29: Additional export sales to third countries without patent extension terms (Brazil, Canada, China, Turkey) by European biosimilar manufacturers under an SPC export waiver, cumulatively in EUR million (based on a sample)

Year	Market size of biosimilar sales in third countries during SPC protection		Additional export sales by European biosimilars to third countries during SPC protection		Share of European biosimilars in biosimilar market in third countries	
	Fast penetration	Slow penetration	Fast penetration	Slow penetration	Fast penetration	Slow penetration
2016	1,459,568	215,797	544,016	80,150	37%	37%
2017	1,705,552	254,680	627,735	93,174	37%	37%
2018	2,029,530	315,267	746,923	115,183	37%	37%
2019	2,303,026	373,745	857,408	136,098	37%	36%
2020	2,342,525	379,012	872,513	138,111	37%	36%
2021	2,363,919	381,883	880,645	139,201	37%	36%
2022	2,364,766	382,072	880,924	139,261	37%	36%
2023	2,373,776	383,862	884,816	140,009	37%	36%
2024	2,395,458	386,981	894,161	141,343	37%	37%
2025	2,427,119	391,451	907,802	143,252	37%	37%
2026	2,450,225	394,948	917,776	144,746	37%	37%
2027	2,451,014	395,122	918,137	144,817	37%	37%

Source: Table 27

It could be argued that the share that European biosimilars could achieve in emerging markets is more uncertain for a number of reasons. Firstly, governments in some emerging markets such as Brazil and Russia are actively investing in their own biosimilar production, so imported biosimilars that are potentially more expensive may find it harder to compete.[279] Secondly, in a number of these markets (e.g. India, China) regulation on biosimilars is or historically was less strict compared to Europe and the US, especially the standards on proving similarity to the originator. For example a 2011 article notes that there were already 40 products called biosimilars in the Indian market and more than 10 companies competing in this area. The same article notes that due to more relaxed regulatory requirements the cost of developing a biosimilar in India can be between USD 10-20 million, considerably smaller than the cost of development in a developed country.[280] According to another article, China[281] has a number of locally manufactured

279 Biosimilars in emerging markets, 5 September 2011. http://www.biosimilarnews.com/biosimilars-in-emerging-markets

280 Indian biosimilars market, 13 October 2011. http://www.biosimilarnews.com/indian-biosimilars-market

follow-on-biologics that compete with originators in the market, which are significantly less expensive.[282] According to another article, the typical discount of biosimilars in China is typically 60%, which is higher than in Europe.[283] One could argue that as a result, it could be more difficult for more expensive European biosimilars to successfully compete in these markets.

To address this concern we re-estimate the effect assuming that the share that European biosimilars can achieve in the four emerging markets in our sample (Brazil, China, Russia and Turkey) is only 10%, down from the 25% used in the previous tables. Table 30 presents the results. If we assume that they can only achieve a 10% share in these four emerging markets, the additional export sales by 2025 would amount to €2.8 billion in the fast penetration scenario (a 5% decline relative to the estimates in Table 27) and €437 million in the slow penetration scenario or 27% of the market (a 6% decline relative to the estimates in Table 27). The effect is not very large as the sales in emerging markets are lower than sales in developed markets in our sample.

Again it should be noted that these estimates are based on a sample of countries and molecules.

281 China does not have an abridged regulatory pathway for biosimilars. Biosimilars need to follow the marketing authorisation route followed by innovative pharmaceuticals.

282 Change of biosimilars in China by Reuters, February 2015. http://www.innoventbio.com/en/News.aspx?key=news&Id=1144&type=%E6%96%B0%E9%97%BB%E4%B8%AD%E5%BF%83

283 Biosimilars in China, February 2013, Philip Miller, Feng Wang, Harshal Kubavat, Deallus Consulting. http://www.pmlive.com/pharma_intelligence/biosimilars_in_china_460090

Table 30: Additional export sales to third countries by European biosimilar manufacturers under an SPC export waiver assuming a lower share of European biosimilars in emerging markets as a sensitivity, cumulatively in EUR million (based on a sample)

Year	Market size of biosimilar sales in third countries during SPC protection		Additional export sales by European biosimilars to third countries during SPC protection		Share of European biosimilars in biosimilar market in third countries	
	Fast penetration	Slow penetration	Fast penetration	Slow penetration	Fast penetration	Slow penetration
2016	3,779,127	595,799	1,044,463	163,358	28%	27%
2017	4,963,581	789,328	1,355,165	213,319	27%	27%
2018	7,492,709	1,204,575	2,023,530	322,713	27%	27%
2019	9,580,553	1,490,346	2,595,273	399,091	27%	27%
2020	9,832,801	1,535,605	2,661,278	410,790	27%	27%
2021	10,067,051	1,578,485	2,721,263	421,691	27%	27%
2022	10,068,367	1,578,743	2,721,510	421,739	27%	27%
2023	10,122,978	1,589,095	2,736,531	424,558	27%	27%
2024	10,263,823	1,609,382	2,777,888	430,616	27%	27%
2025	10,404,118	1,629,409	2,823,419	437,007	27%	27%
2026	10,676,498	1,673,446	2,899,375	449,130	27%	27%
2027	10,727,396	1,680,914	2,912,236	451,014	27%	27%

Source: Table 27, assuming a 10% share by European biosimilars in emerging markets.

Caveats

The following caveats apply to the foregoing analysis for both generics and biosimilars:

- Given that there are other countries that are less regulated compared to Europe such as Argentina, India, Mexico, South Africa, South Korea, Singapore, Venezuela to name a few, the impact that we identify above represents only part of the full potential impact. Moreover, since our analysis was based on a *sample* of products for which the SPC term in Europe is after the protection expiry in the 8 third countries we considered, the estimated effect is only partial (e.g. for Australia our sample included two chemically synthesized molecule with later SPC expiry in Europe and no biological molecules with later SPC expiry in Europe).
- We have made no assumptions regarding growth of the generic and biosimilar pharmaceutical market, which as explained above, can be expected to be high particularly in emerging countries but also in developed countries. Modelling growth would increase the estimated effect.
- The proxy that we used for the share that European generics and biosimilars could achieve in export markets under the export waiver is imperfect. This is

because it relies on aggregate data and assumptions about the share of generics/biosimilars in import statistics, whereas the share that European and biosimilar generic producers can achieve in third countries depends on a number of factors, e.g. complexity of the product, number of other potential suppliers etc. However, based on our research and discussions with the industry there are no reliable public data that could be used as alternative proxies.

- With the exception of Russia and Turkey, for which we have disaggregated IMS Midas data available, the market share disadvantage of producers entering with a delay in other third countries was calculated from the available IMS Midas data, with a focus on the EU5 countries (France, Germany, Italy, Spain and the UK). To the extent that the market share disadvantage is influenced by country specific factors this proxy could be an imperfect one particularly for emerging markets that may have a different profile to developed markets. This affects our estimates of additional generic export sales, as we do not model a first mover advantage effect for biosimilars. As we explained above, the effect of this is likely to be very small (maximum 5%).
- As we do not have data on the biosimilar penetration in the third countries examined, we relied on biosimilar penetration data in the EU5 for a small number of molecules for which biosimilar sales data were available during our period. This is an imperfect proxy as the development of biosimilars could depend on country specific factors, including policies to promote their use, whether their pricing will be regulated (etc.), which could be different to the EU5 experience.

4.5.4. Assessment of potential effect on the EU innovative pharmaceutical industry

In this section we will consider the potential negative effect that an SPC export waiver could have on the European innovative pharmaceutical industry. The European innovative pharmaceutical industry could be negatively affected by an SPC export waiver if it results in increased generic and biosimilar competition in the export markets and therefore lower branded export sales in the third countries considered.

We address non-biologics and biologics separately.

Effect on the export sales of European non-biologic branded medicines

An SPC export waiver enables European generics to start exporting into third countries where there is no corresponding SPC term or where protection has expired earlier, during the period when the SPC applies in Europe. Increased generic competition during the period following protection expiry in third countries could negatively affect European branded medicine sales in these markets. The magnitude of the effect will depend on two factors.

Firstly, the extent to which European innovative companies sell into these markets from European facilities. If sales of branded medicines in third countries are primarily from manufacturing facilities outside Europe, the effect on European manufacturing would be more limited. Most large pharmaceutical companies have manufacturing facilities in a

number of locations globally.[284] Therefore it is important to determine the size of EEA exports of branded pharmaceutical products into the third countries in our sample.

Secondly, the effect will depend on the extent to which an SPC export waiver increases generic competition in these markets. It is reasonable to expect that since generic competition is already intense in less regulated emerging markets but also in developed markets such as the US, EU based originator companies would, even in the absence of an SPC export waiver, face competition from non-European generics producers.[285]

With regards to the first point, a challenge is that we do not have data on Europe manufactured branded medicine export sales into third countries.[286] We therefore rely on a similar method as before to estimate the share that the European branded medicines achieve in pharmaceutical sales in the export markets. In particular we rely on Comtrade trade statistics on non-biological pharmaceutical imports into each of the eight third countries in our sample from the EEA. We then assume that the share of branded to generics in imports from the EEA is the same as the share of branded to generics sales in the domestic pharmaceutical sales market, based on IMS Midas data. We divide the resulting figure by the value of non-biological branded sales in the export markets, based on IMS Midas data to determine the share that European branded medicines could achieve in branded sales in the export markets.[287] Last, we estimate the market size available to branded pharmaceuticals post protection expiry in the export markets for the

284 For example, according to a 2011 KPMG report into the Chinese pharmaceutical market the largest innovative pharmaceutical companies, including Pfizer, GSK, Sanofi, Astra Zeneca had established research and manufacturing facilities in China. China's pharmaceutical industry – poised for the giant leap, 2011 KPMG report, pages 22-23. http://www.kpmg.com/cn/en/issuesandinsights/articlespublications/documents/china-pharmaceutical-201106-2.pdf

285 For example, in the US, for all molecules experiencing entry in 2011-2012, brands retained only 16% of units in year 1, falling to 11% of units for molecules with sales above USD 250 million. Henry Grabowski, Genia Long, Richard Mortimer (2013), *Recent trends in brand-name and generic drug competition,* Journal of Medical Economics. http://fds.duke.edu/db/attachment/2575 . Moreover, the penetration rates of generic products in unprotected sales in the third countries in our sample (see footnote 258) are all very high, implying a high level of generic competition even without an SPC export waiver.

286 We contacted EFPIA and other innovative pharmaceutical associations, however they did not have data on exports to/imports from the EEA innovative industry. We also contacted IMS Health, however even though they had data on imports into some of the third countries in our sample, they could not identify the origin of imports.

287 Using this method we arrive at the following shares that European branded pharmaceuticals can achieve in *branded* non-biological sales in the third countries in our sample (based on 2014 trade figures). For non-biological molecules: Australia (43%), Brazil (13%), Canada (21%), China (13%), Japan (11%), Russia (62%), Turkey (37%) and USA (8%).

molecules in our sample, by assuming no effect on originator prices post generic entry[288] but a reduction in sales volumes of branded pharmaceuticals that corresponds to the average levels of generic penetration observed in these markets.[289]

With regards to the second point, the effect on sales by European branded medicines will depend on the expected number of generic entrants without an SPC export waiver and with an SPC export waiver, as well as on the diversion between European branded and generic medicines in third countries. A number of papers have examined the effect of the number of generic entrants on price and generic penetration. Papers generally find a negative relationship between the average price level post protection expiry and the number of generic entrants and a positive relationship between generic penetration and number of generic entrants.[290] Of course, what is relevant in the present case is the extent to which an SPC export waiver is likely to increase the number of generic entrants in export markets compared to a counterfactual without an SPC export waiver or whether it is likely to change mix of generic entrants (with a higher representation of EU generics). Given the high levels of generic competition in these markets, such a measure is likely to affect primarily the mix of generic entrants.

As we cannot be certain about the effect of the measure on export sales by European branded medicines, we run two scenarios:

1. Case 1: we assume that the SPC export waiver will reduce sales by the European branded medicines in the export markets by 10%.

---

288 Some earlier empirical papers in the US find that originator prices increased post LoE. See for example, Rena M. Conti and Ernst R. Berndt, *Specialty drug prices and utilization after loss of US Patent exclusivity, 2001-2007*, March 2014, NBER Working Paper No. 20016; Caves, R. E., Whinston, M. D. and Hurwitz, M. A. (1991) *Patent expiration, entry, and competition in the US pharmaceutical industry*, Brookings Papers on Economic Activity, Microeconomics, 1–48; Graboski, H. and Vernon, J. (1992) *Brand loyalty, entry and price competition in pharmaceuticals after the 1984 Drug Act*, Journal of Law and Economics, 35(2). More recent papers have found that branded medicines prices do drop somewhat or remain flat following protection expiry in the US, Canada and European markets. See for example Patricia Danzon and Michael Furukawa, *Cross-national evidence on generic pharmaceuticals: pharmacy vs physician driven markets*, NBER WP 17226, July 2011; Atanu Saha, Henry Grabowski, Howard Birnbaum, Paul Greenberg & Oden Bizan (2006), *Generic competition in the US Pharmaceutical industry,* International Journal of the Economics of Business, Vol. 13 (1). This assumption is conservative and would tend to overestimate the sales of branded (including EU branded) products in export markets.

289 For the sources of information on generic penetration in each of the export markets considered, see footnote 258.

290 For example, Atanu Saha et al (2006) based on US data, find a positive relationship between generic penetration and number of generic entrants. Atanu Saha, Henry Grabowski, Howard Birnbaum, Paul Greenberg (2006), *Generic competition in the US Pharmaceutical Industry,* International Journal of the Economics of Business, Vol. 13(1). Grabowski et al (2007) examining the US market, also find a positive relationship between number of generic entrants and the ratio of generic prices post-expiry to branded prices post entry. In particular they find that in the case of one generic entrant, generic prices would be 90% of the price of the branded product, in the case of 3 generic entrants, generic prices would be 75% of the branded price and in the case of 12 generic entrants, generic prices would be 33% of the branded price. Consistently with other papers, they find that as the number of generic entrants increases beyond a certain point, the downward effect on prices is reduced. Henry G. Grabowski, David B. Ridley, and Kevin A. Schulman (2007), "Entry and Competition in Generic Biologics" Managerial and Decision Economics 28 (2007): 439-451. . The EC Pharmaceutical sector inquiry also found that the number of generic entrants had a small positive relationship to the price drop post generic entry. Pharmaceutical Sector Inquiry (2009), Annex to Chapter A – Part 1.

http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part2.pdf

2. Case 2: we assume that the SPC export waiver will reduce sales by European branded medicines in the export markets by 20%.

Given the current high levels of generic competition in these markets, we consider it unlikely that the effect would be higher than a 20% decline in the sales of EU based branded medicines.

Table 31 presents the estimated market size available to branded pharmaceuticals for the sample of molecules considered during the period of SPC protection in Europe, the share that we estimate would be captured by European companies and the decline in sales as a result of the SPC export waiver in each case. The size of the market available to branded producers post protection expiry in the third countries (column [1]) is significantly smaller compared to the size of the market available to generics, as a result of the high average generic penetration in these countries. We estimate the average share that European branded pharmaceuticals achieve in these export markets to be between 14-17%.

Applying the above assumptions on the effect of the SPC export waiver on export sales by European branded medicines in the sample of countries and molecules considered, we arrive at estimated losses between €139 and €278 million by 2025.

Table 31: Potential reduction in export sales by European branded medicines as a result of the SPC export waiver, cumulatively in EUR thousand (based on a sample)

Year	Market size available to branded producers during the period between protection expiry in the third country and SPC protection period in Europe	Estimated sales by European branded pharmaceutical producers during period between protection expiry in the third country and SPC protection period in Europe	Share that European branded pharmaceuticals could achieve in third countries	Reduction in sales assuming 10% decline in sales of EU based branded medicines	Reduction in sales assuming 20% decline in sales of EU based branded medicines
	[1]	[2]	[3]	4 = [2] * 10%	5 = [2] * 20%
2016	3,804,755	637,885	17%	63,789	127,577
2017	5,190,276	824,147	16%	82,415	164,829
2018	5,982,122	929,234	16%	92,923	185,847
2019	6,579,612	1,005,346	15%	100,535	201,069
2020	7,103,357	1,071,338	15%	107,134	214,268
2021	7,876,244	1,159,293	15%	115,929	231,859
2022	8,632,092	1,242,250	14%	124,225	248,450
2023	9,204,855	1,304,740	14%	130,474	260,948
2024	9,635,143	1,353,687	14%	135,369	270,737
2025	9,975,930	1,391,895	14%	139,190	278,379
2026	10,432,277	1,439,601	14%	143,960	287,920
2027	10,913,431	1,486,925	14%	148,692	297,385
2028	11,245,265	1,522,225	14%	152,223	304,445
2029	11,271,596	1,524,342	14%	152,434	304,868
2030	11,271,596	1,524,342	14%	152,434	304,868

Source: CRA analysis on IMS Midas data, Comtrade data and data from EGA

Notes: The years refer to the year of protection expiry for the sample of molecules examined in the following countries: Australia, Brazil, Canada, China, Japan, Russia, Turkey and the US. The sales values shown are *cumulative.* For example, in column [1] the value shown under year 2016 refers to total estimated branded sales for molecules expiring in third countries in 2016 (or earlier if the SPC expiry date in Europe was after 2015) that are still under protection in Europe. The value under year 2017 refers to total estimated branded sales for molecules expiring in third countries in 2016 and 2017 and that are still under SPC protection in Europe, and so on. Similarly the values in column [2] refer to the sales that EEA innovators can achieve in these third countries.

Table 32 presents the additional sales as a result of the SPC export waiver by the European non-biological (generics and branded) pharmaceutical industry taking into account the negative effect on European branded medicines. The net additional sales as a result of the SPC export waiver are estimated to reach €7.3 to €7.4 billion by 2025, depending on assumptions regarding the effect of this measure on sales by European branded pharmaceuticals in these export markets.

Table 32: Additional export sales by the European generic pharmaceutical industry as a result of an SPC export waiver, taking into account potential reduction in sales by EU branded medicines, cumulatively EUR thousand (based on a sample)

Year	Total additional sales to European generic industry as a result of the SPC export waiver	Sales lost by the EU branded pharmaceutical industry due to SPC export waiver (10% reduction in export sales)	Sales lost by the EU branded pharmaceutical industry due to SPC export waiver (20% reduction in export sales)	Net additional sales to the EU non-biological pharmaceutical industry (assuming 10% reduction in export sales by EU branded products)	Net additional sales to the EU non-biological pharmaceutical industry (assuming 20% reduction in export sales by EU branded products)
	[1]	[2]	[3]	[4] = [1] – [2]	[5]=[1] – [3]
2016	2,130,592	63,789	127,577	2,066,803	2,003,015
2017	3,312,134	82,415	164,829	3,229,720	3,147,305
2018	4,624,716	92,923	185,847	4,531,793	4,438,869
2019	5,336,348	100,535	201,069	5,235,813	5,135,279
2020	5,781,445	107,134	214,268	5,674,312	5,567,178
2021	6,219,238	115,929	231,859	6,103,309	5,987,379
2022	6,634,548	124,225	248,450	6,510,323	6,386,098
2023	7,025,585	130,474	260,948	6,895,111	6,764,637
2024	7,341,574	135,369	270,737	7,206,205	7,070,837
2025	7,565,375	139,190	278,379	7,426,186	7,286,996
2026	7,791,830	143,960	287,920	7,647,870	7,503,910
2027	8,058,430	148,692	297,385	7,909,738	7,761,045
2028	8,341,579	152,223	304,445	8,189,356	8,037,134
2029	8,582,936	152,434	304,868	8,430,502	8,278,067
2030	8,652,958	152,434	304,868	8,500,524	8,348,089

Source: Table 20 and Table 31

Effect on the export sales of European biologic innovators

An SPC export waiver enables European biosimilars to start exporting into third countries where there is no corresponding SPC term or where protection has expired earlier, during the period of SPC protection in Europe. By enabling European biosimilars to enter third country markets in a more timely fashion and thereby increasing competition in those markets, an SPC export waiver may result in lower sales by the European reference biologics in these third countries.

The effect on the European innovative industry will depend firstly on the export sales of Eu based reference biologics and secondly on the extent to which the SPC export waiver will result in an increase in the number of biosimilar suppliers in the export markets and the diversion between European reference biologics and biosimilar products.

For the reference biological products the product information page that is available on the EMA website provides information on the name and location of the manufacturer of the active biological substance. We used this information to estimate the share of sales in each third country of the molecules in our sample that would originate in Europe.[291] Last, for the molecules in our sample, we estimate the market size available to originator biologics post protection expiry in the export markets. As discussed above, we have no data to estimate biosimilar penetration in the third country markets, we therefore rely on data on biosimilar penetration in the EU5. As in section 4.5.3 we model two scenarios on biosimilar penetration: a fast penetration case and a slow penetration case. In the fast biosimilar penetration case, the impact on the EU based originator biological pharmaceutical industry is likely to be higher compared to the slow biosimilar penetration case.

Table 33 presents the estimated market size available to all originator biological producers in export markets in the fast penetration and slow penetration case, as well as our estimates on the sales in each case of EU-based originator biologics.

291 In cases where both an EU and a non-EU location was provided in the product information page for the manufacture of the biological active substance, we assumed that 50% of sales of the reference product would be manufactured in the EU and 50% outside the EU. In cases where one of the two manufacturing country was the US, we assumed that US sales of the reference product would be manufactured in the US. Using this method, we estimated that EU-based innovative biologics would achieve the following average share of sales of branded biologicals in the third country markets analysed: Brazil: 34%, Canada: 36%, China: 37%, Japan: 41%, Russia: 92%, US: 36%, Turkey: 100% (only 1 product).

Table 33: Estimated export sales by the EU-based originator biological industry, cumulatively in EUR thousand (based on a sample)

Year	Market size of originator biological medicines during period between protection expiry in third countries and Europe		Sales by EU based originator biological producers during period between protection expiry in third countries and Europe		Share achieved by EU-based originator biologicals in biological sales in export markets	
	Fast biosimilar penetration	Slow biosimilar penetration	Fast biosimilar penetration	Slow biosimilar penetration	Fast biosimilar penetration	Slow biosimilar penetration
2016	8,692,097	11,875,425	3,135,633	4,278,742	36%	36%
2017	11,440,226	15,614,480	4,132,934	5,636,681	36%	36%
2018	17,554,486	23,842,620	6,343,129	8,614,787	36%	36%
2019	20,565,957	28,656,164	7,430,943	10,358,524	36%	36%
2020	21,385,010	29,682,207	7,726,311	10,728,643	36%	36%
2021	22,157,469	30,646,034	8,004,685	11,076,135	36%	36%
2022	22,159,256	30,648,880	8,005,464	11,077,512	36%	36%
2023	22,349,165	30,883,049	8,073,841	11,162,060	36%	36%
2024	22,652,986	31,307,428	8,186,599	11,319,043	36%	36%
2025	22,909,448	31,684,157	8,282,239	11,459,631	36%	36%
2026	23,522,560	32,525,611	8,504,499	11,765,379	36%	36%
2027	23,567,482	32,613,963	8,520,663	11,797,178	36%	36%

Source: CRA analysis on IMS Midas data, Comtrade data and data from EGA

Notes: The years refer to the year of protection expiry for the sample of molecules examined in the following countries: Brazil, Canada, China, Japan, Russia, Turkey and the US. The sales values shown are *cumulative*. For example, the value shown under year 2016 refers to total estimated branded biological sales for molecules expiring in third countries in 2016 (or earlier if the SPC expiry date in Europe was after 2015) that are still under protection in Europe. The value under year 2017 refers to total estimated branded biological sales for molecules expiring in third countries in 2016 and 2017 and that are still under SPC protection in Europe, and so on.

Since the estimated additional export sales by the European biosimilar industry in the slow penetration scenario (presented in Table 27), represent only 4% of the estimated sales of the EU-based originator biological industry, the impact of an SPC export waiver on the EU-based biological (originator and biosimilar) pharmaceutical industry is likely to be small. Assuming that *all* the additional European biosimilar exports identified in the slow penetration scenario would be diverted[292] from export sales by the EU-based originator pharmaceutical industry, there would be no effect of the SPC export waiver to the EU-based biological (originator and biosimilar) industry. However this is an extreme assumption and it is likely that EU-based biosimilars will compete against originator and other biosimilar products produced outside the EU too.

292 In this report the term diversion refers to *shifting sales* from one product to another.

We therefore focus on the effect on the EU based originator biological pharmaceutical industry in the fast biosimilar penetration case. From our discussions with EFPIA we understand that the innovative industry is concerned that an SPC export waiver to third countries would negatively affect sales by the European originator biological industry, particularly in emerging markets that are mainly supplied by European innovators. In our scenario analysis we assume that the negative impact on sales by the European originator biological industry in emerging countries is double the impact in developed countries. We have therefore run the following scenarios regarding the impact of the measure on the European originator biological industry:

1. Case 1: we assume that as a result of the SPC export waiver, export sales by the European originator biological pharmaceutical industry would fall by 10% in developed countries and 20% in emerging countries.
2. Case 2: we assume that as a result of the SPC export waiver, export sales by the European originator biological pharmaceutical industry would fall by 20% in developed countries and 40% in emerging countries.

Table 34 presents the reduction in sales by the European originator biological pharmaceutical industry in export markets as a result of the SPC export waiver for the fast biosimilar penetration scenario under these two cases. We estimate that the SPC export waiver will result in a reduction of export sales by the European originator biologics of €868 million by 2025 in case 1 and €1.7 billion in case 2. The estimated decline in sales by the EU based originator biologics is lower than the estimated additional export sales by the EU based biosimilar industry, because a number of originator biological molecules in our sample are manufactured outside the EU.

Table 34: Potential reduction in export sales by the EU-based originator biological pharmaceutical industry to third countries as a result of the SPC export waiver, fast biosimilar penetration scenario, cumulatively in EUR thousand (based on a sample)

Year	Market size of originator biological medicines during period between protection expiry in third countries and Europe	Sales by EU based originator biological producers during period between protection expiry in third countries and Europe	Reduction in sales by EU-based originator biological medicines – Case 1	Reduction in sales by EU-based originator biological medicines – Case 2
	[1]	[2]	[3] = [2]*{10% for developed; 20% for emerging}	[4] = [2]*{20% for developed; 40% for emerging}
2016	8,692,097	3,135,633	339,190	678,381
2017	11,440,226	4,132,934	442,572	885,143
2018	17,554,486	6,343,129	667,270	1,334,540
2019	20,565,957	7,430,943	780,955	1,561,909
2020	21,385,010	7,726,311	811,484	1,622,967
2021	22,157,469	8,004,685	839,695	1,679,390
2022	22,159,256	8,005,464	839,810	1,679,620
2023	22,349,165	8,073,841	846,828	1,693,657
2024	22,652,986	8,186,599	858,350	1,716,700
2025	22,909,448	8,282,239	868,114	1,736,227
2026	23,522,560	8,504,499	890,449	1,780,899
2027	23,567,482	8,520,663	892,080	1,784,159

Source: Table 33

Notes: The figures relate to the 'Fast penetration' scenario. Case 1 assumes that as a result of the SPC export waiver, export sales by the European originator biological industry would fall by 10% in developed countries and 20% in emerging countries. Case 2 assumes that as a result of the SPC export waiver, export sales by the European originator biological industry would fall by 20% in developed countries and 40% in emerging countries.

Finally, Table 35 presents the net impact of the SPC export waiver on the European biological pharmaceutical industry (originator and biosimilars), by reducing additional sales of the European biosimilar industry by the assumed loss in sales by the European originator biological industry. Based on the assumptions we made regarding the impact to the EU-based originators in the different scenarios, we estimate the net effect of the SPC export waiver on the EU-based pharmaceutical industry as additional sales between €1.2 billion and €2.1 billion in the fast penetration case for the sample of molecules considered.

As discussed above, in the slow biosimilar penetration case the estimated additional export sales by the EU based biosimilar industry represent only a small fraction (4%) of the estimated EU based originator biological sales. Therefore even a small assumed

proportionate change can result in no estimated positive impact effect. We find it unlikely that all additional EU based biosimilar export sales would be diverted from EU based originator biologics. Therefore, for the slow biosimilar penetration scenario, the estimated additional EU biosimilar export sales could be up to a ceiling of €463 million by 2025 (see Table 27) for the sample of molecules and countries analysed.

Table 35: Additional export sales by the European biosimilar pharmaceutical industry as a result of an SPC export waiver, taking into account potential reduction in sales by the EU originator biological industry in the fast penetration scenario, cumulatively in EUR thousand

Year	Additional sales to European biosimilar industry as a result of the SPC export waiver	Lost sales by the European originator biological industry as a result of the SPC export waiver		Net additional sales to the EU biological (originator and biosimilar) pharmaceutical industry	
		Case 1	Case 2	Case 1	Case 2
	[1]	[2]	[3]	[4]=[1]-[2]	[5]=[1]-[3]
2016	1,133,655	339,190	678,381	794,465	455,274
2017	1,465,233	442,572	885,143	1,022,661	580,090
2018	2,154,827	667,270	1,334,540	1,487,557	820,287
2019	2,737,226	780,955	1,561,909	1,956,271	1,175,317
2020	2,805,399	811,484	1,622,967	1,993,915	1,182,432
2021	2,866,626	839,695	1,679,390	2,026,931	1,187,236
2022	2,867,022	839,810	1,679,620	2,027,212	1,187,402
2023	2,882,289	846,828	1,693,657	2,035,461	1,188,632
2024	2,924,086	858,350	1,716,700	2,065,736	1,207,386
2025	2,970,237	868,114	1,736,227	2,102,123	1,234,010
2026	3,046,632	890,449	1,780,899	2,156,183	1,265,733
2027	3,059,492	892,080	1,784,159	2,167,412	1,275,333

Source: Table 27 and Table 31

Notes: The figures relate to the 'fast penetration' scenario. Case 1 assumes that as a result of the SPC export waiver, export sales by the European originator biological industry would fall by 10% in developed countries and 20% in emerging countries. Case 2 assumes that as a result of the SPC export waiver, export sales by the European originator biological industry would fall by 20% in developed countries and 40% in emerging countries.

4.5.5. Assessment of wider impact of the SPC export waiver

In this section we consider the wider impact of an SPC export waiver on incentives to innovate, employment and speed of generic and biosimilar entry.

The proposed measure is unlikely to negatively affect incentives to innovate in Europe as it does not reduce the period of patent or patent term extension either in Europe or outside Europe. Patents and patent extension terms are designed to allow innovative firms a period to recoup and earn a return on the costs of innovation (and compensate for the period lost in delays related to obtaining marketing approval). They are therefore designed to solve the problem of providing incentives to innovate. Since the proposed measure does not enable generic or biosimilar competition *during* the patent or patent extension term but only *after* protection has expired, it cannot be expected to lead to a reduction of incentives to innovate relative to what was intended by the design of the patent and patent extension terms in Europe and other countries. The proposed measure would only negatively affect incentives to innovate if it resulted in generic or biosimilar products destined for export markets to leak into domestic European markets during the period of patent or SPC protection. However, the risk of infringement is likely to dissuade companies from engaging in such activities. Generic entry at risk (i.e. during the period of protection) is possible even without an SPC export waiver and given the infringement risk, it is unlikely that an SPC export waiver will materially increase the incidence of such cases.

The proposed measure is likely to result in increased employment in the European pharmaceutical industry as a result of increased sales by European generic and biosimilar producers. To estimate the potential employment effect associated with the additional sales identified in the previous subsections, we use Eurostat data on production and number of employees in the EU pharmaceutical industry (NACE R2 – Manufacturing of basic pharmaceutical products and pharmaceutical preparations) for the EU28 countries. According to these data in 2013 (the latest year for which data are available) production was €210,523 million and the number of employees was 554,400, resulting in an average production per employee of €379,731.[293] Table 36 calculates the additional workers that correspond to the estimated net additional sales by the European pharmaceutical industry, assuming no change in worker productivity.

The tables below present the calculation of additional jobs in the EU generic industry (Table 36) and EU biosimilar industry in the fast biosimilar penetration scenario (Table 37), assuming no change in worker productivity. In the slow penetration scenario the maximum impact on jobs would be an additional 1,219 jobs by 2025, assuming no change in productivity and no reduction in the sales of EU branded biologics.

As the tables show, in the fast biosimilar penetration scenario, the net additional sales correspond to between approximately 22,400 to 25,000 additional jobs for the non-biologic and biologic pharmaceutical industry (branded as well as generic and biosimilar) by 2025, assuming no change in worker productivity.[294] In the slow biosimilar penetration scenario, the additional jobs in the EU pharmaceutical industry by 2025, would range between the figures presented in Table 36, assuming that all additional EU biosimilar export sales would be diverted from the EU based originator biological industry, to approximately 20,400-20,800 assuming no impact on sales by the EU based originator

293 http://appsso.eurostat.ec.europa.eu/nui/submitViewTableAction.do

294 These are calculated by adding the additional jobs by 2025 presented in Table 36 and Table 37.

biological industry.[295] To put these figures in perspective, according to the EGA the EU generic and biosimilar industry directly employs 160,000 people, therefore an additional 20,000-25,000 jobs represent a 13-16% increase in employment.

Alternatively, the additional sales could increase employment by less, but increase worker productivity. This would still be beneficial to the European economy, as an increase in worker productivity in Europe is likely to positively affect companies' incentives for additional manufacturing investment in the region.

295 The exact figures, assuming no impact to the EU based branded biological industry, are 20,409 to 20,776 additional jobs by 2025 and can be derived by adding the impact on employment of additional sales by the biosimilar industry of €462.9 million (see Table 27), namely 1,216 jobs (€462,938 thousand divided by 380 thousand per employee) to the employment figures shown in Table 36 for year 2025.

Table 36: Implied additional jobs in the EU non-biological (branded and generic) pharmaceutical industry as a result of an SPC export waiver, assuming no change in worker productivity, presented cumulatively (based on a sample)

Year	Cumulative net additional sales to the EU non-biological pharmaceutical industry (10% reduction in export sales by innovators)	Cumulative net additional sales to the EU non-biological pharmaceutical industry (20% reduction in export sales by innovators)	Average production per employee in EU28 pharmaceutical industry (EUR thousand per employee)	Implied additional workers assuming same productivity	Implied additional workers assuming same productivity
	[1]	[2]	[3]	4 = [1] / [3]	5 = [2] / [3]
2016	2,066,803	2,003,015	380	5,443	5,275
2017	3,229,720	3,147,305	380	8,505	8,288
2018	4,531,793	4,438,869	380	11,934	11,690
2019	5,235,813	5,135,279	380	13,788	13,523
2020	5,674,312	5,567,178	380	14,943	14,661
2021	6,103,309	5,987,379	380	16,073	15,767
2022	6,510,323	6,386,098	380	17,145	16,817
2023	6,895,111	6,764,637	380	18,158	17,814
2024	7,206,205	7,070,837	380	18,977	18,621
2025	7,426,186	7,286,996	380	19,556	19,190
2026	7,647,870	7,503,910	380	20,140	19,761
2027	7,909,738	7,761,045	380	20,830	20,438
2028	8,189,356	8,037,134	380	21,566	21,165
2029	8,430,502	8,278,067	380	22,201	21,800
2030	8,500,524	8,348,089	380	22,386	21,984

Source: Eurostat (average production per employee); Table 32

Table 37: Implied additional jobs in the EU biological (originator and biosimilar) pharmaceutical industry as a result of an SPC export waiver, assuming no change in worker productivity (fast biosimilar penetration scenario), presented cumulatively (based on a sample)

Year	Cumulative net additional sales to the EU biological (originator and biosimilar) pharmaceutical industry		Average production (EUR thousand per employee)	Implied additional workers assuming same productivity	
	Case 1	Case 2		Case 1	Case 2
	[1]	[2]	[3]	[4] = [1] / [3]	[5] = [2]/ [3]
2016	794,465	455,274	380	2,092	1,199
2017	1,022,661	580,090	380	2,693	1,528
2018	1,487,557	820,287	380	3,917	2,160
2019	1,956,271	1,175,317	380	5,152	3,095
2020	1,993,915	1,182,432	380	5,251	3,114
2021	2,026,931	1,187,236	380	5,338	3,127
2022	2,027,212	1,187,402	380	5,339	3,127
2023	2,035,461	1,188,632	380	5,360	3,130
2024	2,065,736	1,207,386	380	5,440	3,180
2025	2,102,123	1,234,010	380	5,536	3,250
2026	2,156,183	1,265,733	380	5,678	3,333
2027	2,167,412	1,275,333	380	5,708	3,359

Source: Eurostat (average production per employee); Table 35

Notes: The figures relate to the 'fast penetration' scenario. Case 1 assumes that as a result of the SPC export waiver, export sales by the European originator biological industry would fall by 10% in developed countries and 20% in emerging countries. Case 2 assumes that as a result of the SPC export waiver, export sales by the European originator biological industry would fall by 20% in developed countries and 40% in emerging countries.

In addition to the employment benefits identified above, an SPC export waiver to third countries is likely to increase incentives of generic and biosimilar companies to invest in manufacturing facilities in Europe, as the SPC term in Europe will no longer preclude EU-based firms from competing in markets where the protection has expired (or did not exist in the first place). In the case of biosimilars, since R&D facilities are located near advanced manufacturing facilities, this could also increase R&D investment.

As discussed in section 4.4.3, the combination of an SPC export waiver with an extension of the Bolar exemption to cover the third party supply of APIs within Europe is likely to result in additional EU based API sales and employment.[296]

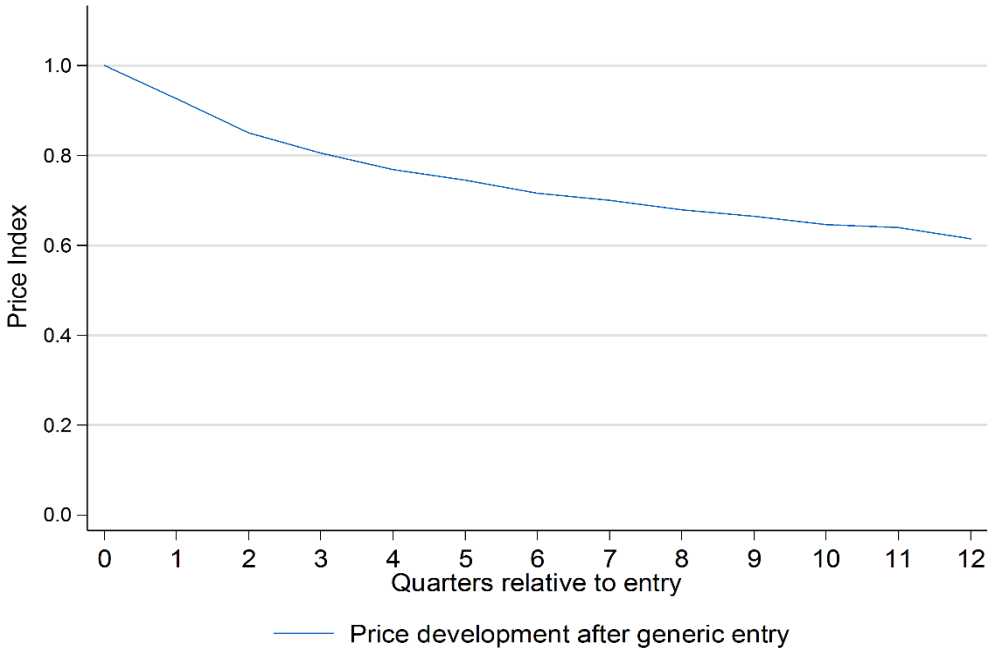
296 The effect on EU based API sales and jobs is presented in Table 14 and Table 17.

A manufacturing export waiver during the SPC term could additionally result in speedier entry of European generics and biosimilars following protection expiry in the EU markets. A biosimilar or generic manufacturer based in Europe who has already set up large scale manufacturing for export would be ready to start selling in the domestic market upon SPC expiry, compared to a manufacturer that is only allowed to start large scale production after the SPC expiry in his domestic market. The benefit could be particularly important for biosimilars, as scaling up production is more complex and consequently requires more time.

A more timely entry by generics and biosimilars can be expected to reduce spending on pharmaceuticals and thus public healthcare costs, as generic and (to a lesser extent) biosimilar entry results in lower prices. Based on generic and biosimilar entry events during our sample period for the EEA countries covered by the IMS data available to us, we have examined the average decline in molecule prices following generic and biosimilar entry relative to prices that prevailed before generic or biosimilar entry.

Following generic entry we find that average prices (weighted average across generics and branded) decline by 15% in the second quarter following entry and by 23% in the 4th quarter following entry. Prices continue to fall thereafter at a declining pace. We estimate that by the end of the three years following generic entry, market prices on average across the EEA countries in our sample are almost 40% lower.[297]

Figure 14: Average price reductions following generic entry, based on generic entry events during the period 2008Q1 to 2014Q3 in EEA countries



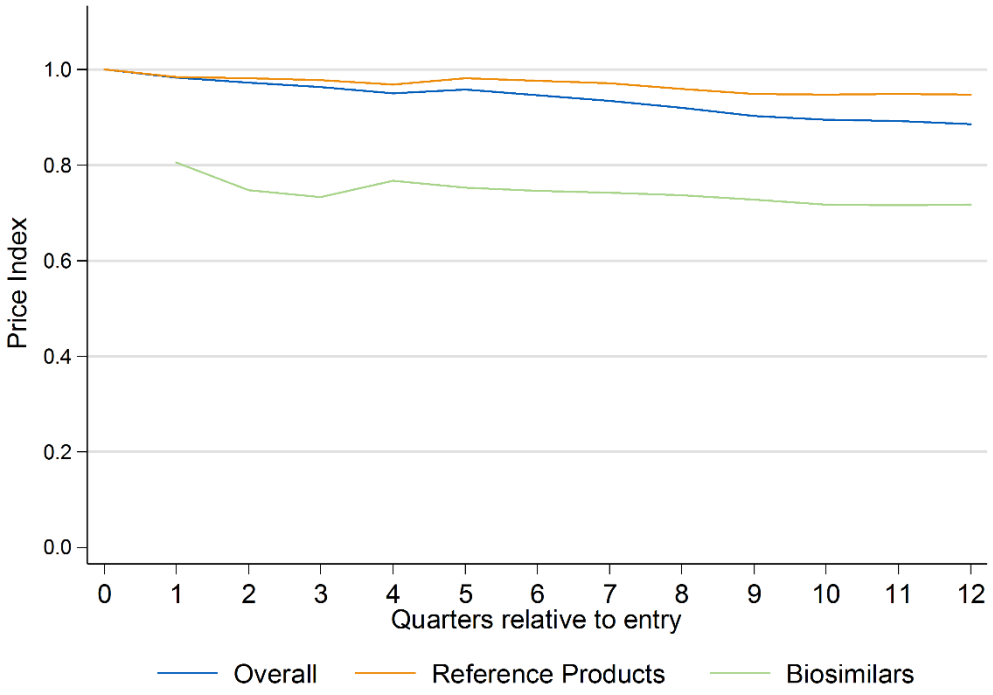
Source: CRA analysis on IMS Midas data

297 These findings are broadly consistent with the findings of the 2009 Pharma Sector Inquiry. The discount figures reported there related to generic prices only, whereas the figures presented above are weighted averages of branded and generic products post entry. During our sample period, generic entry events were observed in the following EEA countries: Austria, Belgium, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden, UK.

Following biosimilar entry we observe a decline in weighted average market prices but the decline is less pronounced than that observed following generic entry.[298] By the second quarter after entry, the average price at the molecule level (including only biosimilar and reference products) is 3% below the pre-entry price. This discount increases to 5% at a year after entry and 10% three years after entry. In the figure below we also present the price development of the biosimilar and reference products following biosimilar entry. Upon entry biosimilars are priced at an average 20% discount relative to the pre-biosimilar entry price of the reference product and the discount increases over time to an average of almost 30% in the third year. The price of the reference product declines marginally following biosimilar entry.

The lower effect of biosimilar entry on market prices relative to generics is the result of the lower penetration of biosimilars, and the lower discounts of biosimilars to their reference products relative to generics. If biosimilar penetration was higher, the savings would be more pronounced.

Figure 15: Average price reductions following biosimilar entry, based on biosimilar entry events during the period 2008Q1 to 2014Q3 in EEA countries



Source: CRA analysis on IMS Midas data

298 Biosimilar entry events were observed in the following EEA countries: Austria, Belgium, Bulgaria, Croatia, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK.

For illustrative purposes we estimate the effect on pharmaceutical expenditures if, as a result of an SPC export waiver, delays in generic entry were reduced for the molecules in our sample with later EU SPC expiry dates.[299] The following assumptions are made:

- **Generics**: we estimate expenditures if generic entry for these molecules occurred in the EEA *immediately* following protection expiry as a result of the SPC export waiver compared to expenditures if generic entry occurred: i) in the third quarter following protection expiry (the EU average delay for generics is 8.2 months); ii) in the second quarter following protection expiry, assuming delays will reduce in the future, without an SPC export waiver.
- **Biosimilars:** we estimate expenditures if biosimilar entry for these molecules in the EEA occurred 6 months following SPC protection expiry with an SPC export waiver compared to1 year without an SPC export waiver.[300]

Our estimates of the savings on pharmaceutical expenditures for the sample of molecules, summarised in Table 19, if generic entry was immediate range between €1.6 billion to €3.1 billion over a three year period or a 4% to 8% saving relative to expenditures with generic entry in the 2nd or 3rd quarter following protection expiry.[301] We estimate savings on pharmaceutical expenditures, for the sample of molecules summarised in Table 25, if the delay in biosimilar entry was 6 months following protection expiry relative to 1 year without an SPC export waiver to amount to €0.6 billion or a 2% saving.[302] These savings are presented graphically in the figures below.

Figure 16 considers the savings for the sample of molecules considered if generic entry as a result of the SPC export waiver was immediate, relative to generic entry occurring in the 3rd quarter. The green area represents the savings if generic entry occurred in the third quarter following protection expiry, while the orange area represents the additional savings if generic entry was immediate. Volumes are assumed fixed at pre-protection expiry levels, therefore the savings presented are entirely due to the faster reduction in market prices from generic entry.

Figure 17 plots the savings from immediate generic entry if generic entry without an SPC export waiver occurred in the 2nd quarter following protection expiry, while Figure 18 plots the savings from biosimilar entry occurring 6 months following protection expiry relative to the savings if biosimilar entry occurred 1 year later.

---

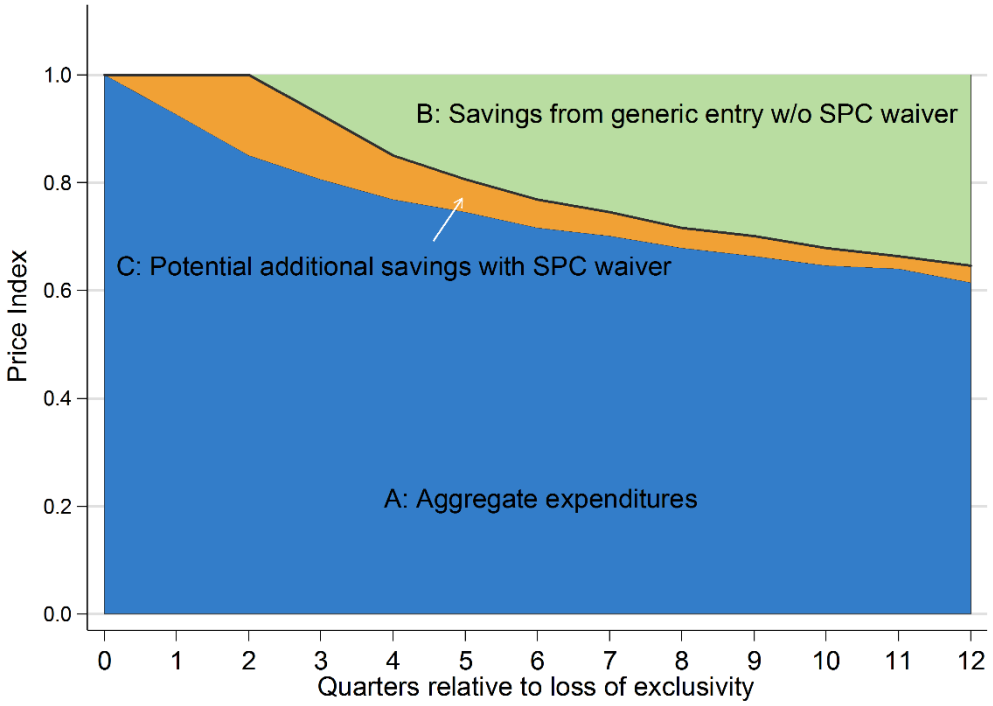
299 We focus on those molecules in our sample whose SPC protection expires in Europe until 2025, i.e. a 10 year period. We estimate expenditures for three years following protection expiry in Europe. So e.g. for a molecule whose SPC expires in Europe in January 2017 we consider expenditures over the period January 2017 to December 2019.

300 As indicated in Table 24 delay in biosimilar entry has reduced over time.

301 Assuming generic entry occurs in the 3rd quarter following protection expiry, we estimate expenditures of €40 billion on the sample of molecules (with later SPC expiries in Europe compared to one of the third countries considered) over a 3 year period. Assuming generic entry occurs in the 2nd quarter following protection expiry we estimate expenditures of €38.4 billion. It should be emphasised that these absolute expenditure amounts are based on a sample of molecules. These expenditures have been calculated assuming constant volumes at pre-generic entry levels.

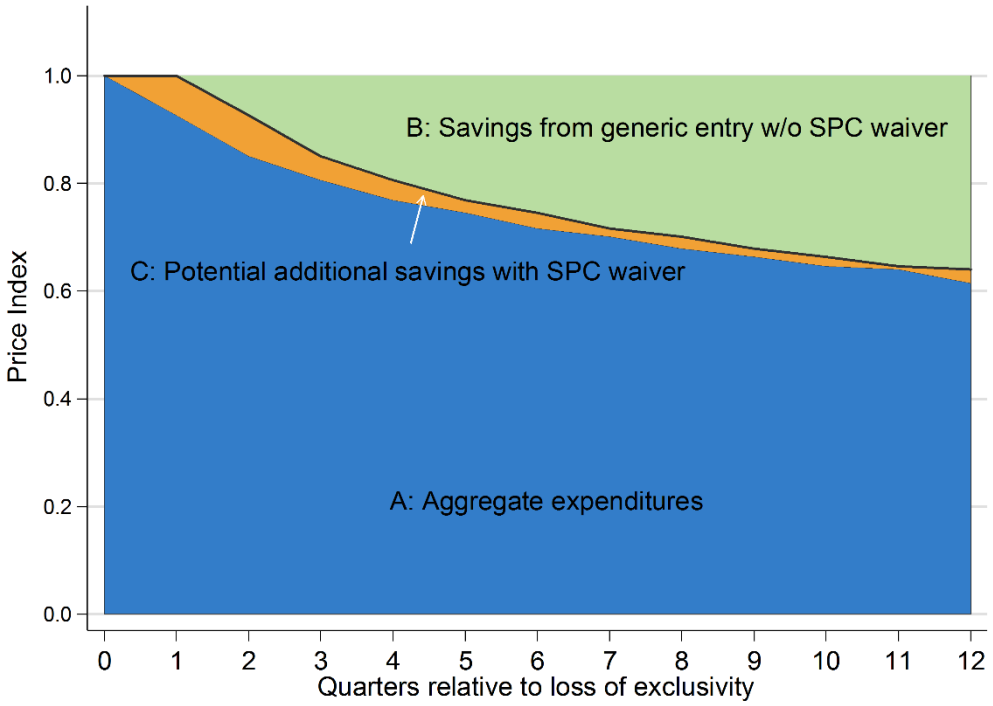
302 For the sample of molecules considered, we estimate three year expenditures of €34.4 billion assuming biosimilar entry one year following protection expiry (at constant pre-protection expiry volumes). Again it should be emphasised that this absolute expenditure amount is based on a sample of biological molecules with later SPC expiry dates in Europe relative to the third countries considered in our analysis.

Figure 16: Illustration of savings if generic entry was immediate relative to hypothetical delay of 3 quarters



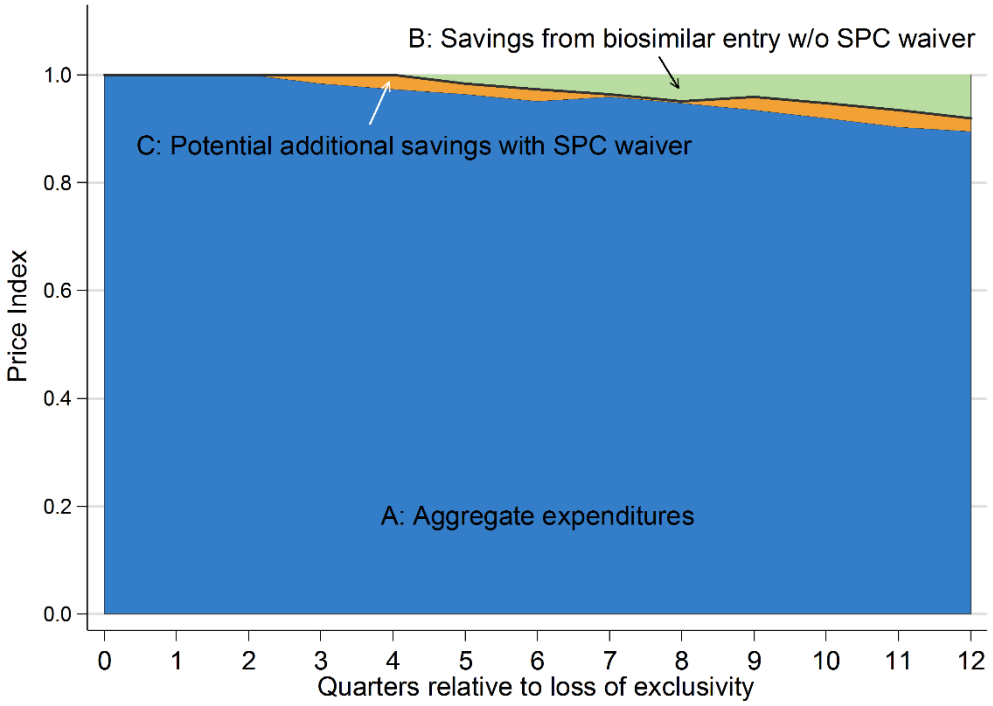
Source: CRA analysis on IMS Midas data

Figure 17: Illustration of savings if generic entry was immediate relative to hypothetical delay of 2 quarters



Source: CRA analysis on IMS Midas data

Figure 18: Illustration of savings if biosimilar entry was delayed by 6 months relative to hypothetical delay of 1 year



Source: CRA analysis on IMS Midas data

These savings are illustrative as they assume that the entire delay in generic and a large part of the delay in biosimilar entry is the result of preparing for large scale production. As explained above and as discussed in more detail in section 4.7.2, the timing of generic and biosimilar entry depends on a number of factors including expected profitability, delays associated with pricing and reimbursement negotiations, demand and supply side policies to promote the take up of generics and biosimilars as well as preparing stocks to enter a local market (as e.g. labelling requirements differ). Our estimates should therefore be considered as illustrative only. In the case of biosimilars, should biosimilar penetration increase in the future, savings from biosimilar entry would be more pronounced compared to the above estimates. It should also be noted that the generic and biosimilar price decay is based on IMS Midas data and does not reflect rebates and other discounts offered by pharmaceutical companies to e.g. hospitals, which can be significant.

4.5.6. Effect of Unitary Patent Protection and Unitary Patent Court

The Unitary Patent should not have an impact on the benefits from an SPC export waiver. However, in the situation without an SPC export waiver, a Unitary SPC may put at disadvantage the generic manufactures operating in Member States with earlier protection expiry dates.

4.6. Scenario 5: Allowing manufacturing of SPC protected medicines in protected (domestic) markets for purposes of selling to other EU Member States where the corresponding patent or SPC has expired

In this subsection we consider the potential effects of allowing manufacturing of SPC protected medicines in protected markets for purposes of selling to other EU Member States where the corresponding patent or SPC has expired or never existed. As mentioned in section 3 above, the way the SPC term is calculated minimises differences among Member States in protection expiry dates for the same medicine that result from differences in national patent filing dates. Thus, in principle, there may be limited possibilities for exporting to another Member State where the SPC term has expired earlier. In practice though, differences in protection expiry dates across Member States can and do arise due to either differences between Member States with respect to when the SPC regulation became effective or due to innovators choosing not to apply for a patent or SPC protection in certain Member States or if the SPC term lapses, e.g. because the annual fees were not paid.

4.6.1. Issue

As a result of these differences in SPC term expiries across EU Member States, generic and biosimilar producers with manufacturing facilities in a Member State where the SPC is still valid are precluded from supplying another European Member State where there is no SPC protection (either because it has expired, lapsed or was never granted in the first place). They might therefore be placed at a disadvantage compared to generics or biosimilar producers with manufacturing locations outside Europe.

In the next subsection (4.6.2) we consider the effect of this measure on the European pharmaceutical industry (both the generic[303] and innovative industry), in section 4.6.3 we consider the wider impact on incentives to innovate, employment and speed of generic entry, while in section 4.6.4 we consider the impact of the introduction of the UPP and UPC.

4.6.2. Assessment of potential effect on the European pharmaceutical industry

Testing hypothesis

The testing hypothesis is that an SPC export waiver within Europe would result in increased sales by European generics and biosimilar producers, as they could start manufacturing for export to EU Member States where the SPC has already expired. The effect on the European generic and biosimilar manufacturing industry is likely to be less significant compared to the effect of an SPC export waiver to third countries for the following reasons:

- There are likely to be relatively few opportunities in Europe as SPC terms are calculated to remove any differences in protection expiry dates within Europe.
- The size of individual European Member States is smaller relative to large export markets such as US, China, Brazil, Russia etc.
- Increased imports from other EU Member States are likely to reduce sales into these markets by EU innovative and generic/biosimilars manufacturers that can

303 As explained further below, the IMS data do not report protection expiry dates for biological molecules, therefore we cannot estimate the effects of an SPC export waiver within Europe for the European biosimilar industry.

already supply these markets (either domestic producers or those located in Member States where there is no protection expiry).

- The European innovative industry could respond to such a measure by choosing to apply for SPCs in all Member States to reduce the scope of such a measure.[304]

Methodology

To assess the potential effect on the European pharmaceutical industry, we use a similar methodology to the one described in section 4.5.3.

1. Using IMS Midas data, we first selected molecules whose SPC term expires over the next 15 years (2016-2030) in any of the top 10 EU pharmaceutical producing countries[305] and expires at least a year later in another top 10 EU country.[306] For each of these molecules we obtained the sales value (in EUR) and volume (in standard units) for the 12 month period ending 2014Q3, in the country (-ies) where the protection expired earlier.
2. Secondly, we estimated for each molecule and importing country the lost sales to European generics manufacturers during the SPC term, by:
    a. Estimating for each molecule/country the market size that would become available to generics producers once the molecules became off patent in the importing Member States. We used the average generic share in that country 1, 2 and 3 years since protection expiry calculated on the basis of available IMS data.
    b. Estimating the share that European generics producers could achieve in these markets if they entered the third markets during the first year of protection expiry, i.e. under the SPC export waiver. As a proxy for the share that European generics could achieve in sales in the EU importing Member States we used the ratio of imports of generic pharmaceuticals in that country from each of the remaining top 10 European pharmaceutical producing Member States (obtained from trade statistics)

304 Differences could in principle still arise in the interim because the SPC regulation was only introduced more recently in Member States that joined the EU later.

305 The top 10 European pharmaceutical producing countries are: Germany, Italy, France, Ireland, UK, Spain, Denmark, Belgium, Sweden and the Netherlands. As the IMS Midas data did not cover Denmark, in the analysis we substitute Denmark with Poland, the next largest pharmaceutical manufacturing country in Europe.

306 These top 10 countries by pharmaceutical production value accounted for 86% of EEA generic pharmaceutical sales and 87% of biosimilar EEA pharmaceutical sales.

divided by generic pharmaceutical sales in that country (based on IMS data).[307]

3. Thirdly, we estimated the additional sales that European generics could achieve in the export Member States following the protection expiry in their domestic market as a result of the first mover advantage (based on the findings of the analysis presented in Appendix C). Additional sales arising from the first mover advantage were estimated for two years following the protection expiry in the domestic market.

4. Fourthly an adjustment was made to account for the possibility that the increased sales by some European generics producers under an SPC export waiver within Europe would be at the expense of other European innovative and generics producers that could already supply the Member States with earlier SPC expiries. Since we do not have the data to estimate the diversion of sales from other European vs non-European producers, we run the following scenarios:

    a. Scenario 1: 20% of additional estimated sales are diverted from other European suppliers

    b. Scenario 2: 40% of additional estimated sales are diverted from other European suppliers

    c. Scenario 3: 60% of additional estimated sales are diverted from other European suppliers

We consider that Scenario 2 is already quite pessimistic and that Scenario 3 is very pessimistic. However even under these pessimistic scenarios we identify a net positive impact.

In this analysis we do not separately estimate sales of European branded pharmaceuticals for the molecules in our sample, as we do not have data on domestic sales of EU-based branded pharmaceuticals.[308] Therefore we report a total diversion from other European pharmaceutical producers under the above assumptions, not differentiating between diversion from other EU generics or branded manufacturers.

---

307 Therefore we assumed that the share of generic sales that a German generic producer could achieve in France was equal to the share of generic sales in France accounted for by generic imports from Germany. Trade statistics do not separate out generics/biosimilars from originator products. To estimate imports of generic/biosimilars in each importing Member State, we assumed that the ratio of imported generics/biosimilars to originator products was the same as the ratio of generic pharmaceutical sales to originator sales in the importing country (calculated on the basis of IMS data). To avoid the inclusion of raw and intermediate products imported from the EEA and further processed in these countries we only examined HS codes that related to products packed for retail sale (HS 3001, 3002, 3004). Because there is significant trade activity within Europe as products pass through borders for processing before their final sale, we encountered some cases where imports exceeded domestic pharmaceutical sales. This was the case for Belgium and the Netherlands. Therefore we have excluded these two countries as potential destinations for other EEA countries' exports, though we do include them when considering them as potential exporting countries (e.g. for molecules whose SPC in these countries expire later compared to other Top 10 European pharmaceutical producing countries).

308 By EU-based pharmaceutical producers, we mean those who manufacture the branded products in our sample in European facilities.

We undertake this analysis on non-biologic molecules, because IMS data do not report protection expiry dates for biological molecules[309], therefore the analysis cannot be conducted for biosimilar molecules.

Generics

Table 38 presents some descriptive statistics for the sample of molecules used in our analysis for the top 10 European pharmaceutical producing countries. For each country the table shows the number of molecules which have a *later* SPC expiry date in that country compared to at least another top 10 European pharmaceutical producing country, as well as the average delay in years. As the table shows, the average delay ranges between 2.2 years for Belgium to 3.6 years for Ireland.

Table 38: Descriptive statistics for a sample of molecules used in analysing the impact of an SPC export waiver

Country	Number of molecules with later SPC expiry in the particular country	Average number of years of delay
Belgium	26	2.2
France	43	2.6
Germany	39	2.9
Ireland	46	3.6
Italy	55	3.3
Netherlands	41	3.2
Poland	26	3.0
Spain	49	3.1
Sweden	50	3.2
UK	42	2.7

Source: CRA analysis on IMS and EGA data

Table 39 presents our estimates of the additional export sales that European generics could capture under an SPC export waiver within Europe, composed of the lost export sales during the period between the protection expiry in the EU Member State with the earlier protection expiry and protection expiry in the 'domestic' market (column [2] in Table 39) plus the first mover advantage that European generic producers would sustain post SPC expiry as a result of entering those markets earlier (column [3] in Table 39). These figures assume no reaction to this measure by the European branded pharmaceutical industry. Moreover, the figures in this table do not yet adjust for the diversion that could occur from other European suppliers. This adjustment is presented in Table 40 for the additional sales during the period of SPC protection in the 'domestic' markets (column [2] of Table 39) and in Table 41 for the total additional sales, i.e.

309 IMS data only report patent expiry dates for biological molecules.

including the estimate of additional sales due to the first mover advantage 2 years following the SPC expiry date in the country with a later SPC expiry.

As the table shows, by 2025 the market size available to generics coming off patent earlier within at least one of the top 10 European countries analysed amounts to €2.6 billion and by 2028 to €2.8 billion. Of this, we estimate that generics producers from the remaining top 10 European countries with later SPC expiries will be able to capture €339.2 million by 2025, going up to €371.2 million by 2028, making no adjustments for diversion of sales from other European producers already selling into these markets. The additional sales that European generics could achieve in no longer protected Member States two years following the SPC expiry in the domestic Member State are estimated to reach €180.6 million by 2025 and €274.4 million by 2028. The total additional sales taking into account the lost sales during the SPC protection period and the additional sales that European generics can achieve due to the first mover advantage of earlier entry, two years following SPC expiry in Europe are estimated to reach €519.8 million by 2025 and €645.6 million by 2028, making no adjustments for diversion of sales from other European pharmaceutical producers already selling into these markets.

Table 40 presents the estimated additional sales during the period 'lost' as a result of the SPC term (excluding the first mover advantage) by making assumptions about the diversion from other European pharmaceutical producers. Table 41 presents the same estimates, including the first mover advantage due to earlier entry, calculated for two years since the later protection expiry.

Table 40 shows that assuming a 20% diversion reduces the additional European pharmaceutical sales related to the delay in entering the export market by 2025 from €339.2 million €271.6 million, assuming a 40% diversion reduces the additional sales by 2025 to €203.6 million and in the pessimistic scenario, assuming a 60% diversion reduces the additional sales to €135.6 million by 2025.

Table 41 shows that assuming a 20% diversion reduces the total additional European pharmaceutical sales by 2025 from €519.8 million to €415.8 million, assuming a 40% diversion reduces the additional sales by 2025 to €311.9 million and in the pessimistic scenario, assuming a 60% diversion reduces the additional sales to €207.9 million by 2025.

Table 39: Additional export sales to other EU Member States by European generics manufacturers under the current SPC regime, cumulative in EUR million (without adjusting for diversion), (based on a sample)

Year	Estimated generic sales during the period between protection expiry in the no longer protected Member State and SPC protection period the protected Member State	Additional export sales by European generics during period between the later and earlier protection expiry date	Additional sales post later SPC expiry in due to first mover advantage relative to status quo (calculated 2 years since protection expiry)	Total additional sales due to the SPC export waiver
	[1]	[2]	[3]	[4] = [2]+[3]
2016	85.1	10.6	2.2	12.8
2017	256.2	32.7	6.5	39.2
2018	533.7	63.7	12.9	76.6
2019	899.8	102.1	23.5	125.6
2020	1,382.5	144.4	40.7	185.1
2021	1,723.5	186.5	65.5	252.0
2022	2,023.6	227.6	103.1	330.7
2023	2,212.5	260.4	142.6	403.0
2024	2,384.9	299.5	166.6	466.1
2025	2,571.3	339.2	180.6	519.8
2026	2,729.9	365.7	207.7	573.4
2027	2,790.2	370.2	247.2	617.4
2028	2,827.1	371.2	274.4	645.6

Source: CRA analysis on IMS Midas data and data from EGA

Table 40: Additional export sales captured by European generics producers during the period between the earlier and later SPC expiry, after adjusting for diversion from other European producers, cumulative in EUR million (based on a sample)

Year	Additional sales resulting from SPC export exemption during period between earlier and later SPC term in Europe	Scenario 1: 20 % of Total sales diverted from other European manufacturers	Scenario 2: 40 % of Total sales diverted from other European manufacturers	Scenario 3: 60 % of Total sales diverted from other European manufacturers *(pessimistic)*
	[1]	[2] = [1] *(1-20%)	[3] = [1] *(1-40%)	[4] = [1]*(1-60%)
2016	10.6	8.5	6.4	4.2
2017	32.7	26.2	19.7	13.0
2018	63.7	51.0	38.3	25.4
2019	102.1	81.8	61.4	40.8
2020	144.4	115.7	86.8	57.7
2021	186.5	149.4	112.0	74.5
2022	227.6	182.3	136.6	90.9
2023	260.4	208.5	156.3	104
2024	299.5	239.8	179.8	119.7
2025	339.2	271.6	203.6	135.6
2026	365.7	292.8	219.5	146.2
2027	370.2	296.4	222.2	148
2028	371.2	297.2	222.8	148.4

Source: CRA analysis based on IMS Midas data and Comtrade import statistics

Table 41: Total additional export sales captured by European generics producers, after adjusting for diversion from other European pharmaceutical producers, cumulative in EUR million (based on a sample)

Year	Total additional sales resulting from SPC export exemption	Scenario 1: 20 % of Total sales diverted from other European manufacturers	Scenario 2: 40 % of Total sales diverted from other European manufacturers	Scenario 3: 60 % of Total sales diverted from other European manufacturers *(pessimistic)*
	[1]	[2] = [1] *(1-20%)	[3] = [1] *(1-40%)	[4] = [1]*(1-60%)
2016	12.8	10.2	7.7	5.1
2017	39.2	31.4	23.5	15.7
2018	76.6	61.3	46.0	30.6
2019	125.6	100.5	75.4	50.2
2020	185.1	148.1	111.1	74.0
2021	252	201.6	151.2	100.8
2022	330.7	264.6	198.4	132.3
2023	403	322.4	241.8	161.2
2024	466.1	372.9	279.7	186.4
2025	519.8	415.8	311.9	207.9
2026	573.4	458.7	344.0	229.4
2027	617.4	493.9	370.4	247.0
2028	645.6	516.5	387.4	258.2

Source: CRA analysis based on IMS Midas data and Comtrade import statistics

As discussed above, it is possible that should such a measure be implemented, the European branded pharmaceutical industry will respond by increasing the coverage of SPC protection across Member States in Europe, particularly for products with high sales. Such a response would be possible only for products for which differences in SPC protection terms were the result of an action or lack of action by the innovator (e.g. not to apply for or renew an SPC). In cases where differences in SPCs arise from differences in the coming into force of the SPC regulation (e.g. for countries that joined the EU later), a response would not be possible.

Assuming that half of the molecules in our sample, those with the largest sales in the top 10 EU pharmaceutical manufacturing countries, no longer have differences in SPC expiry terms as a result of the branded pharmaceutical industry's response, additional estimated sales by 2025 would fall to €11.8 million in the pessimistic scenario assuming a 60% diversion, €17.8 million assuming 40% diversion and €23.7 million assuming 20% diversion. This illustration is pessimistic as it is likely that already innovators ensure full SPC coverage for their highest selling products.

If the branded pharmaceutical industry responded by increasing the coverage of SPC protection to more European Member States to avoid instances where generic producers from protected Member States could manufacture domestically to supply no longer protected Member States, it would incur additional costs in the form of SPC renewal fees. Table 42 presents SPC annual renewal fees for each of the top 10 European manufacturing countries in our sample. Assuming that an SPC export waiver within Europe resulted in innovative firms increasing coverage of SPC protection for half of the molecules analysed (55 of the 110 molecules) to at least one more European Member State, the additional costs from SPC renewal fees would range between €36,135 (Poland) and €915,750 (Germany). The additional costs related to renewal fees are not significant (relative to the estimated additional generic sales). There could be additional costs in the form of employee time required to implement these SPC applications/renewals but we do not have data to estimate these. However it is unlikely that the costs to the innovative industry would exceed the additional estimated generic sales.

Table 42: Illustration of costs of SPC renewal fees to the branded pharmaceutical industry for 55 molecules in EUR

SPC renewal fees	Year 1	Year 2	Year 3	Year 4	Year 5	Total 5 year	Cost of SPC renewal fees
Belgium	650	700	750	800	850	3,750	206,250
France	940	940	940	940	940	4,700	258,500
Germany	2,650	2,940	3,290	3,650	4,120	16,650	915,750
Ireland	468	468	468	468	468	2,340	128,700
Italy	1,011	1,011	1,011	1,011	1,011	5,055	278,025
Netherlands	1,600	1,800	2,000	2,200	2,400	10,000	550,000
Poland	131	131	131	131	131	657	36,135
Spain	812	1,705	2,688	3,768	4,957	13,930	766,167
Sweden	1,068	1,068	1,068	1,068	1,068	5,339	293,645
UK	826	964	1,102	1,239	1,377	5,508	302,913

Source: National patent office websites; www.oanda.com for exchange rate data

Notes: For non-EUR countries, fees were converted to EUR using the average 2015 annual exchange rate as reported by www.oanda.com.

From our discussions with EFPIA we understand that the innovative industry is concerned that an SPC export waiver within Europe would result in a risk of leakage of products into protected markets and that this risk is higher within Europe due to the operation of a single market with no customs controls. Since selling into a protected market would constitute a patent infringement, the risk of litigation may dissuade companies from engaging in such activities. Moreover, since there are already Member States where products are not covered by an SPC protection and can therefore be legally produced

there, the risk of such leakage is already present, even without an SPC export waiver.[310] It is unclear by how much the risk increases with an SPC export waiver within Europe.

Caveats

The following caveats apply to the foregoing analysis:

- The proxy that we used for the share that European generics could achieve in other Member States where the protection has expired is imperfect. This is because it relies on aggregate data and assumptions about the share of generics in import statistics, whereas the share that European generic producers can achieve in export markets depends on a number of factors, including domestic production capacity in the export market, number of other potential suppliers etc. However, based on our research and discussions with the industry there are no reliable public data that could be used as alternative proxies. In the circumstances therefore, we consider it as an adequate proxy.
- Due to lack of data on the diversion of sales from other European branded or generics producers, we relied on scenarios for our analysis. The results are sensitive to the assumed diversion.
- Due to lack of data, the above analysis does not quantify the additional sales that could accrue to biosimilar producers. Due to the costs of relocating production for biosimilars, such a measure can be expected to be particularly beneficial for EU-based biosimilar producers.[311]

4.6.3. Assessment of wider impact of the SPC export waiver within Europe

In this section we discuss the potential impact of an SPC export waiver within Europe on incentives to innovate, employment and generic and biosimilar entry.

Since the SPC export waiver will enable sales by generic and biosimilar producers to those European countries where the SPC has expired or did not exist in the first place, incentives to innovate should not in principle be affected, as the measure will not result in a reduction in the term of patent or SPC protection of originator products. Incentives to innovate could be adversely affected if the measure results in generic and biosimilar products destined for markets without protection to be diverted to protected markets. However, as discussed above, since already there are Member States where products can be legally produced as there is no SPC protection, it is unclear by how much an SPC export waiver could increase such a risk.

In the previous section we estimated the additional sales to European generic manufacturers of an SPC export waiver within Europe under different assumptions regarding the diversion from other European generic and branded producers. In particular, assuming no reaction to this measure by the EU based branded pharmaceutical industry, we estimated cumulative additional sales between €207.9 million and €415.9 million by 2025, depending on what assumptions are made about the degree

310 For example consider a product that is not protected in Slovenia but is protected in other EU Member States. A generic company based in Slovenia could legally be producing this product for sale to the domestic market. Therefore if there is a risk of leakage into other protected Member States, it would already be present even without an SPC export waiver.

311 Should the innovative pharmaceutical industry respond to such a measure by increasing the SPC coverage across Member States, the scope of such a measure would be reduced.

of diversion from other European generic and branded pharmaceutical manufacturers. To estimate the potential employment effect associated with the additional sales identified in the previous subsections, we use Eurostat data on production and number of employees in the EU pharmaceutical industry (NACE R2 – Manufacturing of basic pharmaceutical products and pharmaceutical preparations) for the EU28 countries. According to these data in 2013 (the latest year for which data are available) production was €210,523 million and the number of employees was 554,400, resulting in an average production per employee of €379,731.[312] Table 43 calculates the additional workers that correspond to the estimated additional sales by the European pharmaceutical industry, assuming no change in worker productivity. The additional sales correspond to between 548 and 1,095 jobs by 2025. These relate to the generic industry only as we do not have data to calculate the effect of such a measure to the European biosimilar industry.

Alternatively the additional sales could increase employment by less but increase worker productivity. This will still be beneficial to the European economy as an increase in worker productivity in Europe is likely to positively affect companies' incentives for additional manufacturing investment in the region.

The employment benefits identified below could be reduced assuming a reaction by the branded pharmaceutical industry to remove differences in SPC protection across Europe.

312 http://appsso.eurostat.ec.europa.eu/nui/submitViewTableAction.do

Table 43: Implied additional jobs in the EU pharmaceutical industry as a result of an SPC export waiver within Europe, assuming no change in worker productivity, presented cumulatively (based on a sample)

Year	Total additional sales resulting from SPC export exemption (EUR million)			Production per employee (EUR thousand per employee) EU28	Additional employment assuming no change in average productivity		
	20% diversion	40% diversion	60% diversion		20% diversion	40% diversion	60% diversion
2016	10.2	7.7	5.1	380	27	20	13
2017	31.4	23.5	15.7	380	83	62	41
2018	61.3	46.0	30.6	380	161	121	81
2019	100.5	75.4	50.2	380	265	198	132
2020	148.1	111.1	74.0	380	390	292	195
2021	201.6	151.2	100.8	380	531	398	265
2022	264.6	198.4	132.3	380	697	523	348
2023	322.4	241.8	161.2	380	849	637	425
2024	372.9	279.7	186.4	380	982	736	491
2025	415.8	311.9	207.9	380	1,095	821	548
2026	458.7	344.0	229.4	380	1,208	906	604
2027	493.9	370.4	247.0	380	1,301	976	650
2028	516.5	387.4	258.2	380	1,360	1,020	680

Source: Eurostat (average production per employee in Manufacturing of basic pharmaceutical products and pharmaceutical preparations); Table 41

As discussed in section 4.4.3, the combination of an SPC export waiver with an extension of the Bolar exemption to cover the third party supply of APIs within Europe is likely to result in additional EU based API sales and employment.[313]

Moreover, allowing manufacturing in an SPC protected market for export to another European country where the SPC or patent has expired may speed up the entry of generics and biosimilars in the domestic market upon protection expiry in that market. This could occur as a manufacturer in an SPC protected Member State that exported the product to another Member State where the protection has expired will already have set up the manufacturing for large scale production.

A timelier entry of generic products from the date of protection expiry can be expected to result in savings on pharmaceutical expenditures. Using a similar method to the one

313 The effect on EU based API sales and jobs is presented in Table 14 and Table 17.

described in section 4.5.5, the details of which are presented in Appendix D, we estimate that for the sample of molecules with later European SPC dates, the savings from immediate generic entry could range between €0.4 and €0.7 billion over a three year period. In proportionate terms this represents a saving of 4 to 8% compared to expenditures on pharmaceuticals with generic entry occurring in the second quarter following protection expiry or third quarter following protection expiry.[314]

As discussed previously, these figures are illustrative as they assume that the entire observed delay in generic entry is due to setting up large scale production. However, as discussed before the timing of generic entry depends on a number of other factors including expected profitability, delays related to pricing and reimbursement negotiations, as well as demand and supply side policies to promote generic entry. Secondly, the above estimates on cost savings on pharmaceutical expenditure consider an SPC export waiver within Europe as a standalone measure. If manufacturing for export to third countries is allowed, the incremental impact on speed of entry (due to domestic producers already having set up large scale production) and pharmaceutical expenditures of also allowing manufacturing for exports to no longer protected or unprotected EEA countries is likely to be smaller.

4.6.4. Effect of Unitary Patent Protection and Unitary Patent Court

As discussed in section 3.1.4 it is not clear yet whether SPCs on unitary patents will be granted centrally with unitary effect in all participating Member States or whether SPCs on these patents will be granted nationally, in which case differences in the effective protection term of a product could arise across Member States if patent holders choose not to apply for an SPC in all Member States.

If SPCs on unitary patents have effect in all participating Member States with a single application, then there will be less scope over time for an SPC export waiver within Europe, as there will eventually be no differences in SPC protection expiry dates for unitary patents within Europe. Since unitary patents will start to be granted in the near future, a harmonisation of SPC expiry dates across the EU Member States for unitary patents will materialise in approximately 20 years from now. Harmonisation of SPC expiry dates across the EU Member States may occur earlier, if there is scope within the UPP regulations for existing European patents that have already applied for SPCs at a national level, to switch to a "unitary" SPC protection. In either case, the introduction of UPP and a UPC will over time reduce the role for an SPC export waiver within Europe. Consequently the beneficial effects to the generic industry, employment and savings on pharmaceutical expenditure identified above will also decline over time.

Given that the results of our analysis in the previous sections were based on molecules whose protection expires in Europe within the next 15 years and given that the full effects of the introduction of the UPP and UPC on SPC expiry dates will take some time to materialise, the effects identified could still hold in the interim. Moreover, it can be expected that at least a small number of patents will continue to be filed nationally and therefore there will likely continue to exist some (albeit limited) scope for an SPC export

314 These savings refer to a three year period following protection expiry and have been calculated for *a sample* of molecules whose SPC expiry in at least one EU top 10 Member State is later compared to the other top 10 Member States. The benefit is assumed to occur only in those molecules/countries with later SPC expiries. It should also be noted that the generic price decay is based on IMS Midas data and does not reflect rebates and other discounts offered by pharmaceutical companies to e.g. hospitals that can be significant.

waiver. We are not in a position to estimate by how much the impacts identified in the previous sections will be reduced as this will depend on the number and sales of products that in the future will be covered by national versus unitary patents or European patents with a unitary effect. The upper bound to the impact of the UPP and UPC assuming a unitary SPC effect would be to completely wipe out the benefits of the SPC export waiver within Europe identified in the previous sections.

If SPCs on unitary patents continue to be granted Member State by Member State, then there will continue to be differences in SPC expiry dates between Member States scope for an SPC export waiver within Europe.

4.7. Scenario 6: Allowing manufacturing of SPC protected medicines in protected (domestic) markets for purposes of preparing for entry in the domestic market (with minimal delay) subsequent to patent or SPC expiration i.e. stockpiling

In this section we consider the effects of allowing manufacturing for stockpiling of SPC protected medicines in the domestic market to prepare for entry with minimal delay upon protection expiry in the domestic market. For purposes of this analysis, we have been asked to assume that stockpiling will be allowed during the period beginning 6 months before the SPC expiry.

4.7.1. Issue

Under the current SPC regime, commercial production can only start in a market only after the SPC expires in that market. According to the EGA, the delay associated with manufacturing a generic or biosimilar (including the manufacture of the API) can take up to a year but on average it lasts between 3-6 months. Domestic producers could therefore face a delay between 3-6 months or longer once the protection expires in order to set up large scale manufacturing and prepare stocks for the supply of the market where the protection has expired. On the other hand, manufacturers located outside the protected market would be able to have started production and prepared stock to enter a market as soon as protection expires, assuming no delays in marketing approvals and price and reimbursement negotiations beyond the date of expiry of the SPC of the reference medicine.

The current SPC regime therefore can be considered to disadvantage domestic producers compared to producers with manufacturing facilities in countries without an SPC term or where the equivalent SPC term has expired.

Since stockpiling is only one among a number of determinants of the timing of generic entry, below we first briefly summarise the findings of empirical papers on the determinants of generic entry and speed of entry and in that context we then present an assessment of the effects of this measure on the European generic and biosimilar manufacturing industry.

4.7.2. Determinants of generic entry

A number of factors influence the speed of generic entry and generic penetration in a market, including expected profits from entry, delays associated with obtaining marketing approvals, setting up large scale production and pricing and reimbursement negotiations. Moreover, physicians and patients can exhibit loyalty to branded products resulting in lower willingness to substitute to generics. Demand-side policies, such as INN-

prescribing, automatic generic substitution and incentives to retailers to dispense generics may therefore help to increase generic penetration. On the other hand, supply-side policies may also affect entry and pricing decisions by generic producers. For example, supply-side policies that regulate the prices of generics, may reduce incentives of generic producers to compete more fiercely on price. Entry may be faster in markets where the regulated price is high compared to markets where it is low.

A number of studies have examined the determinants of generic entry. A summary of the more recent studies with a European focus are discussed in Appendix E.

The main take-away points of the papers reviewed are the following:

- The larger the size of the market pre-protection expiry, the higher the probability of generic entry and the speedier generic entry is.
- The more competitive a market is, the lower the likelihood of generic entry.
- Demand-side policies are successful in promoting generic penetration, and generic entry is speedier in markets with demand-side policies that promote the use of generics.
- Supply-side policies may actually hamper generic entry and penetration by resulting in smaller price reduction of generics relative to markets where prices are determined competitively.

The effect of the stockpiling exemption on the speed of entry should therefore be viewed in light of these additional factors that affect the decision to enter and the speed of entry. For example, if pricing and reimbursement negotiations result in significant delays beyond the date of SPC expiry of the reference product, a stockpiling exemption would have limited effect on the speed of entry of generics and on European pharmaceutical manufacturing. Even with stockpiling allowed, generic manufacturers may decide to enter a market later if e.g. expected profits from entering are not as high due to the size of the market or if the market has poor demand side policies to promote usage of generics.

4.7.3. Assessment of potential effects on generic and biosimilar manufacturing in Europe

Testing hypothesis

A stockpiling exemption is likely to benefit the European generic and biosimilar pharmaceutical industry by allowing domestic producers to enter timely in markets where the SPC term of the reference product has expired, putting them on an equal footing to compete in these markets with generic and biosimilar producers located in markets without SPC protection.

The effect of the stockpiling exemption will depend on other factors such as regulatory delays related to pricing and reimbursement negotiations and other regulatory approvals, demand side and supply side policies on generics.

If stockpiling was allowed in some countries and if data were available on the first date of sale and origin of generic sales in that country, we would be able to test the above hypothesis directly. However, no such data are available as stockpiling is not allowed in any developed country. Consequently, we can examine whether there is any *indirect* evidence to support the above hypothesis.

Methodology

To help determine whether manufacturers located in countries where there is no SPC protection or where the protection has already expired, have an advantage in entering first upon protection expiry in other markets, we examined data obtained from the EMA and national medicine agencies on the manufacturing location of finished products for a sample of first generic entrants following protection expiry during the period 2008Q1 to 2014Q3 (the period for which we have IMS Midas data). The data relate to generics only and do not cover biosimilars, therefore the focus of the discussion will be on generics with some comments at the end of this section on the applicability of the results and arguments to biosimilars.

Table 44 presents a summary of the results.[315] The manufacturing countries with the highest frequency of first generic entrants are, with the exception of Germany:

- European countries that, for the sample of molecules considered, are unlikely to have had SPC protection due to their later accession into the EU and their differing transitional arrangements. As explained in section 3.1.2, the countries that joined the EU later, such as Slovenia, Poland, Malta, Hungary and others, only introduced SPC regulation from the date of their accession, namely in 2004. In Spain, Greece and Portugal patentees could not file for an SPC until 1st January 1998.[316] Since the molecules considered in our sample have protection expiry dates in the period 2008 to 2014, they would have been granted patents between 1988 to 1994 or earlier. Therefore it is very likely that a large number of these molecules would not be SPC protected in the countries that joined Europe later, such as Eastern European countries or Spain, Greece and Portugal.
- Countries outside the EU such as India and Israel that either do not have patent extension terms (India) or have shorter average patent extension terms than Europe (Israel).[317]

The high frequency of these countries as manufacturing countries of generic products that entered first following protection expiry in Europe are consistent with lack of an SPC term conferring a benefit to timely entry of generic products. The high frequency of observations for Germany is not clear, as it is a country where the SPC would have applied on most molecules examined. The high frequency could be explained by the presence of manufacturing facilities in that country by a number of large generic players that are active in entering first upon protection expiry.

---

315 Since our unit of observation is country of sale/corporation/product, and since an EMA marketing authorisation holder will sell in more than one EEA countries, the manufacturing location of finished products sold in more Member States is given more weight compared to the manufacturing location of finished products sold in fewer Member States.

316 EU Supplementary Protection Certificates (SPCs) - The most important of pharmaceutical patent expiry http://www.mpasearch.co.uk/eu-supplementary-protection-certificates

317 There is no patent term extension in India. In Israel patent term extension provisions were revised and their scope was significantly curtailed in 2006. The period of extension could not exceed the shortest period in the US, EU-15 and some additional countries and if the product was registered in the US or EU, a patent term extension would only be available if the patent had been extended in the US and at least one more EU-15 country. The amendment resulted in average patent term extensions falling from about 5 years to 2-3 years and in some cases patent term extensions were no longer applicable. See "Patent term extension under Israeli law", May 2011 by Liad Whatstein. http://whoswholegal.com/news/features/article/28962/patent-term-extension-under-israeli-law

Table 44: Manufacturing location finished product of first generic entrants following protection expiry

Country of manufacture of finished product	Number of first entry observations across the EEA	Share of total observations
Germany	195	23%
Slovenia	151	18%
India	126	15%
Poland	106	13%
Spain	100	12%
Malta	94	11%
Hungary	68	8%
Israel	68	8%
Greece	56	7%
Iceland	51	6%
Portugal	43	5%
Switzerland	37	4%
Uk	31	4%
Netherlands	28	3%
Bulgaria	27	3%
Ireland	23	3%
Czech_Republic	22	3%
Turkey	21	3%
Italy	21	3%
Slovakia	20	2%
Croatia	17	2%
France	17	2%
Canada	15	2%
Serbia	15	2%
Romania	14	2%
China	12	1%

Country of manufacture of finished product	Number of first entry observations across the EEA	Share of total observations
Austria	11	1%
Denmark	9	1%
Belgium	8	1%
Oman	4	0%
Australia	3	0%
Russia	2	0%
Us	2	0%
Cyprus	2	0%
Finland	2	0%
Bosnia	1	0%
Korea	1	0%
Vietnam	1	0%
Other	1	0%
Total observations	**832**	**100%**

Source: CRA analysis on EMA data

Note: Since a number of products were manufactured in more than one countries, there is double counting so summing column 2 across the rows results in a higher number of observations than the total observations in our sample and summing column 3 across the rows results in a share greater than 100%

For the EU manufacturing countries for which we have IMS data, we examined the date of protection expiry of the molecules in question and the average difference in protection expiry between the country of manufacture and the country of sale. Table 45 presents for each country of manufacture, the number of observations[318] for which the protection expiry in that country was *earlier* than the date of protection expiry in the country of sale or where the protection expiry in the country of manufacture was *earlier* than the date of sale in the country of sale (column 2) and the average difference in months between the protection expiry/date of sale in the country of sale and the country of manufacture (column 3). There were some cases where the protection expiry date in the country of

318 Here one observation is at the level of country of sale/international corporation/molecule, therefore the results are not directly comparable to those in Table 44, where the unit of observation is country of sale/international corporation/product/molecule.

manufacture was later than the protection expiry date (and date of first sale) in the country of sale. [319]

Ignoring the idiosyncratic cases that result in the protection expiry date in the country of manufacture to be later than the protection expiry or sale date in the country of sale, we find that in many cases the protection expiry in the country of manufacture is a year or longer earlier than the protection expiry in the country of sale. We also however observe some cases where on average the difference in months is less than a year and in two cases the average difference is zero.

These results suggest that manufacturers located in countries where the protection has expired earlier or did not exist in the first place have an advantage in entering first upon protection expiry compared to e.g. domestic producers.

319 Cases where the protection expiry in the country of manufacture was later than the protection expiry in the country of sale are mostly idiosyncratic. Clopidogrel: According to Generics Web, the scope of the patent offering protection in many European countries is restricted to products containing a specific salt form (bisulfate salt) and this has allowed a number of generic firms to enter with generic versions using an alternative salt prior to the protection expiry (http://www.genericsweb.com/index.php?object_id=1086). Olanzapine: According to Generics Web, there exist a number of patent families protecting physical forms that are used in the preparation of olanzapine or the combination of olanzapine with particular salts but which do not constrain generic entry based on other physical forms or using other salts (https://www.genericsweb.com/index.php?object_id=946). Sildenafil: The protection expiry in Spain by IMS is shown as 2015 whereas according to Generics Web it expires in September 2013. According to GenericsWeb, the SPC expiry was based on an incorrect marketing authorisation date and should be three months earlier, i.e. June 2013. http://www.genericsweb.com/index.php?object_id=1124. If the date in Generics Web is taken to be the correct one then the difference in SPC term between the manufacturing country (Spain) and countries of sale is zero. However Generics Web notes that "The Spanish translation of the European patent originally protected only processes for the preparation of Sildenafil and therefore would have been assumed to allow generic entry while remaining in force". This may explain why we observe manufacturing in this country for sale in other regions where the protection expiry appears to be on exactly the same date. Escitalopram was protected by a European patent that expired in June 2009, while the SPC expired in June 2014. A number of generic companies questioned the validity of the SPC and may have launched products at risk. The challenge was overturned by the Brussels Court of Appeal (http://www.mondaq.com/x/205656/Patent/Brussels+Court+Of+Appeal+Confirms+Validity+Of+Escitalopram+Patent+And+SPC).

Table 45: Difference in protection expiry dates between finished product manufacturing country and country of sale

Country of manufacture	# of observations with earlier protection expiry	Average difference in months between Prot. Exp. in country of sale and country of manufacture
Austria	5	0
Belgium	5	7
Finland	2	36
France	10	7
Germany	50	8
Greece	24	14
Hungary	40	19
Ireland	11	0
Italy	12	5
Netherlands	13	14
Poland	32	46
Portugal	12	11
Romania	6	31
Slovakia	12	36
Spain	43	24
UK	15	1

Source: CRA analysis on EMA and national medicine agencies data

These results are generally consistent with the view that a stockpiling exemption may reduce delays in entry following protection expiry, particularly for domestic generic producers in protected markets. However, we cannot precisely estimate the extent of reduction in delays in market entry. For example, the beneficial effects of a 6 month stockpiling exemption are unlikely to materialise in countries or products where there are substantial regulatory delays in launching a product, e.g. prolonged pricing and reimbursement negotiations.

According to a 2009 EGA report,[320] the average delay faced by generics producers due to pricing and reimbursement negotiations since gaining marketing authorisation was less than 50 days in Sweden, Ireland, Denmark and the Netherlands, while in the UK and

320 How to increase patient access to generic medicines in European healthcare systems, a report by the EGA Health Economics Committee, June 2009. http://www.egagenerics.com/images/Website/Market_Barriers_Report_FINAL_update_How_to_Increase_Patient_Access_to_Generic_Medicines.pdf

Germany pricing and reimbursement are decided at the time of grant of the marketing authorisation. A stockpiling exemption is therefore more likely to have a greater impact in these countries compared to countries with significant delays, e.g. Croatia had a delay more than 350 days (almost a year) and Latvia, Romania, Slovakia had a delay greater than 200 days. To the extent that delays have declined from the figures reported in that study, which is likely given the time that has passed since then, it is possible that stockpiling would have a positive effect in more European countries.

The positive effects of a stockpiling exemption are likely to be amplified in markets with demand-side policies that promote the use of generics (e.g. financial incentives to physician and pharmacists to prescribe/dispense generics, policies to improve perceptions of generics etc), as these markets tend to attract more generic producers in the first place.

Biosimilars

A stockpiling exemption is likely to benefit EU-based biosimilars given the complexity of moving from manufacturing pilot batches to advance manufacture. We do not have data on the manufacturing location of biosimilar products to examine whether there is a link between the existence of SPC protection and speed of entry. As discussed in section 4.5.3, the delay to enter markets following protection expiry is currently well in excess of 6 months for biosimilars. We are not in a position to determine how much of the observed delay is due to stockpiling compared to other factors, e.g. delays in development of biosimilars, delays in regulatory approvals or pricing and reimbursement delays. To the extent that some of this delay is due to moving to large scale production, which is likely, a stockpiling exemption can be expected to benefit EU-based biosimilar producers.

4.7.4. Assessment of potential effects on generic and biosimilar entry in Europe

Testing Hypothesis

A stockpiling exemption is likely to result in timelier generic entry following protection expiry, particularly for smaller sized European generic producers that may have limited ability to manufacture in other locations.

Methodology

As there are no developed countries where stockpiling during the patent extension term is currently allowed, there are no data available to allow us to examine the impact of this measure on generic and biosimilar entry. We can examine however the observed speed of generic and biosimilar entry in Europe and make inferences on whether there is room for a stockpiling exemption to reduce the observed delays.

Generics

To make inferences on the potential impact of a stockpiling exemption on the speed of generic entry, we examined the speed of entry of generics in the EEA following protection expiry events during our sample period (2008Q1 to 2014Q3). We first examined the share of molecules whose protection expired during our sample period and that experienced entry, in various time intervals since protection expiry (3 months, 6 months, 1 year and 2 years).[321] We then examined the share of molecule sales (pre-protection sales) that

321 For molecules whose protection expiry was close to the end of our sample period we could not estimate these shares.

experienced entry at various time intervals since protection expiry.[322] Thirdly, we examined the average speed of entry of generics since protection expiry (in number of months[323]), by size of the market (based on pre-protection expiry sales). Last, we examined whether we observe larger generic companies (measured by total generic sales in the EEA based on IMS Midas data for the 12 month period ending 2014 Q3) entering markets faster following protection expiry compared to smaller generic companies. The results are discussed below.

Share of molecules experiencing generic entry at time intervals since protection expiry

Table 46 presents the share of molecules that experienced entry at certain time intervals since protection expiry by Member State. As the table shows, there is variation in the proportion of molecules experiencing entry in the first quarter across Member States. Despite this variation, most Member States experience generic entry during the first quarter since protection expiry, in more than half of the molecules that lost exclusivity during this period. Member States where 70% or more of the molecules experienced entry within the first quarter are: Slovakia, Poland, Romania, Spain and Germany.

Almost all Member States experience entry in more than 70% of the molecules by the first year.

The table in Appendix F shows the share of molecules experiencing entry for molecules in the top quartile of sales and in the bottom quartile of sales. As the table shows a larger proportion of molecules with sales in the top quartile experience entry during the first quarter in each country. In 16 out of 19 countries more than 70% of molecules in the highest quartile experience entry during the first quarter. On the other hand, in most Member States, less than a half of molecules in the bottom quartile experience entry during the first quarter, and in a number of Member States less than a third do so.

These results suggests that there could be scope for a reduction in the delay in generic entry, particularly in smaller markets by terms of sales.

322 We did not count as entry events, generic entry by the company that also owned the protected product (branded generics).

323 Since the IMS Midas data report sales at a quarterly level, we assume that entry occurred in the middle of the quarter unless the protection expiry date is later, in which case we assume that entry occurred in the same month as protection expiry.

Table 46: Timing of entry for molecules experiencing generic entry following protection expiry during period 2008Q1 to 2014Q3, by molecule count

EEA Country	# of markets with observed generic entry during period	Share of molecules observing entry in Q1	Share of molecules observing entry in Q1-Q2	Share of molecules observing entry in Q1-Q4	Share of molecules observing entry in Q1-Q8
Austria	72	62%	71%	76%	92%
Belgium	73	58%	67%	79%	96%
Czech Republic	28	61%	61%	64%	93%
Finland	60	55%	65%	77%	95%
France	89	67%	76%	83%	90%
Germany	102	71%	76%	86%	92%
Greece	47	45%	57%	79%	94%
Hungary	38	45%	53%	74%	89%
Ireland	57	65%	65%	75%	91%
Italy	103	55%	66%	76%	85%
Netherlands	78	62%	71%	86%	97%
Norway	43	51%	67%	84%	98%
Poland	23	78%	78%	91%	100%
Portugal	53	55%	66%	79%	89%
Romania	47	77%	81%	87%	98%
Slovakia	27	81%	81%	81%	89%
Spain	71	73%	76%	86%	93%
Sweden	79	67%	70%	77%	91%
UK	83	60%	70%	82%	93%

Source: CRA analysis of IMS data

In order to control for market size, we also estimated the share *of sales* that lost protection during this period and that experienced entry at various time intervals since protection expiry, (3 months, 6, months, 1 year and 2 years), for each country.[324] This

324 Using sales for a year before protection expiry.

weighting by pre-protection sales of the share of molecules observing entry in different quarters shows that molecules with higher sales experience earlier generic entry, as the shares of sales experiencing earlier generic entry are generally larger than the shares of number of molecules presented in Table 46.

Table 47: Timing of entry for molecules experiencing generic entry following protection expiry during period 2008Q1 to 2014Q3, by molecule sales

EEA Country	# of markets with observed generic entry during period	Share of sales observing entry in Q1	Share of sales observing entry in Q1-Q2	Share of sales observing entry in Q1-Q4	Share of sales observing entry in Q1-Q8
Austria	72	81%	86%	91%	98%
Belgium	73	75%	81%	88%	98%
Czech Republic	28	68%	68%	68%	83%
Finland	60	65%	74%	88%	100%
France	89	75%	82%	91%	94%
Germany	102	79%	83%	92%	98%
Greece	47	47%	56%	87%	97%
Hungary	38	38%	43%	63%	93%
Ireland	57	85%	85%	88%	98%
Italy	103	68%	74%	83%	90%
Netherlands	78	78%	92%	96%	100%
Norway	43	63%	72%	83%	93%
Poland	23	94%	94%	96%	100%
Portugal	53	64%	77%	85%	90%
Romania	47	87%	87%	93%	99%
Slovakia	27	91%	91%	91%	95%
Spain	71	90%	91%	97%	98%
Sweden	79	82%	82%	90%	98%
UK	83	78%	81%	89%	99%

Source: CRA analysis of IMS data

Average speed of entry of generics by size of the market

We examined the speed of entry of generic products in a number of EEA countries where molecules experienced protection expiry during our sample period (2008Q1 to 2014Q3),

by quartile of sales values. Table 48 presents the median entry in number of months since protection expiry in each market. We used median rather than average to summarise the results as averages were affected by a number of outliers.

As the table shows, on average, entry is very speedy in larger markets[325], usually occurring within the first two months or in many cases earlier. Entry is less speedy in the bottom quartile. It ranges between 3 months on average (in Romania) to 17 months (Austria), ignoring the Czech Republic due to the low number of observations. There are some differences across Member States with regards to speed of entry, but the differences are less pronounced the larger the size of the market is in terms of quartile of sale.

325 By market here we refer to a molecule.

Table 48: Median speed of generic entry after protection expiry in months – split by country specific quartiles of the pre-protection expiry market size (EUR sales) (Quartile 1 includes the 25% markets with the smallest sales value)

	Median			
Country	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**
Austria	17	2	2	1
Belgium	9	3	1	0
Czech Republic	19 *	1 *	2 *	1 *
Finland	17	5	2	1
France	6	0	1	0
Germany	4	2	2	0
Greece	8	7	9	2
Hungary	11	12 *	2	10 *
Ireland	10	2	1	0
Italy	7	5	2	1
Netherlands	13	2	2	2
Norway	4	2	8	2
Poland	7 *	2 *	3 *	2 *
Portugal	12	2	6	1
Romania	3	2	1	1
Slovakia	4 *	3 *	1 *	0 *
Spain	10	2	1	0
Sweden	7	2	2	0
UK	8	8	0	0

Source: CRA analysis on IMS data

Notes: * less than 10 observations. 0 indicates entry in the same month as protection expiry, 1 indicates entry 1 month following protection expiry etc. Since our data are quarterly, if we observe entry in Q1 we assume that it occurred in month 2 (unless the protection expiry is in month 3 when we assume that entry occurs in month 3).

Average speed of entry of since protection expiry by size of generic player

Last, we examined the speed of entry of generic products in a number of EEA countries where molecules experienced protection expiry during our sample period (2008Q1 to 2014Q3), by size of corporation, measured by total generic EEA sales. Table 49 presents the median entry by company size in number of months since protection expiry in for each

market.[326] The results above indicate that generally larger companies enter a market more quickly upon protection expiry compared to smaller companies. This could in part be due to larger companies having a network of manufacturing facilities that allow them to be ready to enter more timely upon protection expiry. We also observe in some countries, e.g. Poland and Ireland that this pattern is reversed, i.e. smaller companies enter faster than larger ones. This could be due to the presence of national manufacturers that are quicker in entering their domestic market, due to e.g. domestic market knowledge.

326 By market we refer to molecule market. We used median rather than average to summarise the results as averages were affected by a number of outliers.

Table 49: Median speed of generic entry by company after protection expiry in months – split by quartiles of the 2013-2014 EEA wide sales of generic companies (EUR sales) (Quartile 1 includes the 25% companies with the smallest sales value)

	Median			
Country	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**
Austria	13.5	7	5	3
Belgium	12.5	8.5	5	6.5
Czech Republic	27	17	8	4
Finland	11	13	11.5	5
France	20	6.5	2	1
Germany	6	2	2	2
Greece	18	8	18	14
Hungary	18.5	15	10	11
Ireland	1	8	2	6
Italy	16	10	5	3
Netherlands	9	11	3	2
Norway	9	13	17	5
Poland	25.5	20	18	24
Portugal	18	14	15	14
Romania	16	13.5	10	3
Slovakia	13	7.5	5	5
Spain	17.5	9	8	5
Sweden	8	8	2	3
UK	15	12	7.5	6

Source: CRA analysis on IMS data

Notes: 1 indicates entry 1 month following protection expiry etc. Since our data are quarterly, if we observe entry in Q1 we assume that it occurred in month 2 (unless the protection expiry is in month 3 when we assume that entry occurs in month 3).

Conclusion on effects of stockpiling on generic entry

One can therefore conclude that a stockpiling exemption may reduce observed delays in generic entry particularly in smaller markets, measured by pre-protection sales.

It could also result in more timely entry for smaller generic producers, by levelling the playing field between generic companies that have already ramped up production in an unprotected markets and domestic generic manufacturers.

Biosimilars

As discussed in section 4.5, in the case of biosimilars, we observe a longer delay in entry following patent expiry, though the delay has declined over time.[327] To the extent that some of this delay is related to preparing stocks for entry (recall that the EGA estimates that it can take up to one year to produce a generic or biosimilar from scratch) a stockpiling exemption may result in a timelier entry of biosimilars up to a maximum of 6 months earlier from currently observed delays.

Last, the combined effects of an SPC export waiver and a stockpiling exemption are likely to be mutually reinforcing, as domestic generic and biosimilar producers that have already set up large scale production to supply export markets will also be able to prepare stocks for timely entry upon domestic SPC protection expiry.

4.7.5. Assessment of wider impact of a stockpiling exemption

In this section we discuss the effect of a stockpiling exemption on incentives to innovate, employment and speed of generic and biosimilar entry and related effect on pharmaceutical expenditure.

A stockpiling exemption is unlikely to negatively affect incentives to innovate as it is not intended to reduce the effective period of patent and SPC protection. The aim of such a measure is to reduce delays in generic and biosimilar entry following protection expiry related to preparing stocks to supply a market, thereby levelling the playing field between Europe based generics and biosimilars that are not allowed to stockpile and generics and biosimilars located outside Europe that face no such restrictions. Since the patent term and SPC terms are designed to reward innovative companies for the costs of innovation, a measure that does not affect the effective protection term cannot reduce incentives to innovate. However, if a stockpiling exemption results in generic or biosimilar products entering a market before the expiry of the protection of the reference product, then it is likely to negatively affect incentives to innovate in Europe. Given that entry at risk can already occur by generic companies though e.g. manufacturing outside Europe, it is unclear whether this measure will materially increase these instances.

We expect that the proposal could also attract biosimilar and generic manufacturing investment in Europe as it will enable EU based producers to compete for timely market entry against those producers located in countries without SPCs. In the case of biosimilars, since R&D facilities are located near the manufacturing sites, this measure could also increase investments in R&D facilities in Europe. Such a measure could therefore result in increased manufacturing employment as well as R&D employment in Europe.

Last, a stockpiling exemption can be expected to result in a reduction in pharmaceutical expenditures by reducing delays in entry. We estimate the impact by assuming that for the molecules experiencing protection expiry during our sample period (2008Q1 to 2014Q3) and which experienced generic entry with a delay, generic entry would have occurred 6 months faster.[328] The estimates are illustrative only as they assume that a 6 month delay can be attributed to stockpiling only. Our analysis indicates that if generic

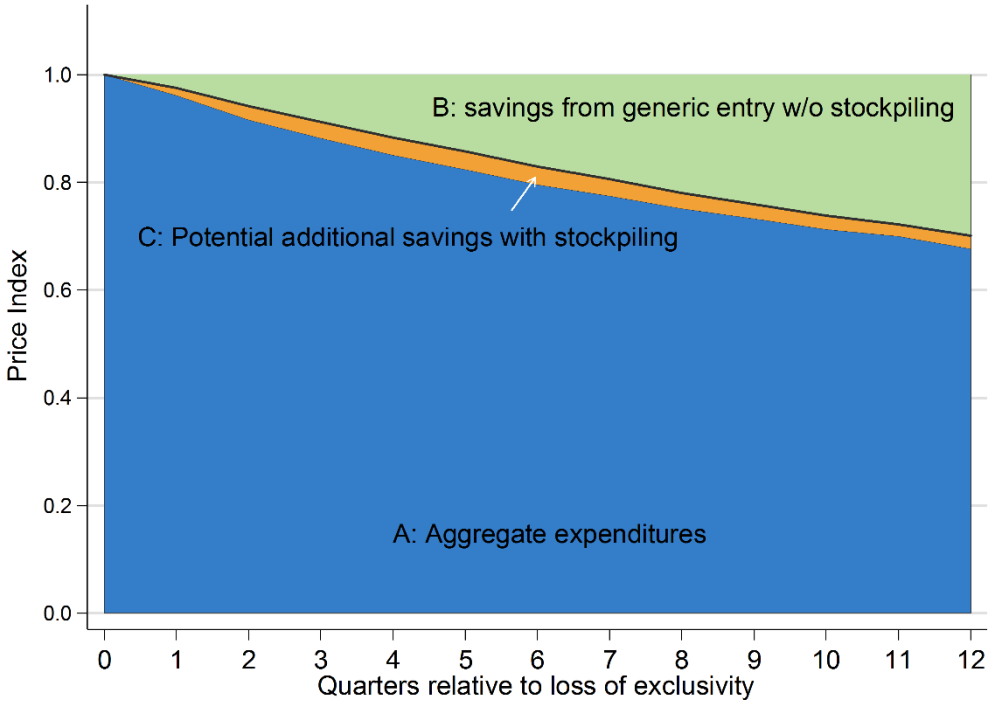
---

327 IMS Midas data does not estimate protection expiry date for biologicals but only provides information on the patent expiry date.

328 In cases where the observed delay was less than 6 months we assume that generic entry would have been immediate.

entry was brought forward by 6 months, savings on pharmaceutical expenditure (at fixed pre-protection expiry volumes) during the period 2008-2014 would amount to €1.1 billion over a three year period as a result of the faster decline in prices, a 4% saving relative to observed delays during our sample period. This is shown graphically below.

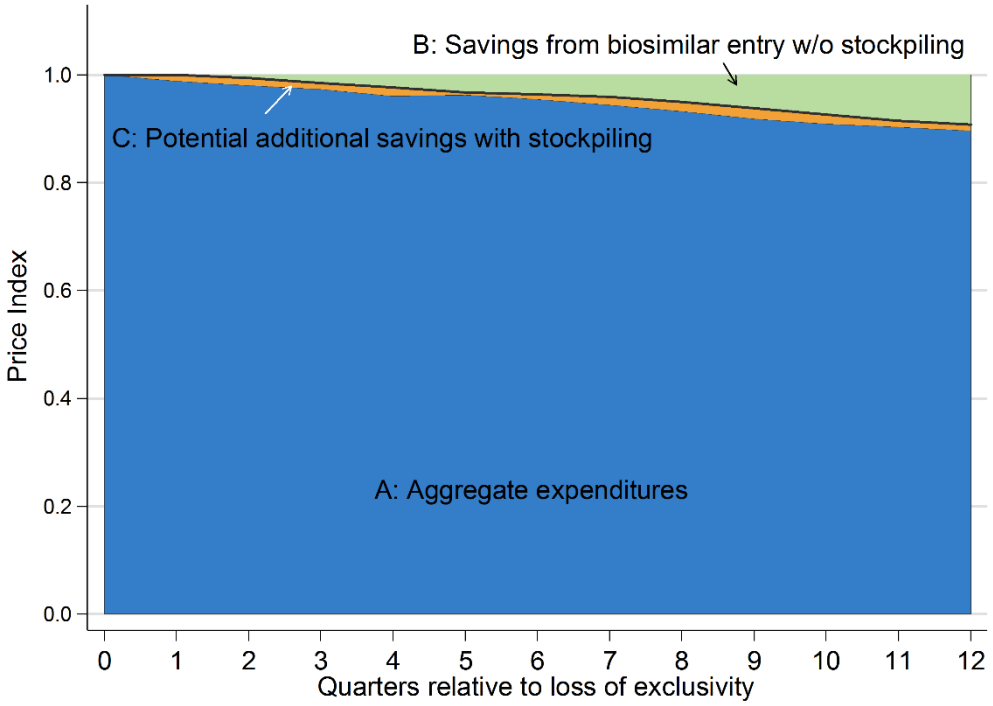
Figure 19: Illustration of savings if generic delay was reduced by 6 months due to the stockpiling exemption



Source: CRA analysis on IMS Midas data

We conduct a similar analysis for biological molecules that experienced patent expiry and biosimilar entry during our sample period. We assume that under a stockpiling exemption biosimilar entry would have occurred 6 months earlier compared to observed delays and estimate the impact on pharmaceutical expenditure of faster biosimilar entry and therefore faster decline in prices. Our calculations suggests total savings of only €15 million (a 1% saving) on pharmaceutical expenditures for the sample of biological molecules considered, assuming pre-protection expiry sales volumes. The low impact is the result of a relatively low biosimilar penetration and the fact that there were a few biosimilar entry events during our sample period. As biosimilar penetration increases over time, the beneficial effects on pharmaceutical expenditure will also increase.

Figure 20: Illustration of savings if biosimilar delay was reduced by 6 months due to the stockpiling exemption



Source: CRA analysis on IMS Midas data

4.7.6. Effect of Unitary Patent Protection and Unitary Patent Court

In this section we discuss the effects of the introduction of UPP and the UPC on the effects of a stockpiling exemption during the SPC term in Europe.

The effects of UPP and the UPC will depend on whether SPCs on unitary patents become effective in all Member States that have ratified the UPC Agreement with a single filing or whether SPCs on unitary patents will continue to be granted separately by Member States. We consider each case below.

If SPCs on unitary patents become effective with a single filing, then SPC protection coverage is likely to increase in Europe over time. The potential beneficial effects of a stockpiling exemption will therefore be amplified as such an exemption would benefit generic and biosimilar producers in more Member States compared to a situation where products are not covered by SPCs in some Member States. Given that unitary patents will be granted in the near future, the effect of the introduction of UPP on stockpiling will not materialise for another 20-25 years.[329] The effect of the UPP on stockpiling will depend on the proportion of patents that will choose the UPP route. The greater the proportion the more likely that a stockpiling will benefit generic and biosimilar producers in more Member States.

329 20 year patent term plus 5 year SPC term. The effect could materialise earlier if existing European patents that have not opted out from the UPC and which currently already have applied for national SPCs can switch to a 'unitary' SPC.

If SPCs on unitary patents continue to be granted on a Member State by Member State basis, then situations where products are not covered by SPC in some Member States could continue to arise. A stockpiling exemption will not affect generic and biosimilar producers in Member States without an SPC protection.

5. CONCLUSIONS

Our study of the economic impacts of changes to exemption provisions during patent and SPC protection term in Europe found the following:

- An extension of the scope of the Bolar across Europe to cover any medicines is likely to benefit the EU based innovative pharmaceutical industry, by reducing costs incurred as a result of the risk of infringement in countries with a narrow Bolar scope, e.g. FTO studies, validity opinions, patent opposition proceedings, costs relating to infringement proceedings. Our econometric analysis did not find robust evidence that countries with a wider Bolar scope had more clinical trials, controlling for other factors. These results should not be interpreted as conclusive evidence that a widening of the Bolar scope will have *no effect* on the innovative pharmaceutical industry. If there was no effect, then it is unlikely that both the UK and Ireland would have amended their patent acts to broaden the scope of the Bolar/ research exemptions recently. The lack of identification of an effect is consistent with responses from the industry suggesting that the scope of the Bolar is *one* among *many* factors influencing the location of clinical trials. While we have attempted to control for a number of these other factors, the proxies we have used (based on data availability) are likely not exhaustive and may also be imperfect measures of the true underlying factors. The proposal is likely to have positive effects on incentives to innovate by increasing the freedom to operate and reducing the costs of patent screening and is likely to increase the number of skilled jobs by increasing the attractiveness of Europe as a location to conduct clinical trials. The introduction of the UPP and UPC could go against the beneficial effects of this measure, should the UPC adopt a narrow interpretation of the Bolar scope.
- An extension of the scope of the Bolar across Europe to cover marketing authorisations in any country could increase the attractiveness of Europe as a location to conduct clinical tests and trials with corresponding benefits to incentives to innovate and employment.[330] Such a measure will also benefit innovative and biosimilar producers by reducing the need to duplicate clinical trials and simplify strategic planning. It will moreover benefit EU based generic producers by enabling them to use results of bioequivalence tests conducted in Europe to obtain marketing authorisations in other countries (where this is allowed). Last it will benefit EU based CRO companies. The introduction of the UPP and UPC could go against the beneficial effects of this measure, should the UPC adopt a narrow interpretation of the Bolar scope.

330 Our econometric analysis did not find robust evidence that countries with a wider Bolar scope had more clinical trials, controlling for other factors. For same reasons as those discussed above, these results should not be interpreted as conclusive evidence that a widening of the Bolar scope will have *no effect* on the innovative pharmaceutical industry.

- We estimate that a widening of the Bolar scope to cove third party supply within Europe could increase EU API sales between 7-29% (€45.2 to €180.8 million, depending on the scenario considered). The combination of an SPC export waiver with an extension of the Bolar exemption to cover the third party supply of APIs within Europe is expected to result in additional EU API sales ranging from €211.8 million to €254.3 million by 2030 depending on the scenario. The additional EU API sales translate into 1,160 to 2,000 additional jobs by 2030. The introduction of the UPP and UPC could go against the beneficial effects of this measure, should the UPC adopt a narrow interpretation of the Bolar scope.

- An SPC export waiver to third countries could result in net additional sales to European generic producers of €7.3 billion to €7.4 billion by 2025, taking into account the potential negative impact on the EU based branded export sales. Expressed in annualised terms, they represent 6-18% of total EEA non-biological export sales to the third countries analysed.[331] Assuming a fast biosimilar penetration in export markets, we estimated net additional sales by EU-based biosimilars of €1.2 billion to €2.1 billion for the sample of molecules analysed, taking into account a potential negative impact to European originator biological pharmaceutical producers. Assuming a slow biosimilar penetration the impact to the EU-based biosimilar industry could reach up to €463 million by 2025. The impact on biosimilars is low because our sample is small. If we had data on all molecules and countries, the size would be correspondingly larger, e.g. if the true available market size in third countries was €20 billion, the additional sales by EU biosimilar producers could be €5.7 billion (29% of €20 billion).[332] The proposed measure is likely to result in increased employment in the European pharmaceutical industry. We estimate the potential employment effect associated with the additional sales (both biological and non-biological molecules) to between approximately 20,000 to 25,000 additional jobs by 2025, assuming no change in worker productivity.[333] To put these figures in perspective, according to the EGA the EU generic and biosimilar industry directly employs 160,000 people, therefore an additional 20,000-25,000 jobs represent a 13-16% increase in employment. The employment figures represent lower bounds as they are based on a sample of 117 non-biological and 17 biological molecules. More manufacturing and R&D employment can be expected to

331 Based on Comtrade statistics, EEA exports to Brazil, Canada, China, Japan, Russia, Turkey and the US amounted to €40 billion in 2014. The €7.3 - €7.4 billion in cumulative sales during the period of SPC protection in Europe, correspond to almost €2.3 billion in cumulative annualised sales, representing a 6% share of €40 billion in 2014. Since our sample represents 32% by count of the molecules whose SPC expires in Europe during the period 2016-2030, the impact could range between 6% to 18% (3 times 6%).

332 29% is the share we estimate EU based biosimilar producers could achieve in the third country markets in our sample. Considering more third countries could change the weighted average share that EU based biosimilars can achieve in export markets (given that the 29% is based on the 8 third countries considered). The purpose of the above illustration is to show that the effect would be correspondingly higher if we had a fuller dataset rather than a sample. This illustrative figure does not take into account a potential reduction in sales by EU based innovative biological medicines producers.

333 We use Eurostat data on production and number of employees in the EU pharmaceutical industry (NACE R2 – Manufacturing of basic pharmaceutical products and pharmaceutical preparations) for the EU28 countries to calculate average production per employee and divide the additional sales by this figure to arrive an estimate of additional employment assuming no change in productivity. http://appsso.eurostat.ec.europa.eu/nui/submitViewTableAction.do.

materialise in the future, as generic and biosimilar producers are more likely to invest in Europe if they are allowed to compete timely in export markets from EU manufacturing locations. Last, the measure could result in more timely entry of generics and biosimilars in domestic EU markets following SPC protection expiry. As an illustration, we estimate that if an SPC export waiver resulted in generic entry occurring immediately after protection expiry it would result in savings of €1.6 to €3.1 billion over a three year period for the sample of molecules examined or 4% to 8% depending on when we assume generic entry would occur without an SPC export waiver. We estimate savings on pharmaceutical expenditure if the delay in biosimilar entry was 6 months following protection expiry relative to 1 year without protection expiry to amount to €0.6 billion for the sample of molecules examined or a 2% saving.

- We estimate the net additional sales to EU-based generic producers that could result from an SPC export waiver within Europe to range between €207.9 million to €416 million by 2025, depending on assumptions regarding the diversion from other European generic and branded producers. Assuming a response by the European innovative industry to increase the coverage of SPC protection across Member States in Europe, these benefits could be reduced. The proposed measure is likely to result in an increase of employment in the European pharmaceutical industry as a result of an increase of sales by European generic and biosimilar producers. We estimate the potential employment effect associated with the additional generic sales to between approximately 550 and 1,000 by 2025 additional jobs by 2025, assuming no change in worker productivity and no reaction by the EU-based innovative industry.[334] A manufacturing export waiver during the SPC term within the EU could additionally result in speedier entry of European generics and biosimilars following protection expiry in the domestic market. For illustrative purposes, we estimate that if an SPC export waiver resulted in generic entry occurring immediately after protection expiry relative to a delay of up to 8 months this would result in savings of €0.4 to €0.7 billion over a three year period for the sample of molecules examined or 4% to 8% depending on when we assume generic entry would occur without an SPC export waiver. The introduction of the UPP and UPC could limit the scope of an intra-EU export waiver in the future should SPCs on unitary patents also have unitary effect.

- Data on the manufacturing location of first generic entrants in the EEA are generally consistent with an advantage to generic manufacturers located in countries without SPCs. Evidence on the speed of entry following protection expiry suggests that there is some scope to reduce delays which a stockpiling exemption could help achieve, particularly for smaller sized EU based producers and less lucrative markets. A stockpiling exemption is also likely to increase incentives by generic and biosimilar producers to invest in manufacturing and R&D production in Europe, by enabling them to compete timely in unprotected or

334 We use Eurostat data on production and number of employees in the EU pharmaceutical industry (NACE R2 – Manufacturing of basic pharmaceutical products and pharmaceutical preparations) for the EU28 countries to calculate average production per employee and divide the additional sales by this figure to arrive an estimate of additional employment assuming no change in productivity. http://appsso.eurostat.ec.europa.eu/nui/submitViewTableAction.do. Due to data limitations we were not able to quantify an effect on employment of additional biosimilar sales.

no longer protected markets from European facilities. The combined effect of an SPC export waiver and a stockpiling exemption can be expected to be mutually reinforcing. Moreover, a stockpiling exemption can be expected to result in a reduction in pharmaceutical expenditures by reducing delays in entry by generic and biosimilar producers. For illustrative purposes we estimate the impact if observed delays in generic entry during our sample period were reduced by up to 6 months. Our analysis indicates that if generic entry was brought forward by 6 months, savings on pharmaceutical spending for the sample of molecules considered (at fixed pre-protection expiry volumes) would amount to €1.1 billion over a three year period since protection expiry, as a result of the faster decline in prices, a 4% saving. For biosimilars the savings for the sample of molecules considered are estimated to be €15 million, a 1% saving. The low impact is the result of a relatively low biosimilar penetration and the fact that there were a few biosimilar entry events during our sample period. As biosimilar penetration increases over time, the beneficial effects on pharmaceutical expenditures will also increase.

APPENDIX A: BOLAR EXEMPTION IN KEY EUROPEAN COUNTRIES

France

In France the Bolar provision came into force in February 2007 through an added subparagraph (d) to Article L. 613-5 of the Intellectual Property Code:

> *"The rights conferred by the patent shall not extend to:*
>
> *a) …;*
>
> *b) acts done for experimental purpose relating to the subject-matter of the patented invention;*
>
> *c) …*
>
> *d) studies and trials necessary for obtaining a marketing authorisation for a medicine, as well as to acts necessary to carry out such studies and trials and to obtain the authorisation."*

The wording of the *Bolar* exemption in France is broader than the wording used in the Directive and covers any medicine. Moreover, the wording of the text does not specifically mention that the provision covers marketing authorisations in specific countries, therefore it can be considered broad in scope. [335]

Germany

In Germany, the experimental use exemption is recognised under Section 11 (2) of the German Patent Act. The German Supreme Court has adopted a broad interpretation of the experimental use exemption that covers not only acts done solely for scientific purposes, but also acts done for commercial purposes as long as they are directed at technical findings of the patented invention and are not merely used to clarify commercial factors, such as e.g. market demand.[336] The experimental use exemption therefore covers tests carried out:

- to find indications and contra-indications for existing and new therapeutic uses;
- to analyse the pharmaceutical form and dosage of an active substance to discover a cure for or alleviate certain illnesses;
- to find clinically-relevant differences over other products, in particular regarding effectiveness and tolerance.

In addition to the experimental use exemption, Germany introduced the *Bolar* exemption in 2005 in section 11 (2b) of the German Patents Act, which provides that:

> *"The right granted by a patent does not extend to:*
>
> *1. …*

---

335 http://www.taylorwessing.com/synapse/ti_bolarexemptions.html . See also, AIPPI Working Group Q202, https://www.aippi.org/download/commitees/202/GR202france.pdf

336 This broad interpretation was adopted in the Supreme Court decisions *Klinische Versuche I* (1995) which exempted experiments aimed at finding new, unknown uses of a drug and in *Klinische Versuche II* (1997) which exempted experiments aimed at finding data on the characteristics and effects of the patented active substance within the limits of indications already known. See AIPPI Working Committee Q202 at https://www.aippi.org/download/commitees/202/GR202germany_en.pdf

2. acts performed for experimental purposes in relation to the subject of the patented invention

2.a …

2.b Studies and trials and the resulting practical requirements which are necessary in order to obtain an authorisation to market a medicinal product in the European Union or to obtain an authorisation for a medicinal product in one of the Member States of the European Union or a third country."

The German *Bolar* exemption is broader compared to the wording of the Directive as it covers any medicinal product including generics and innovative drugs. Moreover it covers studies and trials that use patented products to obtain marketing authorisation not only in Germany or the EU but in any other country. Last, the provision covers "*studies, trials and the resulting practical requirements"* which extends to the making, import and use of patented active substances by the entity seeking a marketing authorisation as long as this is necessary for obtaining marketing approval in any country.[337]

Italy

In Italy the Bolar provision came into force in April 2006. According to Article 68(1)(a) of the Code of Industrial Property Act, the patent protection does not extend to acts performed privately and for non-commercial purposes, or for experimental purposes, including those aimed at obtaining marketing authorisation for a medicinal product in any country, and subsequent practical requirements, including the preparation and the use of the active pharmaceutical ingredients if they are absolutely necessary.

The Italian law therefore has a broader wording than the European Directive as it extends to all medicines, it covers trials to obtain marketing authorisations in any country, not just the EEA.[338] Moreover, the wording of the patent exemption explicitly covers the preparation and use of APIs strictly for purposes of obtaining marketing authorisation. The wording though is still not sufficiently clear as to whether a third party supplier of APIs not directly involved in the testing of the generic medicine is covered when selling to a generic producer for testing purposes.

Spain

In Spain the experimental use exemption was covered in Article 52 (b) of the Spanish Patent Act 1986. In 2006 Spain amended Article 52 to be in line with the *Bolar* provisions as set out in Directive 2001/83/EC as amended in 2004. The Bolar provision in the Spanish Patent Act notes that *"The rights conferred by the patent shall not extend to: (b) acts carried out for experimental purposes related to the subject matter of the patented invention, in particular, the studies and the tests carried out to obtain regulatory approval of generic drugs, either in Spain and abroad, and the subsequent practical requirements, including preparation, obtaining and use of the active pharmaceutical ingredient for this purpose".*[339]

Thus, the *Bolar* provision in Spain is wide and covers any medicine and marketing authorisations not just in the EEA but in any country. Moreover, the Spanish Patent Act

337 http://www.taylorwessing.com/synapse/ti_bolarexemptions.html

338 *Supra* footnote 335 and AIPPI Working Group Q202 at https://www.aippi.org/download/commitees/202/GR202italy.pdf

339 AIPPI Working Group Q202 at https://www.aippi.org/download/commitees/202/GR202spain.pdf

explicitly refers to the preparation, obtaining and use of APIs that are necessary for obtaining a marketing authorisation. However, as in the case of Italy, it is not clear whether a third party API supplier selling to a generic producer for testing purposes is covered under the Bolar provision.

United Kingdom

In the UK, the *Bolar* provision, is covered by Section 60.5(i) of the UK Patents Act 1977. Section 60.5(i) before the recent amendment stated that the following acts are exempt from patent infringement:

> *(i) an act done in conducting a study, test or trial which is necessary for and is conducted with a view to the application of paragraphs 1 to 5 of article 13 of Directive 2001/82/EC or paragraphs 1 to 4 of article 10 of Directive 2001/83/EC, or*
>
> *(ii) any other act which is required for the purpose of the application of those paragraphs*

As the wording suggests, this provision closely resembled the wording of the Directive. Therefore, the UK Bolar exemption before the October 2014 amendment discussed below, was narrow in scope.[340]

In addition to the *Bolar* provision, section 60.5(b) the UK Patents Act 1977 includes an experimental use exemption that exempts acts of using a patent protected product for experimental purposes. The wording is as follows:

> *"(5) An act which, apart from this subsection, would constitute an infringement of a patent for an invention shall not do so if:*
>
> *…….*
>
> *(b) it is done for experimental purposes relating to the subject-matter of the invention"*

According to the UK response to a set of questions by the International Association for the Protection of Intellectual Property (AIPPI) the experimental use exemption has been considered by the UK Courts in a number of cases and the Courts have chosen a narrow interpretation of this exemption.[341] In the Court of Appeal judgement in the *Monsanto v Stauffer* (1985) RPC 155 (CA) case, the Court considered that *"trials carried out in order to discover something unknown, or to test a hypothesis, or even to find out whether something which is known to work in specific conditions… will work in different conditions can fairly…. be regarded as experiments"*. This however, does not cover trials to demonstrate to a third party, e.g. a regulator, that a product works as claimed or that it is bioequivalent to a reference product.

The narrow implementation of the *Bolar* and experimental use exemptions in the UK created problems for innovative drugs. In order to obtain a marketing authorisation innovative drugs need to run clinical trials to prove their safety and efficacy relative to the current standard-of-care therapy, running the risk of patent infringement if the current standard-of-care is patent protected. Moreover, in the UK medicines are reimbursed by the NHS only if they have received a positive Health Technology Assessment by the NICE. Health Technology Assessments assess the costs and benefits of the therapy

340 "The Legislative Reform (Patents) Order 2014", Explanatory note by the EPO to the Parliament", para 1.5-1.6.

341 AIPPI Committee Q202 at https://www.aippi.org/download/commitees/202/GR202united_kingdom.pdf

compared to other available substitute therapies. In order to provide information for the purposes of a Health Technology Assessment, an owner of a new drug needs to use a potentially patent protected product in trials, thus again running the risk of patent infringement.

For these reasons the UK IPO launched a consultation in 2011 on the subject. The overwhelming majority of respondents (both from the innovative and from the generic/biosimilar side) agreed that the Patent Act should be amended to remove this legal uncertainty for innovative products.[342] According to respondents to the initial consultation, the UK legislation did not provide a level playing field for innovative drug companies and favoured generic companies instead. Moreover, the lack of certainty could result in injunctions and halt clinical trials with significant cost implications. Respondents also noted that the risk of infringement is one of a number of factors that they consider when deciding where to run clinical trials. A pharmaceutical company noted that whereas the UK was their 4th largest location for clinical trials in 2006, by 2008 it ranked 12th. The BioIndustry Association (BIA) noted that the UK share of clinical trials fell from 6% to 2% in the last decade. Another respondent noted that they have run clinical trials in Eastern Europe in part because of the risk of infringement in the UK. The majority of respondents were in favour of extending the exemption to cover activities carried out to obtain regulatory approvals for innovative drugs and for health technology assessments.[343] The respondents noted that the costs to the UK economy of the current legislation included loss of skills and expertise if a trial is run abroad, the public health costs of delays associated with new products reaching the market and considered that the proposed changes would improve the clinical trials environment, making the UK a more desirable location in which to perform clinical trials. Due to the difficulties involved in monetising the costs and benefits of the proposed change, the Impact Assessment did not include a quantification of the effects.[344]

As a result of this consultation, in October 2014 the UK experimental use exemptions were extended to cover the use of patent protected medicines by innovative drugs in trials for the purposes of obtaining a marketing authorisation or for running Health Technology Assessments, in the UK or elsewhere. The new Sections 60(6D) and 60(6E) read as follows:

> *(6D) For the purposes of subsection (5)(b), anything done in or for the purposes of a medicinal product assessment which would otherwise constitute an infringement of a patent for an invention is to be regarded as done for experimental purposes relating to the subject-matter of the invention.*
>
> *(6E) In subsection (6D), "medicinal product assessment" means any testing, course of testing or other activity undertaken with a view to providing data for any of the following purposes—*

342 "The research and Bolar exemptions: an informal consultation on patent infringement in pharmaceutical clinical and field trials", http://webarchive.nationalarchives.gov.uk/20140603093549/http://www.ipo.gov.uk/response-2011-bolar.pdf

343 "The research and Bolar exemptions: Proposals to exempt clinical and field trials using innovative drugs from patent infringement", Government response, February 2013, http://webarchive.nationalarchives.gov.uk/20140603093549/http://www.ipo.gov.uk/response-2012-bolar.pdf

344 See Annex D of the Explanatory document of the UK IPO on The Legislative Reform (Patents) Order 2014 http://www.legislation.gov.uk/uksi/2014/1997/pdfs/uksiod_20141997_en.pdf

(a) obtaining or varying an authorisation to sell or supply, or offer to sell or supply, a medicinal product (whether in the United Kingdom or elsewhere);

(b) complying with any regulatory requirement imposed (whether in the United Kingdom or elsewhere) in relation to such an authorisation;

(c) enabling a government or public authority (whether in the United Kingdom or elsewhere), or a person (whether in the United Kingdom or elsewhere) with functions of—

(i) providing health care on behalf of such a government or public authority, or

(ii) providing advice to, or on behalf of, such a government or public authority about the provision of health care, to carry out an assessment of suitability of a medicinal product for human use for the purpose of determining whether to use it, or recommend its use, in the provision of health care.

The new wording "anything done in or for the purposes of a medicinal product assessment" could be interpreted as potentially encompassing also acts of supply of a patented compound to a company wishing to run trials. However there is no clarity on how this issue will be decided by the courts.

Ireland

In Ireland the experimental use exemption is covered in Section 42(b) of the Irish Patents Act 1992. Ireland, like the UK has a narrow definition of what experiments are covered by the experimental use exemption. Only experiments with a purely scientific purpose are covered and this excludes clinical trials aimed at obtaining regulatory approval.[345]

In addition to the experimental use exemption, a *Bolar* type exemption was introduced in 2006 under section 42(g) of the Patents Act. This exempted from patent infringement:

(g) acts done in relation to the subject matter of the relevant patented invention which consist of:

(i) acts done in conducting the necessary studies, tests and trials which are conducted with a view to satisfying the application requirements of paragraphs 1, 2, 3 and 4 of Article 10 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 (as last amended by Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004) for a marketing authorisation in respect of a medicinal product for human use, or

(ii) acts done in conducting the necessary studies, tests and trials which are conducted with a view to satisfying the application requirements of paragraphs 1 to 5 of Article 13 of Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 (as last amended by Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004) for a marketing authorisation in respect of a veterinary medicinal product, or

345 AIPPI Working Group Q202, https://www.aippi.org/download/commitees/202/GR202ireland.pdf. In its response to the AIPPI Working Group questionnaire the Irish authorities referenced the UK Court of Appeal *Monsanto v Stauffer* (1984) case which ruled that clinical trials aimed at obtaining regulatory approval are not covered by the experimental use exemption.

(iii) any other act which is required as a consequence of the acts referred to in subparagraph (i) or (ii) for the purposes specified in those subparagraphs, as appropriate.

Thus, similarly to the UK, the *Bolar* exemption in Ireland was narrow in scope as it covered only medicines following the abridged marketing authorisation procedure, and it applied to acts aimed at obtaining a marketing authorisation within the EEA only. Consequently, given also the narrow definition of the experimental use exemption, innovative pharmaceutical companies carrying out trials in Ireland could be at risk of infringement as they were not covered by either exemption.

To resolve this problem, in line with the approach followed by the UK, a new Bill was introduced in 2014 that extended the *Bolar* type provision to cover not only generic and biosimilar drugs but also new drugs and to extend the protection to companies seeking marketing authorisation in any country. The wording of new section 42(h) of the Irish Patents Act is as follows:

"(h) insofar as paragraph (g) does not apply, acts done in relation to the subject matter of the relevant patented invention which consist of—

(i) acts done in conducting studies, tests, experiments and trials (including clinical trials and field trials) with a view to satisfying the application requirements for a marketing authorisation or similar instrument (howsoever described) that is required by the law of the State or of any other state in order to sell or supply or offer to sell or supply—

(I) a medicinal product for human use, within the meaning of subsection (2), or

(II) a veterinary medicinal product, within the meaning of subsection (2),

or

(ii) any other act done which is required as a consequence of the acts referred to in subparagraph (i) for the purposes specified in that subparagraph, as appropriate."

The Department of Jobs, Enterprise and Innovation in its Impact Assessment considered that the amendments would provide R&D companies with greater legal protection when carrying out experiments and trials for the purposes of obtaining regulatory approvals and would thus increase the attractiveness of Ireland as a location to undertake R&D, thereby increasing skilled jobs and exports of the pharmaceutical industry which is a significant contributor to the domestic economy (through jobs and tax revenues) and trade. No quantification of the benefits to employment and tax revenues was undertaken in the impact assessment.[346]

346 Department of Jobs, Enterprise and Innovation, "Regulatory Impact Analysis: Review of the Research Exemption Provision", https://www.djei.ie/en/Legislation/Legislation-Files/Regulatory-Impact-Analysis-Review-of-the-Research-Exemption-Provision-Section-42g-of-the-Patents-Act-1992.pdf

APPENDIX B: REGRESSION RESULTS FOR SCENARIO 2

In section 4.2.3 we presented the results of the econometric estimation of the effect of a wide Bolar exemption on the number of clinical trials run in a country where another medicinal product was used. In Table 50 we present a similar estimation performed on all clinical trials, i.e. not limiting the sample to comparator clinical trials where another medicine was used.

In our preferred specification (Model 5), the fact that a country has a wide Bolar scope is statistically insignificant in all specifications. Population and licensed physicians density are significant at the 5% level and have a positive coefficient, while hospital beds density and R&D researchers' density coefficients are not significant. The strongest effect is associated with licensed physicians: a 10% increase of the number of licensed physicians is associated with a 9% increase in the number of clinical trials run in a country.

Table 50: Econometric estimation of the effect of a Wide Bolar exemption on the number of clinical trials run in a country

Dependent variable	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Dummy Wide	-0.0693	-0.0463	-0.1477	-0.1124	-0.2431	-0.2492	-0.2304
	(0.20506)	(0.19973)	(0.19678)	(0.18514)	(0.18024)	(0.18748)	(0.19575)
Population	0.5376***	0.5736***	0.5753***	0.6193***	0.6288***	0.6304***	0.6382***
	(0.09388)	(0.10896)	(0.07422)	(0.07759)	(0.09831)	(0.10026)	(0.09886)
R&D researchers		0.2012		0.2645	0.2404	0.2561	0.2413
		(0.19029)		(0.20873)	(0.16899)	(0.18705)	(0.18894)
Licensed physicians			1.0255**	1.0696**	0.9070**	0.9435**	0.9101*
			(0.46416)	(0.41007)	(0.37283)	(0.42753)	(0.44202)
Hospital beds					0.4949*	0.4854*	0.4675
					(0.25377)	(0.25170)	(0.26671)
Year						-0.0109	
						(0.02002)	
Constant	-3.1765*	-5.4388	-12.3748**	-15.6523***	-18.3411**	3.2709	-18.4015**
	(1.62209)	(3.16281)	(4.35588)	(4.86395)	(6.00442)	(36.10296)	(6.65755)
Observations	126	111	107	96	65	65	65
R2	0.52	0.52	0.73	0.74	0.84	0.85	0.86
Adjusted R2	0.51	0.50	0.72	0.73	0.83	0.83	0.82

Source: CRA analysis on EMA data on clinical trials and WHO and OECD data

Notes: All density variables are per million inhabitants and taken in logarithms, as is the number of clinical trials run. The parameters are estimated using Ordinary Least Squares (OLS) regression. Standard errors reported in brackets. * p<0,1, ** p<0,05, *** p<0,01. Robust standard errors used. The coefficients for year dummies are not reported in Model 7

APPENDIX C: MARKET SHARE DISADVANTAGE OF LATER ENTRANTS

In section 4.5.3 we presented our assessment of allowing manufacturing of SPC protected medicines in protected (domestic) markets for purposes of selling to third countries where the corresponding patent or SPC has expired. Manufacturers located in protected domestic markets are subject to market share disadvantage due to later entry under the present SPC term.

In order to estimate the market share disadvantage of later entrants, we use the IMS Midas data and identify entrants coming in 1 to 3 years after protection expiry. As we want to maximise our sample size, we also consider entrants in surrounding quarters:

- Entrants with 1 year of delay are entrants selling for the first time either 3, 4 or 5 quarters after loss of exclusivity.
- Entrants with 2 years of delay are entrants selling for the first time either 7, 8 or 9 quarters after loss of exclusivity.
- Entrants with 3 years of delay are entrants selling for the first time either 11, 12 or 13 quarters after loss of exclusivity.

For each molecule for which there were entrants 1, 2 or 3 years after loss of exclusivity, we then compute market shares of later entrants over their first year after entry or second year after entry. We sum these shares across all entrants at similar points in time (e.g. entrants with 1 year of delay) and compare them with the sum of shares of first entrants.

We therefore have two measures of market share disadvantage for each category of entrants (1, 2, 3 years of delay). The first one is evaluated over the first year after entry of the later entrant while the second one is evaluated over the second year after entry of the later entrant.

Finally we take the average market share disadvantages across molecules for each country. It gives us the average market share disadvantage per country, for generic firms entering with 1, 2 or 3 years of delay, evaluated at the first year and second year after entry.

Using these data, we are able to estimate the market share disadvantage of exporters from countries with a later protection expiry. As the differences in loss of exclusivity dates between countries do not always match our definition of 1, 2 or 3 years of delay described above (some countries might have a 6 quarters loss of exclusivity difference), we make the following hypothesis:

- If the difference in loss of exclusivity between countries is less than a year, we take the average market share disadvantage for entrants with 1 year of delay.
- If the difference in loss of exclusivity between countries is more than a year, we take the average market share disadvantage for entrants with 2 years of delay.

APPENDIX D: CALCULATION OF PRICE DECLINE AND SAVINGS ON PHARMACEUTICAL SPEND FROM GENERIC AND BIOSIMILAR ENTRY

In section 4.5.5 we consider the potential impact of the effect of an SPC export waiver on European pharmaceutical spending due to the timelier entry of European generics and biosimilars following protection expiry in the EU market. In this appendix we set out the methodology we used to estimate price declines following generic and biosimilar entry and the assumptions we made to estimate the effect of timelier entry on pharmaceutical spend.

Generics

Based on generic entry events[347] during our sample period (2008Q1 to 2014Q3) for the EEA countries covered by the IMS data available to us, we examined the average decline in molecule prices following generic entry relative to prices that prevailed before generic entry. We calculated average prices at the molecule/country level by dividing the EUR sales value by the IMS Standard Units. We indexed the average price during the period of four quarters before generic entry to 1. Following generic entry market prices were expressed relative to pre-generic entry prices. Averages across the EEA and molecules were weighted by country level/molecule sales.[348]

To estimate the effect on pharmaceutical spending of timelier entry in domestic markets as a result of an SPC export waiver, we used the sample of non-biological molecules with later EU SPC expiry dates compared to at least one of the third countries analysed (Australia, Brazil, Canada, China, Japan, Russia, Turkey, US). We limited the molecules in our sample to those expiring in Europe up to and including year 2025, i.e. we considered a 10 year period. For each molecule, we estimated pharmaceutical expenditures (based on IMS sales data) without and with an SPC export waiver for a period of three years since the European SPC protection expiry, assuming volumes fixed at the pre-protection expiry levels.

We assumed that:

- Under an SPC export waiver, generic entry for the sample of molecules would be immediate following protection expiry in Europe.
- Without an SPC export waiver, generic entry for these molecules would be delayed by:

347 We identified generic entry as occurring in the first quarter in which we observe generic sales following protection expiry. We did not count as generic entry, entry by the originator in the generic segment. We exclude from our analysis cases with generic entry at risk (i.e. during the protection period).

348 During our sample period, generic entry events were observed in the following EEA countries: Austria, Belgium, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden, UK. Biosimilar entry events were observed in the following EEA countries: Austria, Belgium, Bulgaria, Croatia, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK.

- 3 quarters (the EEA average delay is 8.2 months) [349]
- 2 quarters, assuming that delay in the future would in any case reduce.

We then took the difference between the two to arrive at an estimate of pharmaceutical expenditure savings if entry under the SPC export waiver was immediate.

Biosimilars

Based on biosimilar entry events[350] during our sample period (2008Q1 to 2014Q3) for the EEA countries covered by the IMS data available to us, we examined the average decline in molecule prices following biosimilar entry relative to prices that prevailed before biosimilar entry. We calculated average prices at the molecule/SKU/country level by dividing the EUR sales value by the IMS Standard Units. We indexed the average price during the period of four quarters before biosimilar entry to 1. Following biosimilar entry market prices were expressed relative to pre-biosimilar entry prices. Averages across the EEA and molecules were weighted by country level/molecule/SKU sales.

To estimate the effect on pharmaceutical spending of timely entry in domestic markets as a result of an SPC export waiver, we used the sample of biological molecules with later EU SPC expiry dates compared to at least one of the third countries analysed (Brazil, Canada, China, Japan, Russia, Turkey, US). We limited the molecules in our sample to those expiring in Europe up to and including year 2025, i.e. we considered a 10 year period. For each molecule, we estimated pharmaceutical spend (based on IMS sales data) without and with an SPC export waiver for a period of three years since the European SPC protection expiry, assuming volumes fixed at the pre-protection expiry levels.

We assumed that:

- Under an SPC export waiver was implemented, biosimilar entry for the sample of molecules would occur 6 months following protection expiry in Europe.[351]
- Without an SPC export waiver, biosimilar entry for these molecules would be delayed by 1 year.

We then took the difference between the two to arrive at an estimate of pharmaceutical expenditure savings if biosimilar entry under the SPC export waiver was delayed by 6 months.

349 Since we have quarterly data, to estimate the delay in generic entry we assume that entry occurred in the middle of a quarter when generic sales first appear in our data. If however the protection expiry date is in the third month of the quarter, we assume that entry occurred in the last month of the quarter. We then round the average delay we observe for generics of 8.2 months to three quarters.

350 We identified biosimilar entry as occurring in the first quarter in which we observe sales of the biosimilar product. We did not count as entry events cases where non-reference biological products started selling into a market.

351 We used a 6 month period as a delay as biosimilars tend to enter with a longer delay compared to generics, due in part to the longer development times.

APPENDIX E: SUMMARY OF PAPERS ON DETERMINANTS OF GENERIC ENTRY

Kavavos (2014)[352], using data on 101 molecules that lost protection expiry over the period 1998 to 2010, measures the performance of generic drug policies in 12 EU Member States[353], which he groups into three categories based on the level of generic prescribing and supply-side policies (e.g. competitive pricing versus price linkage or other form of price regulation), with group 1 having high levels of generic prescribing and competitive pricing while group 3 had fewer demand side policies to promote generic prescribing and implemented price cap regulation.[354]

He finds that:

- The first group of countries had a significantly higher rate of generic availability[355] compared to the third group of countries. This was also true considering the top and bottom decile of the markets. The number of molecules not experiencing generic entry post LoE was higher in the third group of countries compared to the first group.
- More than 60% of sales were genericised within the first 3 months of LoE in most group 1 countries (except the Netherlands) compared to group 2 and 3 markets, with some countries having significant lower generic penetration within this period (e.g. Austria 34%, Sweden 32%, Greece 12%).
- The size of the market is an important determinant of the number of generic competitors entering the market, with larger countries in terms of population experiencing a higher number of generic competitors in a given period compared to smaller population size markets. Also, within a given country, molecules in the top decile experience a larger number of generic competitors within a given period compared to molecules in the bottom decile in terms of sales.
- There is variation in the degree and speed of price erosion over time, with prices within the first 12 months declining faster and at a higher rate in the group 1 countries compared to group 2 and group 3 countries. Though in the majority of markets the price of originator drugs is lower following LoE, in Germany and Denmark, they find that the prices of originators appear to increase within 2 years of LoE.

352 Kanavos P. (2014), *Measuring performance in off-patent drug markets: a methodological framework and empirical evidence from twelve EU Member States,* Health Policy.

353 Austria, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Portugal, Spain, Sweden and the UK.

354 The first group (Denmark, Germany, the Netherlands and the UK) had high levels of generic prescribing and allowed competitive pricing of pharmaceutical products, including generics. The second group (Austria, Finland, France, Spain and Sweden) had moderate levels of generic prescribing and had policies of generic price reduction (e.g. price linkage). The third group (Italy, Greece and Portugal), implemented price caps on generics and had fewer policies to promote generic substitution.

355 Measured as i) the share of total molecules studied that experienced generic entry within the first 12 and 24 months following LoE, ii) share of sales facing generic entry over the same period, iii) the share of sales facing generic entry in top and bottom decile of each market.

Costa-i-Font et al (2014)[356] analyse the delay in generic launch since the first global launch of a generic in 20 major pharmaceutical markets over the period 1999 to 2008. They find that generic delay has reduced considerably over the period 1995-2008 compared to earlier periods and they attribute this to the policy changes implemented in a number of these countries over this period, including the harmonisation of EC pharmaceutical regulations in 2001 and the introduction of the Bolar exemption in 2004, as well as the earlier introduction of the Hatch-Waxman Act in the US in 1984. They also find that i) expected generic prices determine the time to launch with greater delays in markets where the regulated prices are very low and ii) expected generic market size is a significant determinant of the probability of generic entry.

Danzon & Furukawa (2011)[357], analyse the impact of regulation and competition in generic markets in ten countries (US, Canada, France, Germany, UK, Italy, Spain, Japan, Australia, Mexico, Chile and Brazil) over the period 1998-2009 using IMS data. The countries studied are categorised as pharmacy-driven markets, where the pharmacies are allowed to offer any generic substitute (US, Canada and UK) and physician driven markets, where the decision on which brand to prescribe is taken by the physician, as pharmacies are not allowed to or are not incentivised to substitute the cheapest generic alternative.

A number of European markets, including Germany, France, Italy and Spain, introduced reference pricing of generics (and sometimes also originators) during the 2000s accompanied with demand-side measures, such as allowing generic substitution by the pharmacy and providing incentives to pharmacies to dispense the cheapest generic.

The authors find that:

- The number of generic entrants is positively related to the size of the market (lagged sales) and the response is higher for unbranded generics compared to branded generics, suggesting that unbranded generics, due to lower prices, need a larger market to make entry worthwhile.
- Originator defence strategies, such as launching alternative formulations prior to patent expiry deter entry and reduce the number of generic entrants in Canada and the US, but not in other countries. The authors interpret this as being consistent with the hypothesis that in markets where prices are regulated, there are fewer incentives to launch alternative formulations, as the prices will be determined by those of older versions (unless the new ones are patented).
- The number of generic entrants is negatively associated with the share of hospital sales in a market, indicating that originators compete more aggressively in hospital markets compared to retail markets, making generic entry less profitable. Also generic entry is lower in more complex formulations, such as sustained release injections, due to the higher costs of production.
- Generic prices are negatively related to the number of unbranded generics in most countries. In France they find no effect of the number of competitors on

356 Joan Costa-i-Font, Alistair McGuire, Nebibe Varol, (2014), *Determinants of generic medicine adoption,* CEPR http://www.voxeu.org/article/determinants-generic-medicine-adoption

357 Danzon P., Furukawa M., (2011), *Cross-national evidence on generic pharmaceuticals: pharmacy vs physician-driven markets,* NBER Working paper 17226.

prices suggesting that price regulation in this market may have blunted price competition.

- Originator prices are unaffected by the number of generics (unbranded or branded) in the US, but are negatively affected by the number of unbranded generics in some European countries (France, Italy and Spain), suggesting that the reference pricing systems in these countries have reduced originator prices.
- The policy changes introduced in European countries during the 2000s to promote generic substitution have had a positive impact on generic entry and on the number of unbranded generic competitors in these markets.

The European Commission Chief Economist Team conducted an empirical study of the determinants of generic entry in 2009.[358] Using a sample of molecules that experienced LoE during the period 2000-2007, the estimated how the probability of generic entry is affected by a number of factors. They found that:

- The per capita sales of the originator product, pre-LoE were a significant determinant of the probability of generic entry.
- The geographical size of the market also attracts entry by generics.
- Molecules with a higher number of formulations tend to attract more entry than others.
- Policies involving compulsory generic substitution by the pharmacist positively affect the probability of generic entry.
- Price regulation in the form of price caps negatively affects the probability of entry.
- The probability of entry is higher in markets where the originator entered a licence agreement with a generic producer before the protection expiry date.
- The higher the number of countries in which the molecule lost LoE, the higher the probability of generic entry.

The ECT examined factors affecting the delay of generic entry. They found that generic entry is faster:

- In markets with a higher number of formulations per capita.
- In markets with higher per capita sales pre-LoE.
- In markets with a lower pre-expiry price. It is not clear whether this is the result of originators reducing prices before LoE to compete against generics.
- In markets that experienced LoE in a larger number of countries.
- In markets that have compulsory generic substitution and where physicists are encouraged to prescribe the INN rather than the brand.
- In markets without price caps, but this effect is not very strong and does not hold in robustness checks

358 Elzbieta Glowicka, Szabolcs Lorincz, Enrico Pesaresi, Lluis Sauri Romero, Vincent Verouden (2009), *Generic entry in prescription medicines in the EU: main characteristics, determinants and effects.* http://ec.europa.eu/dgs/competition/economist/prescription_medicines.pdf

The ECT also examined factors affecting generic prices and generic penetration. With respect to prices they found that:

- The larger the number of generic entrants the larger is the price drop, though the effect is small.
- Regulatory variables, such as compulsory generic substitution, INN prescribing, lowest price policy[359], frequent adjustment[360] and differential co-payment are associated with larger price drops, whereas the presence of price caps is associated with higher generic prices.
- The larger the per capita sales before LoE the larger the generic price drop.
- The larger the number of formulations, the lower the generic price drop, suggesting that markets with a larger number of formulations are more differentiated and can support higher prices.

With respect to generic penetration, they found that:

- The lower the generic price and the higher the originator price the higher is generic penetration.
- Regulation on compulsory substitution, INN prescribing and frequent price adjustments are positively related to generic penetration, whereas price caps are negatively related.
- The pre-expiry value per capita has a positive impact on generic penetration.

Kanavos (2008), uses IMS data on sales of thirteen molecules in seven countries (Germany, France, Italy, Spain, UK, US and Canada) and considers: i) the effect of generic competition on the price of originator drugs, ii) the effect of generic competition on the price of generics and iii) factors explaining generic penetration. Using aggregate level data, he finds that:

- The price of originator drugs is not significantly affected by the penetration of generics.
- The price of generic drugs is negatively affected by generic penetration in markets without reference pricing, i.e. where prices are determined competitively (UK and the US out of the 7 markets studied), whereas in countries where reference pricing exists there is no statistically significant impact of generic penetration on generic prices.
- Downstream retail competition (measured by the number of pharmacies) positively affects generic penetration. Also higher reference prices are positively associated with generic penetration suggesting that a higher reference price attracts more generic entrants.

Using more disaggregated level data, at the competitor level, he finds that a higher number of generic entrants is associated with higher generic prices in the UK whereas the number of generic entrants has no effect on generic prices in Germany and the US, suggesting that generic entry may not be a sufficient prerequisite for lower generic prices, as competition takes the form of product differentiation (different presentation, pack size,

359 Where the reimbursement level is set by reference to the price of the cheapest generic in the market.

360 Frequent adjustment indicates cases where reimbursement rates are adjusted frequently, once every 6 months.

dosage etc) which may not result in lower prices. Generally, the results suggest that generic prices are sluggish downwards, especially in markets where prices are not set competitively, suggesting that reference pricing may stifle price competition among generics.

Puig-Junoy et al (2009)[361] examine how changes in the Spanish reference pricing system have affected the likelihood of entry. They find that the likelihood of generic entry is positively affected by the market size, but negatively affected by the number of existing competitors for the product and the number of substitutes for the active ingredient. They also find that the system of generic reference pricing constrains generic entry, as the reference price acts as a ceiling, reducing incentives to compete on price to gain market share.

Magazzini et al (2004) [362] examine the determinants of generic entry following protection expiry during the period 1988 to 1995 in the UK, Germany and France. They find that i) generic entry and diffusion of unbranded generics is higher in larger sized markets, ii) the number of different brand names on the market (which suggests less loyalty to the originator brand) has a positive effect on generic diffusion; and iii) the size of the hospital segment has a negative impact on generic market shares. They conclude that the development of generic prices and generic product penetration vary significantly across countries and that the use of price regulation on patented products may act as an obstacle generic entry.

Some papers have also examined how reference pricing regulation has affected generic entry. Rudholm (2001) and Ekelund (2001) examined the relationship between reference pricing and generic entry in the Swedish market.[363] Whereas Ekelund found that the proportion of molecules experiencing entry following protection expiry is lower when the reference price system was set up, Rudholm was not able to identify an effect.

Last, Fiona Scott Morton (1999)[364] examined the determinants of generic entry in the US based on generic drug entries over the period 1984-1994. She found that firms tend to enter markets with demand and supply characteristics similar to their existing markets. Additionally, she found that entry was more likely in larger markets, markets with a higher share of hospital sales and in markets that treat chronic conditions.

361 Moreno-Torres I., Puig-Junoy J., Borrell J., (2009), *Generic entry into the regulated Spanish pharmaceutical market*, Review of Industrial Organisation, June 2009, Vol 34, Issue 4.

362 L. Magazzini, F. Pammolli and M. Riccaboni. (2004), *Dynamic Competition in Pharmaceuticals: Patent Expiry, Generic Penetration, and Industry Structure*, European Journal of Health Economics; 5: 175–182.

363 N. Rudholm (2001), *Entry and the number of firms in the Swedish pharmaceutical market*, Review of Industrial Organisation; 19: 351-364; and M. Ekelund (2001), *Generic entry before and after the introduction of reference pricing*, M. Ekelund (Ed.), Competition and innovation in the Swedish pharmaceutical market (Chap. 4,).

364 Fiona Scott Morton (1999), *Entry decisions in the generic pharmaceutical industry,* RAND Journal of Economics, Vol. 30 No. 3, Autumn 1999, pp421-440.

APPENDIX F: SPEED OF GENERIC ENTRY

Table 51: Markets experiencing generic entry following protection expiry during period 2008Q1 to 2014Q3, top 25% of molecules by pre-protection sales

		All molecules				Molecules in top 25% of sales				Molecules in bottom 25% of sales			
EEA Country	# of markets with observed generic entry during period	Share of molecules observing entry in Q1	Share of molecules observing entry in Q1-Q2	Share of molecules observing entry in Q1-Q4	Share of molecules observing entry in Q1-Q8	Share of molecules observing entry in Q1	Share of molecules observing entry in Q1-Q2	Share of molecules observing entry in Q1-Q4	Share of molecules observing entry in Q1-Q8	Share of molecules observing entry in Q1	Share of molecules observing entry in Q1-Q2	Share of molecules observing entry in Q1-Q4	Share of molecules observing entry in Q1-Q8
Austria	72	63%	71%	76%	92%	89%	94%	100%	100%	22%	39%	44%	72%
Belgium	73	58%	67%	79%	96%	78%	83%	89%	100%	37%	47%	63%	89%
Czech Republic	28	61%	61%	64%	93%	86%	86%	86%	86%	29%	29%	43%	86%
Finland	60	55%	65%	77%	95%	67%	80%	93%	100%	33%	33%	47%	80%
France	89	67%	76%	83%	90%	77%	86%	91%	95%	48%	61%	61%	74%
Germany	102	71%	76%	86%	92%	80%	84%	96%	100%	54%	62%	69%	77%
Greece	47	45%	57%	79%	94%	55%	64%	100%	100%	42%	58%	75%	92%
Hungary	38	45%	53%	74%	89%	33%	44%	67%	89%	30%	40%	70%	80%
Ireland	57	65%	65%	75%	91%	93%	93%	93%	100%	47%	47%	67%	87%
Italy	103	55%	66%	76%	85%	72%	80%	88%	92%	42%	54%	62%	69%
Netherlands	78	62%	71%	86%	97%	74%	89%	89%	100%	20%	35%	65%	90%
Norway	43	51%	67%	84%	98%	70%	70%	80%	90%	55%	82%	91%	100%
Poland	23	78%	78%	91%	100%	100%	100%	100%	100%	50%	50%	83%	100%
Portugal	53	55%	66%	79%	89%	77%	85%	92%	92%	29%	50%	64%	79%
Romania	47	77%	81%	87%	98%	91%	91%	91%	100%	58%	75%	75%	100%
Slovakia	27	81%	81%	81%	89%	100%	100%	100%	100%	71%	71%	71%	86%
Spain	71	73%	76%	86%	93%	94%	94%	100%	100%	44%	50%	67%	83%
Sweden	79	67%	70%	77%	91%	89%	89%	95%	100%	45%	55%	55%	80%
UK	83	60%	70%	82%	93%	75%	75%	90%	100%	38%	52%	67%	81%

Source: CRA analysis on IMS data

HOW TO OBTAIN EU PUBLICATIONS

Free publications:

- one copy:
  via EU Bookshop (http://bookshop.europa.eu);

- more than one copy or posters/maps:
  from the European Union's representations (http://ec.europa.eu/represent_en.htm);
  from the delegations in non-EU countries
  (http://eeas.europa.eu/delegations/index_en.htm);
  by contacting the Europe Direct service (http://europa.eu/europedirect/index_en.htm)
  or calling 00 800 6 7 8 9 10 11 (freephone number from anywhere in the EU) (*).

  (*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Priced publications:

- via EU Bookshop (http://bookshop.europa.eu).

Priced subscriptions:

- via one of the sales agents of the Publications Office of the European Union
  (http://publications.europa.eu/others/agents/index_en.htm).

ET-04-17-817-EN-N

Publications Office

doi: 10.2873/673124