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Assessing the impact on the life sciences industry of a change in the UK relationship with the EU

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Table of contents

Executive summary vi

1. Introduction 1
1.1. Background to this report 1
1.2. The approach to the project 2
1.2.1. Scenarios on the UK relationship post Brexit 2
1.2.2. Evidence on the impact on life sciences industry in UK and EU 3
1.3. Structure of the report 4

2. How integrated is the life sciences industry in the UK with that in Europe and what impact could a change in the EU relationship have 5
2.1. Activities undertaken by the UK Life sciences industry 5
2.2. Basic research 6
2.2.1. The role of EU legislation 9
2.3. Product development and approval regulation 13
2.3.1. The role of EU legislation 15
2.4. Manufacturing and trade 17
2.4.1. The role of the EU legislation 17
2.5. Market Access 19
2.5.1. The role of EU legislation 19
2.6. Summary 21

3. Learning from the experience of Norway, Switzerland and Canada 23
3.1. Drawing from the Norwegian experience to understand the impact of EEA membership 24
3.1.1. Basic research and product discovery. 24
3.1.2. Product development and approval regulation 26
3.1.3. Manufacturing and trade 29
3.1.4. Market Access 30
3.1.5. Conclusion and implications for the UK 31
3.2. Drawing from the Swiss experience to understand the impact of multiple sectoral bilateral agreements with the EU 32
3.2.1. Basic research and product discovery 33
3.2.2. Product development and approval regulation 36
3.2.3. Manufacturing and trade 39
3.2.4. Market Access 42
3.2.5. Conclusion and implications for the UK 42

3.3. Drawing from the Canadian experience to understand the impact of "comprehensive" FTA with the EU 44
3.3.1. Basic research and product discovery 45
3.3.2. Product development and approval regulation 46
3.3.3. Manufacturing and trade 47
3.3.4. Market Access 49
3.3.5. Conclusion and implications for the UK 50

4. Learning from life science industry stakeholders 52
4.1. Basic research and product discovery 52
4.1.1. Collaboration 52
4.1.2. Funding 54
4.1.3. Ensuring researcher mobility 55
4.1.4. Patent enforcement 56
4.1.1. Conclusion on impact of Brexit on research and product discovery 57
4.2. Product development and approval regulation 60
4.2.1. Product development regulation 60
4.2.2. The centralised authorisation procedure 61
4.2.3. Conclusion on impact of Brexit on product development 63
4.3. Manufacturing and Trade 65
4.3.1. EU legal manufacturing framework 65
4.3.2. Access to the EU single market (tariff and customs union) 66
4.3.3. Trade agreements with countries outside of the EU 66
4.3.4. Labour availability 67
4.3.5. Investment decisions 68
4.3.6. Conclusion on impact on manufacturing and trade 68
4.4. Market Access 71
4.4.1. Pricing and reimbursement 71
4.4.2. Compliance to the EU competition policy 72
4.4.3. Falsified medicines directive (e.g. traceability) 73
4.4.4. Conclusion on market access 73
4.5. Summary table 77

5. The transition 79
5.1. Impact on industry 80
5.2. Impact on EMA and regulatory process 84

Appendix 87

Table of Figures

Figure 1: Summary of the impact of three Brexit scenarios on the life sciences industry in the UK x
Figure 2: The healthcare biotech value chain 5
Figure 3: Proportion of biotechnology research institutions ranked in the top 200 publishing institutions, by country 7
Figure 4: Top 40 companies by number of collaborations 8
Figure 5: Flow of funds between the UK and EU 2007 – 2013 (€ billion) 11
Figure 6: UK expenditure on research and development by source of funding. 2007 – 2013 12
Figure 7: The number of clinical trials 14
Figure 8: Rapporteur by country 16
Figure 9: Clinical trials in Europe 27
Figure 10: Timeline for negotiating CETA 44
Figure 11: EMA staff composition – by nationality 85

Table of Tables

Table 1: Comparing the UK to scenario countries 23
Table 2: Comparison of Swiss Human Research Act and EU Clinical Trials Regulation 37
Table 3: Average negotiation time for Canadian FTA with third countries 49
Table 4: Summary of the impact of Brexit on components of basic research and product discovery from the perspective of the UK and European life sciences industry 57
Table 5: Impact of Brexit on basic research and product discovery under the 3 “Brexit” scenarios from the perspective of the UK and European life sciences industry 60
Table 6: Summary of the impact of Brexit on components of product development and approval from the perspective of the UK and European life sciences industry 63
Table 7: Impact of Brexit on product development and approval regulation from the perspective of the UK and European life sciences industry 65
Table 8: Summary of the impact of Brexit on components of manufacturing and trade by the UK and European life sciences industry 68
Table 9: Impact of Brexit on Manufacturing and Trade from the perspective of the UK and European life sciences industry 70
Table 10: Summary of the impact of Brexit on components of market access from the perspective of the UK and European life sciences industry 73
Table 11: Impact of Brexit on pharmaceutical market access from the perspective of the UK and European life sciences industry 75
Table 12: Implications of a change in UK relationship for activities along the value chain 77
Table 13: Interviews conducted 87
Table 14: Comparing Regulatory Approval by EMA vs SwissMedic 88
Table 15: Comparing Regulatory Approval by EMA vs Health Canada 89
Table 16: EU-Korea Free Trade Agreement vs EU-Korea Free Trade Agreement 90

Executive summary

The European Federation of Pharmaceutical Industries and Associations (EFPIA) asked Charles River Associates (CRA) to conduct an independent and objective assessment of the impact on the life sciences industry in Europe of a withdrawal of the United Kingdom from the European Union (commonly described as British exit from the EU or 'Brexit'). The broad goal of this project is to identify, from both a UK and a European perspective, the positive and negative impacts that a change in the relationship might have upon activities along the industry's value chain. Specifically, we have looked at:

- The potential gains and losses to European life sciences industry;
- The key arguments for the industry to use when formulating and communicating a position on Brexit from a European perspective.

To investigate the impact of the UK developing a new relationship with the EU, we need to set out how this relationship might work in practice. As is common in assessments of Brexit, we have considered different scenarios: European Economic Area (EEA) membership (similar to Norway), multiple sectoral bilateral agreements with the EU (similar to Switzerland), a "comprehensive" Free Trade Agreement with the EU (similar to Canada) and a Full Break model governed solely by WTO free trade rules, i.e. no specific agreement with the EU. However, it is important from the outset to highlight that a change in the UK's relationship with the EU will not change all of the rules governing life sciences in the UK. The life sciences industry is a global industry, and this has implications for how it is regulated and how trade is conducted. Whichever scenario occurs, we do not envisage tariffs being applied to Active Ingredients (AIs) or finished pharmaceutical products or the UK departing from international agreements on how medicines are regulated. To investigate the impact under these different scenarios, we have looked in detail at the situation in Norway, Switzerland, and Canada along the life sciences value chain and undertaken 30 interviews involving industry trade associations, large multinational companies, small biotech companies based in the UK, specialist research organisations located in the UK, UK universities with researchers involved in collaborative projects with the life sciences industry, and charities involved in funding R&D.

Current integration of the UK life sciences industry and the potential impact of Brexit

The life sciences industry operates globally – from basic research to product development, manufacturing and commercialisation. The long tradition of bioscience research excellence in academia and clinical research in leading UK hospitals plus associated industrial investment in a growing number of UK life science 'clusters' has made the UK one of the leading centres in the world for developing new medicines. The life sciences industry in the UK is remarkably successful (in terms of academic publications or investment in R&D or its ultimate contribution to developing successful medicines) for a range of different reasons relating to its history, academic links and industrial policy. European regulation has played an important role in the evolution of the industry in Europe and in the UK, and hence the UK leaving the European Union has the *potential* to have a significant impact along the value chain:

- Basic research: European collaborative projects and funding are material factors in supporting basic research activities in the UK. If the UK were to leave the EU, access to European research funding would clearly change. This could reduce the amount of research ongoing in the UK (depending on the degree to which the UK government

replaced the level of funding), and it could also change the willingness of academic centres to collaborate with the UK. Researchers might need to apply for visas, and there could be additional complications in terms of hiring from outside of the UK and for UK researchers finding work in the EU. It is possible that companies would lose the benefit of applying for a unitary patent that covers the UK as part of the EU and this would lead to the need to apply for both a UK and a European patent. However, there is a counterargument that public funding at a national level is less bureaucratic and this could lead to more responsive and efficient research funding focusing on the UK's strengths.

- Product development: The UK is an important location for clinical trials, regulated under European rules and fully integrated into the European medicine approval system. If the UK was outside of the EU, theoretically it would have the choice of either complying with EU clinical trial regulation or developing its own regulatory process (which would increase costs to the UK but allow it to develop its more liberal rules) as well as its own rules on data protection. This could possibly reduce regulatory costs falling on innovative companies (for example, it could have allowed the UK to avoid the impact of the Clinical Trials Directive) and increase the attractiveness of undertaking trials in the UK. However, given that UK clinical trials, particularly larger Phase III trials, will inevitably be part of broader international programmes, this might add to the complexity of co-ordinating trials, with the potential to lead to fewer trials being undertaken in the UK. For Europe, the UK leaving the EU reduces the value of the European clinical trials rules and therefore appears to make undertaking trials in Europe marginally less attractive.
- Manufacturing and trade: Membership of the EU has brought some significant benefits to the UK, for example, in the recognition of Good Manufacturing Practice (GMP) standards; however, there are also areas where European regulation may have increased costs, such as from the imposition of REACh. Therefore leaving the EU has the potential to increase or reduce costs. Turning to trade, in terms of impact on Free Trade Agreements (FTAs) with other countries, clearly the UK is able to exploit agreements agreed by the EU, but it can also be argued that the UK would have been able to negotiate improved terms outside of the EU.
- Market access: Market access is primarily determined by national rules, and European regulation has had relatively little impact on the UK. However, as described above, a separate marketing authorisation process in the UK post Brexit could translate into delayed market access for some products. Furthermore, some EU initiatives have improved market access by encouraging innovation (such as the development of an orphan medicine regime) and the UK might not be able to participate in these going forward. However, it is also possible to argue that European rules reduce market access (such as the way in which EU competition law facilitates parallel trade) and Brexit could be beneficial to the industry in the UK and to UK patients.

Learning from the experiences of Norway, Switzerland and Canada

One way to look at the impact of a change in the relationship between the UK and the EU is to look at other countries and the relationships they have with the EU. We have considered the experience of the life sciences industries in Norway, Switzerland and Canada and the extent to which lessons are applicable to the UK.

Participation in EU science programmes

A number of countries outside the EU have succeeded in negotiating access to all or some parts of the EU research programme. Norway benefits from full participation in EU science programmes like Horizon 2020 but has had to make a substantial financial contribution to obtain participation. Norway's contributions to the major EU programmes for research and innovation, education, and culture amounted to around €3.2 billion. In contrast, Switzerland has only partial access. The proposed limitations on freedom of movement, following the February 2014 referendum on curbing immigration, have led to restrictions on access to European funding through Horizon 2020 and uncertainty regarding how this will evolve in the future, with significant concerns from academia and the industry in Switzerland. Under a Canadian type bilateral agreement model, the UK would have even less access to the EU research programme.

Compliance with EU regulations

EEA members such as Norway are bound by EU regulations (although in practice there are a number of exceptions where Norway does not comply with EU rules) but have no influence on the legislative process. The result of this is that Norway adopts marketing authorisations issued by the EU. Turning to Switzerland, there has been a close on-going dialogue with the EMA but Switzerland has maintained much of its own regulatory framework for issuing product licenses for pharmaceuticals under the control of the national medicines agency (SwissMedic). Similarly, Health Canada is solely responsible for evaluating drug approval packages and issuing Canadian product marketing licenses, although there is a collaboration programme with EMA allowing some exchange of information on pre- and post-authorisation applications. Collaboration is possible under all the models but where countries have separate regulatory process, there is a delay. Experience from both Switzerland and Canada shows that marketing approvals often occur later than those in the EU, on average 157 days after EMA approval for Switzerland and 144 days later for Canada.

Ability to conduct trade deals

Countries that are not a member of the EU can conduct trade deals with third countries or remain out of some key EU policies such as the common agricultural policies or the EU foreign/security policies. However, it can be argued that such components have little or no impact on the life sciences sector. Both Norway and Switzerland's ability to conduct its own trade deals has not brought significant benefits to the life sciences industry. In addition, individually renegotiating these deals with third countries takes a significant amount of time. Looking at the experience of CETA and other Canada FTAs, we find that a bespoke UK-EU trade agreement would be complex to negotiate and would take many years.

Learning from life sciences industry stakeholders

However, the UK is not Norway, Canada or Switzerland. To look at the specific issues for the UK and the EU, we interviewed current participants in the life sciences value chain and asked them what would happen under different Brexit scenarios to the industry and their organisation. In general, EEA membership would have the least impact on the life sciences industry because of its many similarities to the current EU membership (however, the industry in the UK would lose significant influence in terms of policies affecting the European market), while both of the bilateral agreements and a full break from the EU would have greater ramifications (Figure 1). In all alternative scenarios, the EU would also face negative implications.

Looking along the value chain, the impact is most significant for the basic research, then for product development and approval, then for manufacturing and trade, with only a minor impact on market access. Our conclusions for each stage of the value chain are as follows:

- Basic research: With bilateral agreements or a full break it could be expected that access to EU research funding would be limited, whether partially or completely. This would diminish the UK's reputation for life sciences, and although collaboration would continue, it would be negatively affected. UK academic researchers and Small and Medium Enterprises (SME) report that it would be more challenging to collaborate with EU experts without EU collaborative frameworks. Based on past performance, it seems reasonable to conclude national funding would not replace the lost European research funding. Limitations on the free movement of people would have a negative impact on both the UK and EU academic research and SMEs.
- Product development and approval: Under a bilateral agreement or if the UK took a full break from the EU, the UK would not be bound by EU regulation and would need to develop its own regulatory framework for pharmaceuticals. If the UK did not comply with the European Clinical Trials rules, then the attractiveness of the UK and to a much lesser extent also the EU as a location for later stage clinical trials (Phase II, Phase III) would be reduced. In terms of product approval it is unlikely that the UK would develop regulations that are significantly different from the current EU standards, although over time some differences in regulatory standards would no doubt emerge. Most companies interviewed stressed that there would not be any advantage for the UK in developing a market authorisation process that was divergent from the EMA. This would be likely to cause delays in marketing authorisation (even if the process itself was faster) and additional costs for companies and would adversely affect access to medicines, especially products that are not subject to the health technology assessment process (for example, some orphan medicinal products). In this case, the UK and EU would lose some of the benefits of sharing expertise in drug regulatory processes.
- Manufacturing and trade: The impact of Brexit on manufacturing and trade would depend largely on the type of agreement that the UK was able to negotiate in terms of mutual recognition of manufacturing regulations and arrangements as well as limitations on labour market mobility. Mutual recognition of GMP inspections is an important issue and saves the pharmaceutical industry significant costs, and it is likely (although not certain) that the UK would be able to negotiate such a deal over time. In terms of freedom to negotiate FTAs with other countries (under a bilateral agreement or a full break), we do not find the prospect of the UK being able to negotiate its own trade agreements compelling from a life science perspective (on the contrary, losing access to EU negotiated treaties is likely to be detrimental). Both UK and EU life sciences industry rely on each other for skilled staff (including managerial and operational) so that a limitation on the free movement of people would have a negative impact on manufacturing (as well as other activities along the value chain).
- Market Access: Brexit would have little direct impact on the rules determining price and reimbursement and market access. Under bilateral agreements or a full break scenario, the UK would no longer be subject to the EU Transparency Directive or part of ongoing initiatives to improve access. However, we conclude this is unlikely to have a significant impact. There would be more freedom regarding the application of rules on state aid and the rules governing parallel trade, which could be beneficial to the industry in the UK and patients. However, we again do not believe these benefits will be significant.

In other areas it is likely that the UK would continue to comply from outside the EU – for example, with the Falsified Medicines Directive. However, the delay in marketing authorisation could delay access to some products. For example, a 6 month delay seems likely given the experience of other countries.

This is summarised in the table below.

Figure 1: Summary of the impact of three Brexit scenarios on the life sciences industry in the UK

Trade model	Assumptions	Basic Research	Collaboration	Product development	Regulatory Approval	Manufacturing & Trade	Market Access	Overall assessment
EEA like member model	• Full access to EU single market • Free movement of people • Full access to EU R&I framework (HR 2020) • Full adoption of EU regulatory framework • Conduct its own trade deals (outside EU negotiating platform)	Little impact- Full access to EU research programme . UK science base risk losing leadership role	No impact- Full access to EU research funds & collaborative programme	EU Clinical Trials Directive Standards & Conditions Some loss of influence over regulatory framework	Applications continued to be processed by EMA. Some loss of influence of regulatory framework	Full compliance with EU GMP framework UK likely lose negotiating power to ensure strong IP agenda	No change to P&R system or compliance with regulation	Limited impact but loss of influence over future of regulation
Bilateral treaties model	• Likely to have access to EU single market • Some restriction on free movement of people but visa waver prog for scientists • "associated country" status to EU R&I framework • Own regulatory framework but some regulatory alignment expected • Conduct its own trade deals (outside EU negotiating platform)	UK universities lose funding and coordinator role More limited access to major EU science progs.	SME lose funding and but keep ability to collaborate.	More difficult for biopharmaceutical companies to conduct multinational clinical trials	Companies face extra cost of MA approval Separate regulatory approach (even based on consistent approach) will lead to regulatory delay	UK would need to ensure mutual recognition of GMP standard UK likely lose negotiating power to ensure strong IP agenda	Possibility to ban parallel trade and benefit from state aid Delay in regulatory approval would delay access (for some products) & loss of influence on wider policies affecting market access	Some added complexities to pharmaceutical operations but no direct business risk
Full break: WTO model	• WTO general trade & tariff principles apply • WTO dispute resolution mechanisms • Framework for bilateral treaties • No access to EU research programme, • Little or no regulatory alignment between UK and EU • MHRA would likely set EMA / FDA compatible standards & issue UK product licenses	Loss of credibility as science leader in Europe UK funding does not replace EU funding	Reduced opportunities to collaborate and no platform/mechanism to join research consortium (e.g. IMI) - weakened research clusters and fewer biotech start-ups	No regulatory alignment between UK and EU Significant barriers for SMEs Reduction in clinical trial activity	Additional costs and time to get MA approval outside UK Likely delays in approval and access to medicines	Lack of mutual recognition of GMP standard but outside of REACh UK would need configure its own trade relations with other countries and likely to lose negotiating power to ensure strong IP agenda	Possibility to ban parallel trade and benefit from state aid Delay in regulatory approval delays access & loss of influence on wider policies affecting market access	Makes operation of pharmaceutical companies significantly more complex This model might open up greater flexibility for UK policy but benefits are modest

Source: CRA analysis

Legend

	Minor impact	Some impact	Significant impact	Major impact
Positive impact				
Negative impact				

The transition

We now turn to assessing the impact that the transition period would have on the life sciences industry in the UK and in Europe more broadly. Even where commentators disagree on the benefits or costs of Brexit, most agree that a vote to leave the EU would lead to a period of uncertainty during the transition period with negative economic consequences. Looking at a range of different trade agreements negotiated by our case study countries these typically take years to negotiate. Even though regulation affecting the life sciences industry would be aligned (as the UK applies those rules today), issues affecting other industries will lead to complex negotiation and delay. It seems reasonable to conclude that there would be considerable uncertainty over the first two years and potentially for 5-10 years. There are many questions about the transition period we do not know the answer to.

The life sciences industry is unusual in that investments occur periodically, in terms of the location of research hubs, clinical trial programmes and manufacturing plants, but these decisions determine the location of activity for many years (reflecting the life cycle of the products is over twenty years) and once the decision is taken it is difficult to change. Drawing on economic theory, empirical analysis and the interviews, we find that although the long-term outcome of these questions might not have a significant impact on the attractiveness of the UK for locating life sciences activities, the uncertainty during the transition will lead to a reduction in investment in R&D and manufacturing that will have consequences for many years.

More broadly in terms of the life sciences in Europe, leaving aside the macroeconomic impact, the biggest impact during the transition is the need to relocate the EMA. This will have a number of consequences including the disruption during the physical move, the loss of staff, the loss of capacity to undertake reviews, and the loss of experience**.** We conclude that as the reputation and expertise of the EMA is now well established, relocation after a sensible long-term transitional period should not constitute a serious threat to the EMA continuing to grant timely access for innovative medicines to all EU markets. However, it is possible that the transition would lead to delays. For example, if it reduced the capacity of the EMA to review products in line with loss of UK capacity, this could result in a delay of 2-3 months for two years.

Conclusion

The industry position at a European level and in the UK is to support the UK remaining in the EU. Brexit would add a number of unnecessary barriers to undertaking activities in the UK along the value chain and add considerable uncertainty during the transition. In the case that the free movement of people is restricted, the UK life sciences industry would also face additional challenges to accessing EU staff for scientific, managerial and operational positions, as well as consequences for EU research funding. As a global industry, the life sciences industry would not stop investing entirely in the UK, but it is clear from our analysis that this would have short and long-term consequences in terms of the competitiveness of the UK. There would be very few advantages from Brexit for participants in the life sciences industry. This is consistent with the industry position.[1] More importantly,

1 The Guardian – Observer (2016), "Brexit 'will put UK access to cutting-edge medicines at risk. – Letter from top drug companies offers boost to David Cameron and remain campaign in EU referendum." Available at: http://www.theguardian.com/politics/2016/may/07/brexit-uk-medicines-cameron-eu-referendum

however, is the impact on patients. The industry's purpose is to develop medicines to serve patients and improve the provision of healthcare. We can find no advantages from the perspective of the patients; indeed, the UK's withdrawal from the EU is only likely to delay the introduction of new medicines.

1. Introduction

The European Federation of Pharmaceutical Industries and Associations (EFPIA) asked Charles River Associates (CRA) to conduct an independent and objective assessment of the impact on the life sciences industry in Europe of a withdrawal of the United Kingdom from the European Union (commonly described as British exit from the EU or 'Brexit'). The broad goal of this project is to identify from both a UK and a European perspective, the positive and negative impacts that a change in the relationship might have upon activities along the industry's value chain. Specifically, we have looked at:

- The potential gains and losses to European health life sciences industry;
- The key arguments for the industry to use when formulating and communicating a position on Brexit from a European perspective.

1.1. Background to this report

There has been an active debate in the media and between politicians regarding the political and economic case for a change in the relationship between the UK and the EU. Many other industries have set out their position on the impact of a change in the UK relationship; for example, the automotive industry[2], the travel industry[3] and the energy sector.[4] The position of the innovative health biosciences industry has also been discussed in a series of reports and positions over the last five years.[5] In March 2016, EFPIA published an outline preliminary statement suggesting that the UK remaining within the EU would be in the best interest of the industry.[6] In addition, some individual EFPIA member companies have commented publicly on the benefits of maintaining the current relationship.[7] Although, there have been some academic papers and events considering the pros and cons of a Brexit for particular parts of the industry,[8] there has not been a report considering the whole of the Life Science eco-systems in the UK and Europe and the impact

2 KPMG (2014) The UK Automotive Industry and the EU; An economic assessment of the interaction of the UK's Automotive Industry with the European Union

3 Deloitte (2015) What Brexit might mean for UK travel. https://www2.deloitte.com/content/dam/Deloitte/uk/Documents/consumer-business/deloitte-uk-brexit-report-abta-march-2016.pdf

4 Vivid Economics (2015) Impact of Brexit on the UK energy sector. http://www.vivideconomics.com/publications/the-impact-of-brexit-on-the-uk-energy-sector

5 For example "EU- UK :What Brexit would mean for our industry –EFPIA Statement 2013"; "EU impact on Life Sciences" A report by Open Europe (January 2014).

6 See EFPIA web site http://efpia.eu/blog/2/21/EU-UK-What-Brexit-would-mean-for-our-industry

7 See GSK statement reported in the UK Sunday Times http://www.thesundaytimes.co.uk/sto/business/Finance/article1680007.ece

8 For example, there have been discussion initiated by lawyers such as Hogans Lovells "UK pharma: getting ahead of the Brexit debate" and public affairs agencies, such as Burson-Marsteller "Brexit, Health Policy and Pharmaceuticals" and in Scrip "18 ways a Brexit would affect Pharma" and most recently the comment in the Lancet considering the impact on healthcare "Brexit: a European perspective" Josep Tabernaro and Fortunato Ciardiello, Lancet Oncology, 17,5,558-559,May 2016.

of a Brexit upon them over the short, medium and long-term. This is the objective of this report.

1.2. The approach to the project

To investigate the impact of the UK leaving the EU and developing a new relationship we need to set out how this relationship would work in practice. We know from the EU treaties that there is provision for a country leaving the EU. Article 50 of the current EU Treaty[9] specifies the terms under which a Member state may leave and procedure to be followed. This also provides some guidance on timescale. The UK would cease to be an EU Member State either at the date of entry into force of the withdrawal agreement or, 'failing that', two years after the notification of its intention to withdraw from the EU, unless the European Council and the UK unanimously agree to extend that period. However, this process does not *per se* specify the type of relationship that will result from this negotiation, which will depend on negotiations between the UK and the EU, which in turn may depend upon other changes in the geopolitical and macroeconomic arena.

1.2.1. Scenarios on the UK relationship post Brexit

There are many reports that already have discussed the range and flavour of macro or high level political, social and economic scenarios; many of these have focussed strongly upon the economic consequences – our aim is not to repeat this debate but focus on the impact on life sciences industry.[10,11] However, it is important from the outset to highlight that a change in the UK's relationship with the EU will not change all of the rules governing life sciences in the UK. The life sciences industry is a global industry and this has implications for how it is regulated and how trade is conducted:

- Regulation: There are global standards that would apply under any of the scenarios. For example, the UK would continue to follow the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). This sets out guidelines that are adopted by most developed markets.
- Trade: It is important to note that none of the scenarios considered would result in tariffs being applied to pharmaceutical products. The Pharmaceutical Tariff Elimination Agreement was agreed by 22 countries during the Uruguay Trade Round and entered into force on 1st January 1995. It eliminated tariffs on thousands of pharmaceutical entities and includes a commitment not to replace tariff barriers with non-tariff barriers

9 12002E/TXT, Treaty establishing the European Community (consolidated version), Official Journal C 325 , 24/12/2002 P. 0033 – 0184, Official Journal C 340 , 10/11/1997 P. 0173 - Consolidated version

10 For example, the UK Government has recently released a report which explores possible alternatives to EU membership and looks at the potential models for the UK's relationship with the EU. HM Government (2016) "Alternatives to membership: possible models for the United Kingdom, outside the European Union", March 2016; presented to Parliament pursuant to section 7 of the European Union Referendum Act 2015

11 The Financial times (February 9, 2015) "If Britain goes: Counting the cost of 'Brexit' Chris Giles and Ferdinando Giugliano"; accessible at http://www.ft.com/intl/cms/s/0/8e10bb3c-a7d1-11e4-be63-00144feab7de.html#axzz3yv9AWK00

and even extends to products imported from states not signatory to the Agreement. All finished pharmaceutical products are automatically covered by the Agreement.[12]

As is common in assessments of Brexit, we have considered different scenarios: EEA membership, multiple sectoral bilateral agreements with the EU, a "comprehensive" Free Trade Agreement with the EU and Full Break, i.e. no specific agreement with the EU.

1.2.2. Evidence on the impact on life sciences industry in UK and EU

To understand how the Health Life Science industry is affected under the different scenarios we have undertaken:

- A literature review on the performance of the industry in the UK today and its integration with the EU.
- Interviews with the industry associations in markets closely identified with each scenario (Interfarma in Switzerland, Innovative Medicines in Canada, Legemiddelindustrien (LMI) in Norway) about their perspective on their country's current relationship with the EU, the future and degree to which this has lessons for the UK.
- Interviews with stakeholders involved in the life sciences eco-system to understand their perspective on a change in the UK relationship on both the industry in the UK and in Europe. This includes:
    - The UK industry trade associations – the ABPI and BIA.
    - Large multinational companies with (1) their global headquarters in the UK (2) European headquarters in the UK (3) US headquartered companies with research and manufacturing in the UK (4) Swiss headquartered companies with research and manufacturing in the UK.
    - Small biotech companies with headquarters in the UK.
    - Specialist research organisations located in the UK that work with innovative pharmaceutical companies in product development.
    - UK universities with researchers involved in collaborative projects with the life sciences industry.
    - Charities involved in funding R&D.

The full set of 30 completed interviews are listed in the appendix. For some organisations multiple interviews were undertaken to reflect the perspective of those involved in different activities in the value chain. These were conducted under the agreement that we would not directly quote individuals or their organisation and these were the views of the individuals interviewed.[13]

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12 However, active ingredients and intermediates (used in the manufacture of finished pharmaceuticals) do not automatically qualify for zero tariffs and must be formally added to the list of eligible products http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+WQ+E-2004-0213+0+DOC+XML+V0//EN&language=bg

13 In addition, CRA approached a number of public bodies involved in life sciences value chain for their perspective on the impact of Brexit but they were not available for an interview.

1.3. Structure of the report

The report is structured as follows:

- Chapter 2 assesses the current integration of the life sciences industry in the UK, the role of European regulation and the theoretical impact of Brexit along the value chain from R&D through to commercialization. This highlights the potential losses and gains of a Brexit to the life sciences industry in the UK and in Europe.
- Chapter 3 considers the lessons from Switzerland, Norway and Canada.
- Chapter 4 draws directly from the interview programme to consider the impact of Brexit for each stage of the value chain.
- Chapter 5 looks specifically at the transition to any new relationship and what would happen during this period.

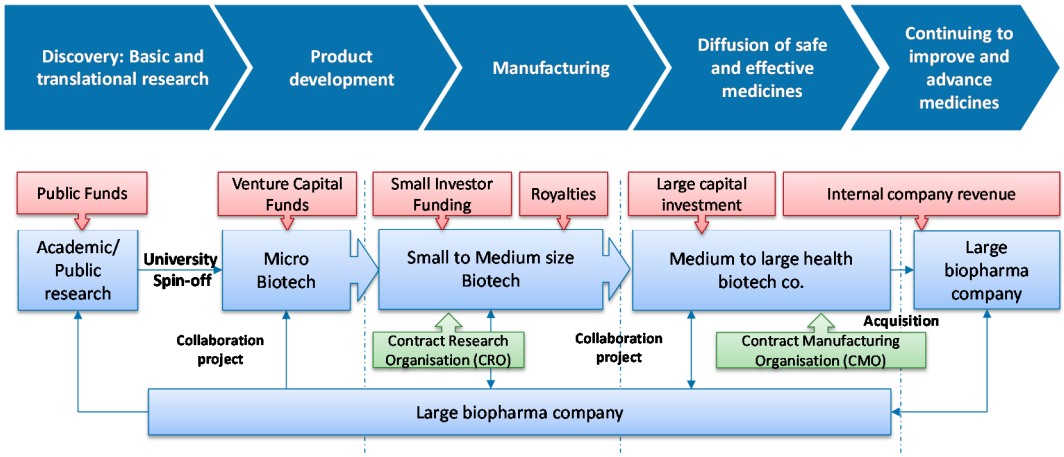
2. How integrated is the life sciences industry in the UK with that in Europe and what impact could a change in the EU relationship have

To work out the impact of Brexit on the activities undertaken by the life sciences industry in the UK and Europe, we need to start from the situation today. We consider the extent to which this is affected by European legislation and then ask the question what could be the impact of the different Brexit scenario along the different stages of the pharmaceutical value chain, from research and development through to commercialisation. This also considers the potential impact of those directly linked to the pharmaceutical industry; e.g. academic research and suppliers.

2.1. Activities undertaken by the UK Life sciences industry

The life sciences industry is a global industry with activities from discovery, development, manufacture and distribution of innovative medicines governed by legislation at both a national and international level.

Figure 2: The healthcare biotech value chain



Source: CRA analysis

The global nature of the industry is easy to illustrate, looking at an individual medicine, this product might have derived from original research by a team in the US, working in collaboration with UK and French academic centres. It could have been patented by a biotech company in Belgium, and then developed in partnership with a global pharmaceutical company in Switzerland, and then marketed in association with a UK company, with the API being manufactured in China and formulated and packaged in Germany.

Another way to illustrate the global nature of the industry, the ABPI has 54 full member companies, only 6 are headquartered in the UK, 20 in the EU and 3 more in the rest of Europe. If we consider smaller life sciences companies with activities in the UK, they are more likely to be headquartered in the UK. For example, looking at the membership of the BIA, this has 158 members with 133 in the UK, 8 in the EU and 2 more in the rest of Europe. Indeed, although it is common to think of the industry in terms of large multinational companies with research activities in the golden triangle of Oxford, Cambridge and London, the industry is heterogeneous and has a geographical spread comprising of commercially

mature clusters in England, a strong contract research organisations and clinical presence in Scotland, and a growing medtech sector in Wales.

The UK has a successful and growing life sciences industry as illustrated by the number of pharmaceutical companies operating in the UK growing over the last five years. According to the Office for National Statistics, by 2015 the number of enterprises operating in the UK was 529.[14] The industry in the UK is clearly important to both the UK economy and to the overall European Life Sciences industry.

- The contribution of the UK life sciences industry to the UK economy is significant as reported regularly by the ABPI. They document the industry contribution to employment with 73,000 people directly employed in the UK.[15] The purchases and collaboration leads to thousands of additional jobs in related industries across the broad life sciences sector, which includes the biotechnology, medical technology and diagnostics industries. The industry is part of a much wider ecosystem which extends across universities, charities, research bodies and numerous collaborative projects and networks across the UK.
- It makes a significant contribution to economic performance, with gross value added of around £13 billion which is 0.8% of the UK economy,[16] R&D of £4.1 billion representing 22% of all expenditure on R&D in UK businesses in 2013[17], and a trade surplus of £3bn for the UK per year.[18]
- From a European perspective the activities of the industry in the UK represent 16% of R&D spend, 10% of employment, 8% of production.[19] To put this into context, the UK market is only 9% of the European pharmaceutical market.

2.2. Basic research

The UK is one of the strongest countries in Europe for basic research. The UK is recognised as a global leader in health research with a mature research ecosystem comprising world-class universities, institutes and government agencies.[20] The UK has some of the leading biomedical universities in the world. According to the Nature Publishing Index Global Top 200[21] (which ranks biomedical research institutions according to the number of primary

14 "Adapting the Innovation Landscape UK Biopharma R&D Sourcebook 2015" ABPI

15 EFPIA Fact and Figure 2015 accessible at http://www.efpia.eu/uploads/Figures_2015_Key_data.pdf

16 ONS GDP(O) low level aggregates (March 2016) as reported in HM Government (2016), "HM Treasury analysis: the long-term economic impact of EU membership and the alternatives." Available at: https://www.gov.uk/government/publications/hm-treasury-analysis-the-long-term-economic-impact-of-eu-membership-and-the-alternatives. Gross Value Added (GVA) is the contribution made by businesses, industries or sectors to the UK's national income – in other words, an industry's contribution to gross Domestic Product (GDP).

17 "Adapting the Innovation Landscape UK Biopharma R&D Sourcebook 2015" ABPI

18 "Delivering value to the UK The contribution of the pharmaceutical industry to patients, the NHS and the economy" ABPI, Amended January 2016.

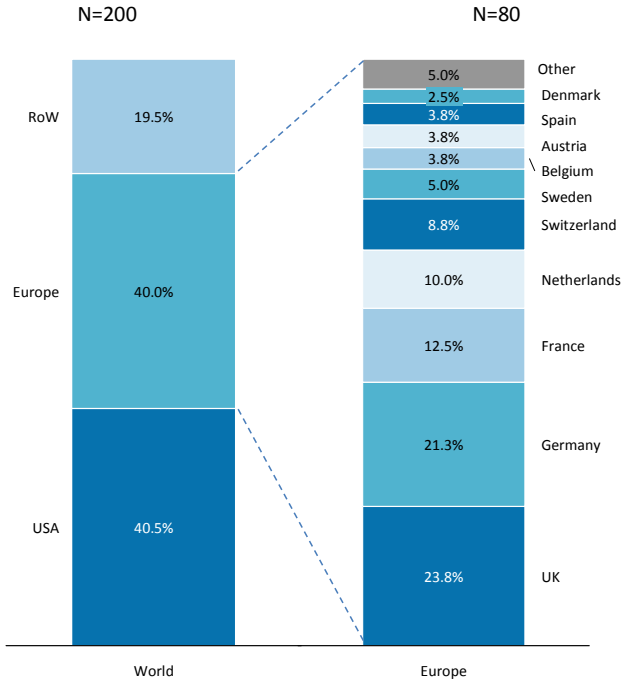
19 "The Pharmaceutical Industry in Figures" EFPIA 2015

20 Medical Research Council. 2012. UKCRC. UK Health Research Analysis. London: UK Clinical Research Collaboration. http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC008927

21 Nature Asia. Nature Publishing Index Global 2012 available at http://www.natureasia.com/en/publishing-index/

research articles they publish in Nature journals), institutions in the United States and Europe dominate, each being responsible for 40% of publications. Within Europe, the UK has a strong presence, with key centres such as the Universities of Cambridge and Oxford, which sit in the top 20; overall the UK is responsible for 24% of the ranked European institutions (as illustrated in Figure 3).

Figure 3: Proportion of biotechnology research institutions ranked in the top 200 publishing institutions, by country



Source: CRA analysis using Nature Publishing Index - Global Top 200

Although an imperfect measure of the extent of basic and translational research activity, the number of patents illustrate the UK as second only to Germany. The UK produces 6.9% of global scientific output as measured by published papers and has 3.3% of the world's scientific researchers (with a population representing 0.9%).[22] However, research in inherently international. Over 35 per cent of articles published in peer reviewed journals have co-authors based in more than one country.[23]

The research that takes place in the UK, is also often undertaken by international teams drawing on talent internationally. We cannot find a detailed breakdown but it is estimated that 15% of academic staff at UK institutions are non-UK EU nationals, a figure that rises to 20% among elite universities.[24] We have not been able to find estimates of the proportion of researchers in life sciences companies from within the UK, the rest of EU and from outside of the EU. However, researchers from the EU make up a significant proportion of

22 The UNESCO science report

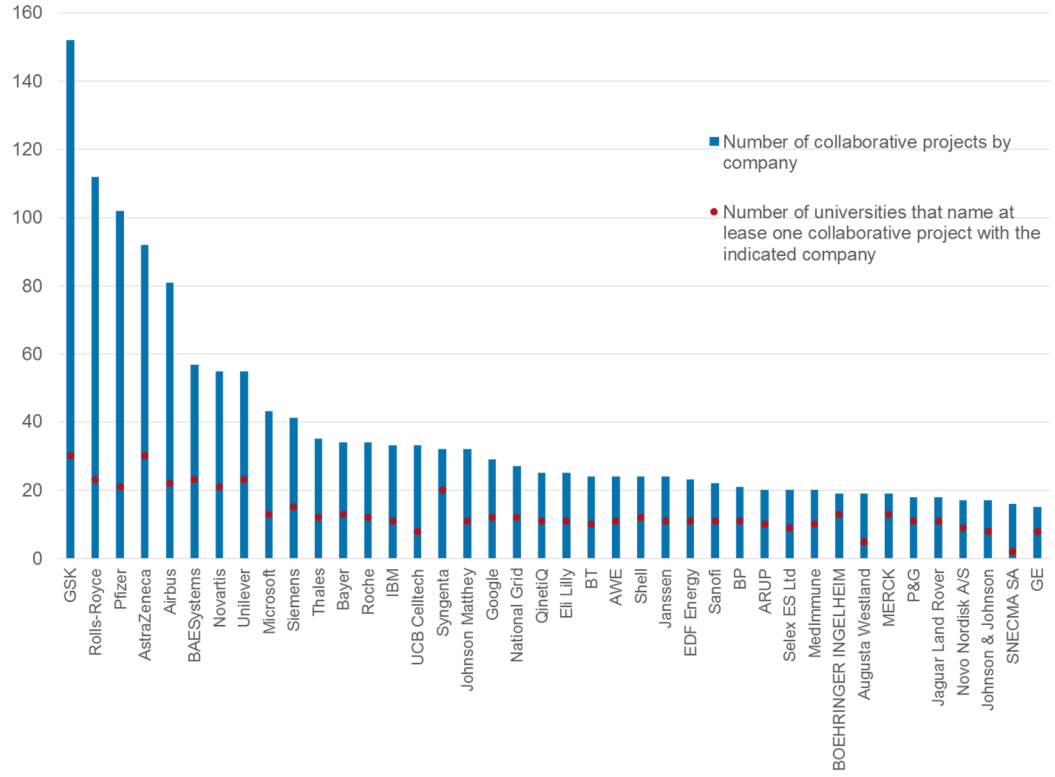
23 The Royal Society. 2011. 'Knowledge, networks and nations: Global scientific collaboration in the 21st century.' London: The Royal Society.

24 Cressey, D. (2016, February 4). "Academics across Europe join 'Brexit' debate"; accessible at http://www.nature.com/news/academics-across-europe-join-brexit-debate-1.19282

the workforce across the UK. For example, in Cancer Research UK's Beatson Institute, roughly 50% of the researchers are from the EU, compared to 20% from the UK and 28% from the rest of the world.[25] The importance of access to international labour market is clear. A recent survey of the recruitment concerns of pharmaceutical, biopharmaceutical and contract research organisations by the ABPI has shown that several skill areas are still major concerns for UK based biopharmaceutical companies developing new medicines, despite UK-initiatives to increase the supply of people with the required skills.[26]

The strength of the UK's performance in basic research derives from the development of successful clusters and collaborations between academia and industry. The Dowling Report team identified that compared to other sectors, the life sciences were represented by a relatively small number of companies but each of these companies had many collaborations. Seven of the top 15 companies by number of collaborations are biopharmaceutical companies.

Figure 4: Top 40 companies by number of collaborations



Source: Dowling Report

Collaborations are not within countries, but often between academic groups in different countries and often involving diverse industry participation. Nowhere is this more obvious than through the development of public private partnerships such as the Innovative Medicines Initiative (IMI) which engages major pharma companies but also biotech SME and academic researcher to address bottlenecks in drug discovery, in part by building the

25 Written evidence submitted by the Association of Medical Research Charities (UKL0025)

26 Written evidence submitted by the Association of the British Pharmaceutical Industry (UKL0029)

networks across the industry and academia.[27] Interviewed SMEs indicated that IMI was important because it enhanced the ability to collaborate with EU institutions facilitating the scientific ecosystem of UK start-ups.

2.2.1. The role of EU legislation

The factors needs to be successful in attracting basic research are clearly many (as will be discussed in later chapters) but they are clearly affected by EU legislation in a number of ways.

EU funding of basic research and discovery activities

Much has already been discussed in the media about the role of EU support for basic research and pre-competitive research activities, particularly the:

- Framework Programmes for Research and Technological Development (covering FP1 through FP7 with 'FP8' being named 'Horizon 2020'). These are funding programmes created by the European Union/European Commission to support and foster research in the European Research Area (ERA) and the activities of Small and Medium Enterprises.
- Public private partnership between the European Commission and the innovative pharmaceutical industry, the innovative medicines initiative (IMI). IMI is the single largest public private partnership to advance research and to speed translation of findings into better and safer medicines for patients. The total budget for IMI 2 is €3.3 billion, of which the EU will contribute up to €1.6 billion from Horizon 2020.

The evidence suggests that the UK has been successful in applying and winning funding through FP7 and in Horizon 2020.

- As part of FP7 (2007-2013), the UK received approximately €7 billion, representing 15.5% of total funding, second only to Germany. In practical terms this meant the UK had 17,379 participants in FP7 projects.[28] In terms of UK ERC Performance under FP7 1,259 ERC awards were made to UK institutions (22.7% of the total); these institutions received €1.7bn (22.2% of the total) - more than any other EU member state. Approximately 30% of these awards are categorised as life sciences research.
- Under Horizon 2020 (H2020), which will run from 2014-2020, the UK has already received €1.4 billion, again second only to Germany.[29] To date, the UK has secured 15.4% of Horizon 2020 funding. In terms of UK ERC Performance under H2020, the UK was awarded €336.5m (20.95% of total) - more than any other EU member state with approximately 30% of these awards are categorised as life sciences research.
- In addition to Horizon 2020 funding, €1.6bn of the UK's allocation of EU Structural and Investment Funds for 2014-2020 will be spent on research and innovation projects.[30]

27 IMI (2016), "About Innovative Medicines Initiative". Available at: http://www.imi.europa.eu/content/mission.

28 Skentelbery, C. (2015). "Brexit Effect: A Blow To UK Life Science Leadership"; accessible at http://scientistsforeu.uk/2015/11/the-brexit-effect-a-blow-to-uk-life-science-leadership/

29 Written evidence submitted by Research Councils UK (UJL0027)

30 Written evidence submitted by the Department of Business, Innovation and Skills (UKL0028)

The funding is clearly one part of being involved in EU collaborative projects but this also represents an opportunity to work closely with other institutions. The UK benefits specifically from its role as project co-ordinators. Of the projects in which the UK participated in the FP7 Health program, it coordinated almost 23%. In H2020, the coordination percentage is 34%, the highest in Europe.[31] This is significant as research shows collaboration increases in the impact of research. Based on a bibliometric analysis of publications from FP7 projects, the impact of research was correlated to collaboration across all EU Member States.[32]

There is also EU funding to support the activities of small and medium size enterprises. In this area, it is recognised that UK has not performed so strongly. UK SMEs received the third-highest SME contribution under the FP7 Health programme, with €64m, behind Germany at €134m and France at €90m. The UK was also ranked 21st out of 27 countries in terms of the percentage of EU funds allocated to SMEs as part of the total national contribution, with just 9.6% of EU funds awarded to the UK going to SMEs.[33]

In terms of Innovative Medicines Initiative (IMI) and IMI2. UK organisations have been strong participants in IMI.[34] Since IMI launched in 2007, the UK has received €303 million (28.05% of the total awarded), far more than any other EU Member State.[35]

Overall, it seems clear that the UK has been very successful at attracting EU public funding for basic research and is a net beneficiary of public funding, getting more out of EU R&D funding than it puts into it as illustrated in Figure 5.

31 Skentelbery, C. (2015). "Brexit Effect: A Blow To UK Life Science Leadership"; accessible at http://scientistsforeu.uk/2015/11/the-brexit-effect-a-blow-to-uk-life-science-leadership/

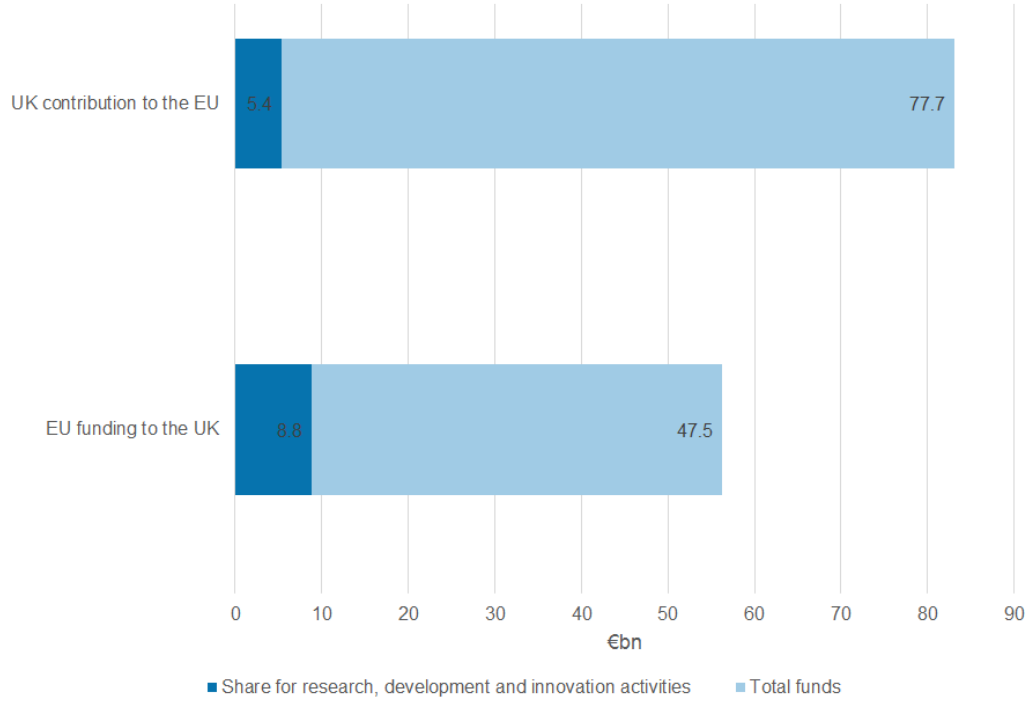
32 Thomson Reuters. 2010. Expert Group of the Interim Evaluation of Framework Programme 7. Bibliometric analysis – final report. Leeds, UK: Evidence, Thomson Reuters.

33 Skentelbery, C. (2015). "Brexit Effect: A Blow To UK Life Science Leadership"; accessible at http://scientistsforeu.uk/2015/11/the-brexit-effect-a-blow-to-uk-life-science-leadership/

34 Written evidence submitted by the Association of the British Pharmaceutical Industry (UKL0029)

35 Written evidence submitted by Research Councils UK (UJL0027)

Figure 5: Flow of funds between the UK and EU 2007 – 2013 (€ billion)

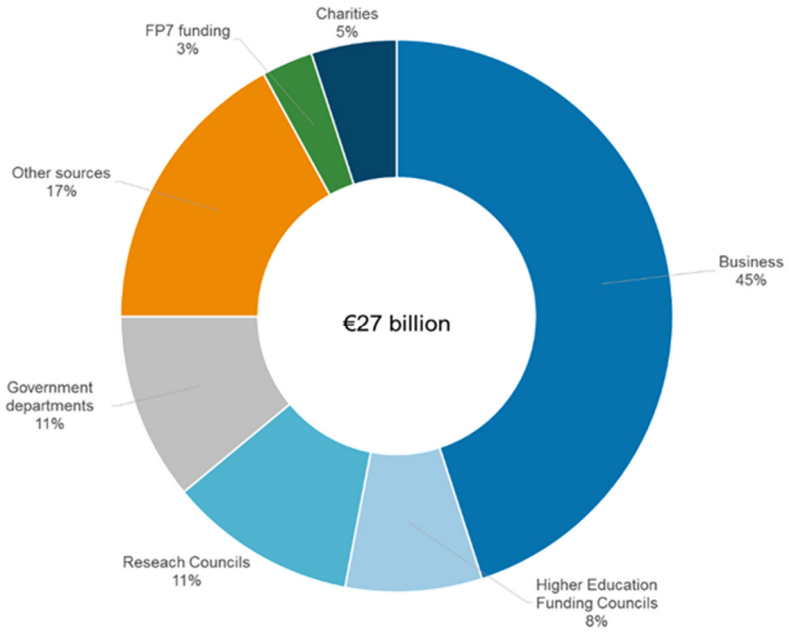


Source: UK research and the European Union: the role of the EU in funding UK research

However, it is important to put this into context. Although the UK is a net beneficiary of EU public funding, and this represents close to €10 billion, this only represent a small fraction of R&D spending in the UK.[36]

36 However, as the Royal Society note "EU research and innovation funding through structural funds is not captured in this as only some of these activities fall under the ONS definition of research and development used to calculate the domestic data below. The real figure is therefore likely to be higher than 3%."

Figure 6: UK expenditure on research and development by source of funding. 2007 – 2013



Source: Royal Society report

If the UK were to leave the EU, the access to European research funding would clearly change. This could reduce the amount of research on-going in the UK (depending on the degree to which the UK government replaced the level of funding) but it could also change the willingness of academic centres to collaborate with the UK. However, there is a counter argument that public funding at a national level is less bureaucratic and this could lead to more responsive and efficient research funding focusing on the UK's strengths. For example, "while the FP7 requirement that consortia include partners from at least three Member States provided a real incentive for cross-country collaboration, it also added another level of complexity to the process of coordinating and developing proposals, submitting bids and managing projects."[37]

From a European perspective, this would reduce the overall investment fund, but would increase the funds available to other countries.

Free movement of labour and accessing scientific talent base

There is considerable evidence on the strength of UK research and how the UK out-performs other countries of the same size. However, how this relies on international talent and collaboration. The free movement of labour within Europe is clearly beneficial in terms of researchers from the rest of Europe working in the UK and vice versa.

If the UK was to leave the Europe, researchers would need to apply for a visa and there would be an additional complication in terms of hiring from outside of the UK and for UK researchers to work in the EU. However, the impact of this clearly depends on how the visa system worked in practice.

37 "Scoping the impact of UK membership of the EU on UK health research" Daniel Brooker, Siobhán Ní Chonaill, Rand Europe.

The EU patent system

Since 1992, the European Commission regulation for Supplementary Protection Certificate (SPC) allows the extension of patent rights to a maximum of five years for pharmaceutical products. The SPC seeks to offset the patent term lost due to compulsory testing. More recently, the European Commission is developing the Unitary Patent system (the European patent with unitary effect) and the Unified Patent Court. The unitary patent is a legal title that will provide uniform protection across 26 EU countries on a 'one-stop-shop' basis, with the objective of reducing cost and administrative burdens for industry. The package will also set up a Unified Patent Court that will offer a single, specialised patent jurisdiction, one of the central divisions of which is based in London (specifically the one which will deal with pharmaceuticals and life sciences). The unitary patent protection will make it possible for inventors to protect their invention in 26 EU countries by submitting a 'single patent application'.

Both of these regulations should incentivise further innovation and reduce costs as after the patent is granted, there will be no need to validate it in each country reducing translation requirements in participating countries. Therefore, it is argued that this will stimulate research, development and investment in innovation, helping to boost growth in the EU. The objective is for the Unitary Patent package to come into force by the end of 2016.

If the UK was to leave Europe, it is possible that companies will lose the benefit of applying for a unitary patent that covers the UK and this will lead to the need to apply for a UK and a European patent. This will reduce cost savings from the unitary patent, however, it is unclear that this would reduce the incentive to undertake basic research in the UK or in Europe.

2.3. Product development and approval regulation

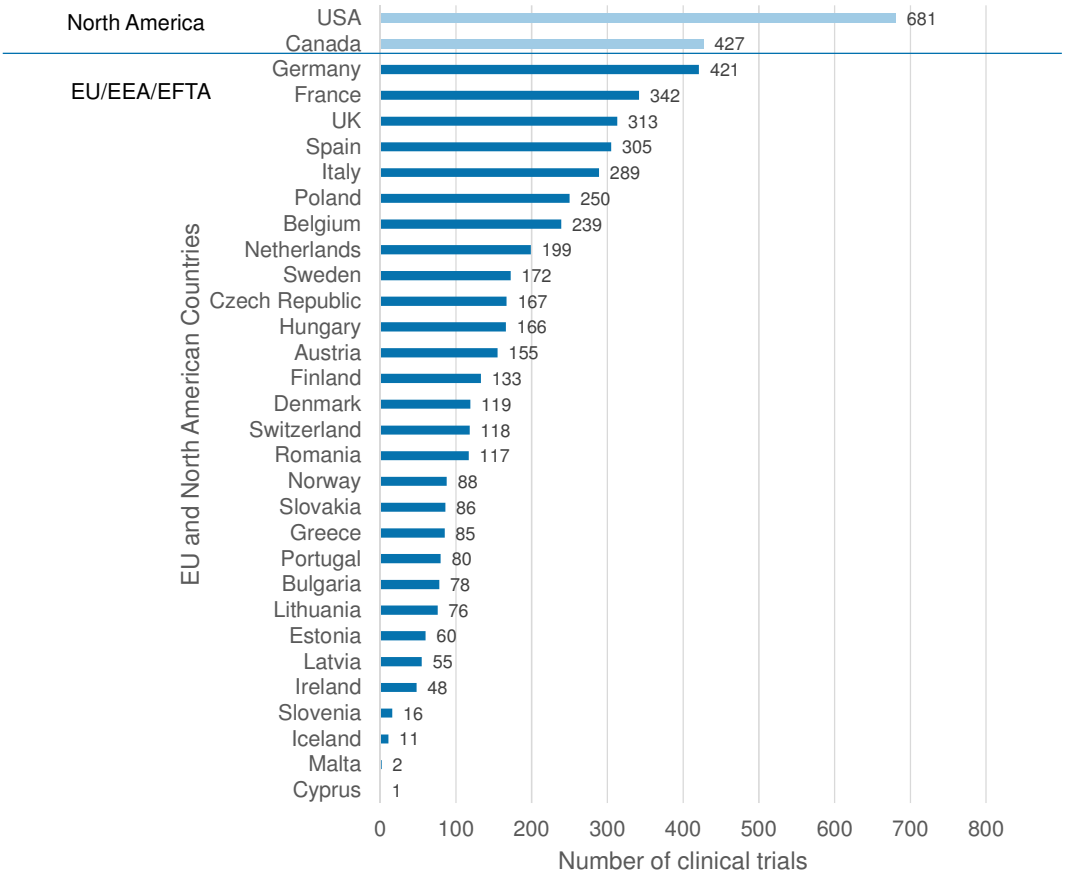
Turning to product development, most clinical trial programmes are international, involving patients from a range of countries but the UK has traditionally performed strongly reflecting the strength of its teaching hospital centres in London and other major cities across the UK, the quality and experience managing trial programmes and the capacity to undertake large clinical trials efficiently. However, the share taking place in the UK has reduced in recent years.

Over the last decade, there has been a clear trend to undertaking more trials outside of the traditional markets, particularly, the US, Japan and Europe. Reflecting this, the UK share of global clinical trials has declined over recent years but remains high given its population. Out of global trials, the UK has a share of around 5% compared to a share of global population of 1% and pharmaceutical spending of 2.4%.[38] However, between 2000 and 2010, the UK's global share of patients in clinical trials fell by 14%.[39]

38 "Adapting the Innovation Landscape UK Biopharma R&D Sourcebook 2015" ABPI

39 "Delivering value to the UK The contribution of the pharmaceutical industry to patients, the NHS and the economy" ABPI, Amended January 2016.

Figure 7: The number of clinical trials



Source: "Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency Overview of patient recruitment and the geographical location of investigator sites Containing data from 2005 to 2011" EMA 2013

In terms of absolute number the number of clinical trials has shown some recent recovery. According to the MHRA's figures, the number of applications for clinical trials amounted to 760 applications received in 2014.[40] The UK National Institute for Health Research (NIHR) calculated that more than 618,000 people participated in clinical research in the NHS in England in 2014, with 35,000 participants recruited to studies sponsored by the biopharmaceutical industry (an increase of 35% over the previous year). To put this in global context, in 2013, biopharmaceutical companies sponsored 6,199 trials across the US involving 1.1 million participants. However, this performance varies by phase:

- The UK performs well in terms of early phase I and phase II trials, with the UK performance similar to Germany.
- However, it has performed less well in term of Phase III trials lagging behind countries such as Germany and only just ahead of countries such as France, Poland.

40 Not all of these applications will have been supported and ultimately have been undertaken.

In addition to clinical trials undertaken in the UK, the UK is also associated with a strong contract research organisation (CRO) capability. These are independent organisations that undertake the development process once a pharma company has identified a promising new molecule. Examples of CROs include Envigo, Covance, Quintiles, Orion and CCRA.

The management of the regulatory process is an important part of ensuring a successful product development programme. Although it has been difficult to find hard data on the proportion or regulatory activities in the UK, it is clear that some companies locate their European regulatory teams in the UK, given the advantages of physical proximity to the EMA.

2.3.1. The role of EU legislation

Product development involves a series of activities (often described in terms of the phases of clinical development) all of which must be efficiently coordinated over time in order to generate safety and quality data and evidence that demonstrates the product's efficacy. Many of these activities are regulated at the European level, with particular note given to:

- EU legal framework for developing medicinal products for human and paediatric use (these include regulations on how animals are used for scientific purposes, orphan drug regulations, clinical trial regulations and pharmacovigilance regulation);
- EU framework for marketing authorisation (EMA, scientific advice from EMA, EMA Adaptive Pathway);
- EU framework for data protection.

The EU clinical trial regulations

Clinical trial regulation is largely determined at the European level and is set out in the EU Clinical Trials Directive and the new EU Regulation on clinical trials on medicinal products for human use that was adopted by the European Parliament and the Council of the EU prior to its publication in the Official Journal in May 2014.

According to existing studies, EU rules have affected the amount of clinical trial activity undertaken in the UK. For example, the 2001 Clinical Trials Directive is attributed with a 25% decline in the number of new trials undertaken in the EU between 2007 and 2011.[41] It is associated with increased costs and a reduction in the attractiveness of undertaking trials in the UK, specifically:

- Staff needs for industry sponsors to handle the authorisation process have more than doubled;
- Non-commercial sponsors have seen a 98% increase in administrative costs;
- Insurance fees have increased by 800% for industry sponsors;
- The average delay for launching a clinical trial has increased by 90% to 152 days.

However, the new regulation, although still subject to some criticism, is seen as learning from the previous directive and reflective of the competitive pressure from competing developed countries outside of the EU and some Middle Income Countries (MICs) in attracting clinical trial studies away from the EU. Indeed, some parts of the new EU

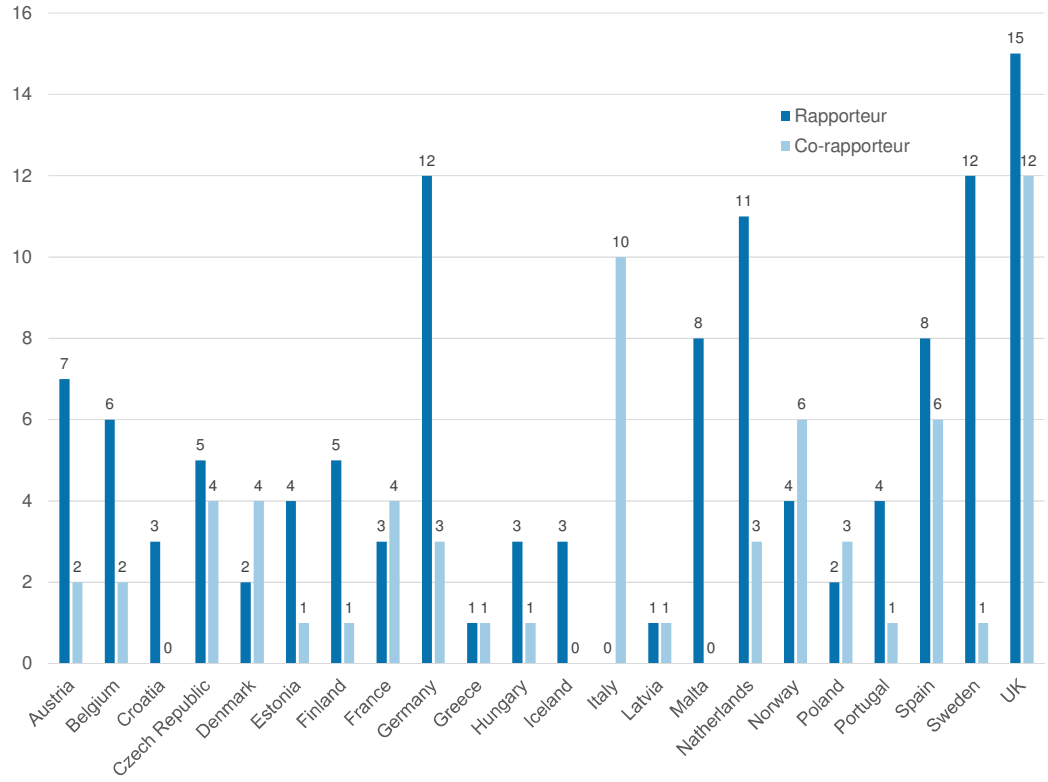
41 "Fresh Start Project: The EU impact on the UK Life Science sector" George Freeman MP. January 2014

Regulation on clinical trials are seen as useful in encouraging clinical trial activity. In particular, by allowing the use of a single trial protocol across EU countries supporting robust data collection, this could reduce the delays in drug development. By creating a "one stop" submission, it will challenge Member States, simplify the process for undertaking clinical trials in Europe benefiting all countries in Europe.

The European Medicines Agency

In terms of marketing authorisation, the UK is entirely integrated into the EU process. The EMA grants pharmaceutical companies a single marketing authorisation, providing access across the whole of the EU market. The EMA has been located in London since 1995 and is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. The UK's Medicines and Healthcare products Regulatory Authority (MHRA) is co-located with the EMA and play an important role as one of the inputting national agencies. Indeed, the MHRA is the most common rapporteur for EMA assessment as illustrated in Figure 8 below.

Figure 8: Rapporteur by country



Source: EMA Annual report 2014

There is near universal agreement that the EMA has been a very successful regulatory development. The EMA is one of the leading global regulators alongside the FDA and JPMDA. It has reduced the time for marketing authorisation and been innovative in terms of developing innovative programmes such as adaptive licenses and conditional approvals.

Data protection

The EU Data Protection Directive also affects the ability to undertake clinical trials and the attractiveness of undertaking these in Europe. The updated Regulation on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation) is awaiting formal adoption and will replace

the existing Directive. The proposed text is to be put to European Council for adoption and subsequently to the EU Parliament (scheduled for April 2016). However, there were clearly concerns that this could have been detrimental to the clinical trial environment in the UK. There was a concern that amendments to the directive intended to support personal data protection and privacy, would result in making health research involving personal data 'at worst illegal, and at best unworkable'.[42] This was seen as particularly problematic for the UK because of the unitary nature of the NHS means it has a huge pool of patient data on which to draw which is seen as an important advantage for encouraging research and product development in the UK. However, in practice the UK government has reported "It is proportionate and supports the research use of personal data, which aids keeping the sensible approach to data protection, and is consistent with the current UK legal framework".[43] This seems consistent with more recent EU regulation taking into account the concern about the innovative environment and mitigating harmful impact.

If the UK was outside of the European Union, theoretically it would have the choice of complying with the EU clinical trial regulation, or developing its own regulatory process (which would increase costs to the UK) and its own rules of data protection. This could reduce regulatory costs falling on innovative companies (for example, hypothetically it could have allowed the UK to avoid the impact of the first Clinical Trials Directive) and increase the attractiveness of undertaking trials in the UK. However, given that clinical trials, particularly larger Phase III trials, will inevitably be international this increases the complexity of undertaking trials in the UK and has the potential to lead to trials being undertaken elsewhere. This reduces the value of the European clinical trials rules and therefore makes undertaking trials in Europe marginally less attractive.

2.4. Manufacturing and trade

As set out in the introduction to this chapter, the strength of the Life Sciences industry in the UK is around innovation, however, the value of manufacturing and trade should not be understated. According to the Office for National Statistics the number of enterprises for manufacturing pharmaceuticals (basic pharmaceutical products and preparations) was 528 in 2013 employing 44,000 people. The UK exported £21.4bn of pharmaceuticals in 2014, 54% of which was to the EU – equivalent to £11.5bn of pharmaceuticals or £32m worth of pharmaceuticals each day.[44]

2.4.1. The role of the EU legislation

The UK membership of the EU is often argued around the role of the single market and its impact on barriers to trade (specifically tariffs and non-tariff barriers). However, as set out in chapter 1, the impact of this on trade in pharmaceuticals within Europe seems small. Even outside of the EU, existing trade rules would prevent tariffs being imposed on medicines imported into the EU or vice versa. However, this does not mean that the UK manufacturing and trade performance is unaffected by European legislation, in particular, it affects:

42 "Scoping the impact of UK membership of the EU on UK health research" Daniel Brooker, Siobhán Ní Chonaill, Rand Europe.

43 Written evidence submitted by the Department of Business, Innovation and Skills (UKL0028)

44 Written evidence submitted by the Department of Business, Innovation and Skills (UKL0028)

- Trade with the Rest of World and the flexibility to negotiate trade deal with others third countries;
- EU manufacturing regulation (Good Manufacturing Practice guidelines);
- REACh regulation on substances that can be used in the production process.

Trade with Rest of World

In terms of exporting medicines, it is possible that the UK benefits from being part of the free trade agreements agreed under the EU. However, it is noteworthy that recent free trade agreement have not included particular provisions for pharmaceuticals. In the future, there could of course be significant trade agreements such as the on-gong negotiation of TTIP and those between the EU and China.[45] Beyond tariffs, it is possible that this could have a significant impact on the life sciences industry, particularly if it affects the intellectual property rights that pharmaceutical companies receive. However, these rights would be applied to companies inside the EU and outside the EU. This could increase the freedom to invest in China, to the advantage of European pharmaceutical companies. Again, given that the majority of international pharmaceutical companies are global and have affiliates in China, this would appear a benefit that is not tied to the UK participation in Europe (although it could have a bigger impact on smaller companies).

EU manufacturing regulation (Good Manufacturing Practice guidelines)

There are global standards on good manufacturing practice, however, there is still a need for rules on mutual recognition of inspections. Within the EU, all countries recognise the national inspections undertaken by another member state. This significantly reduces the cost of complying with GMP standards and facilitates trade.

REACH

The manufacturing of pharmaceuticals is affected by legislation aimed primarily at other industries. For example REACh. REACh is the European Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals in force since 2007. REACh includes an authorisation requirement to ensure that the risks from substances of very high concern (SVHCs) are properly controlled and that those substances are progressively replaced by suitable alternative substances or technologies. Substances subject to authorisation are listed in Annex XIV to the REACh Regulation. Once included in this Annex, a substance cannot be placed on the market for a use or used after a given date (the so-called 'sunset date') unless the companies concerned are granted an authorisation for the specific use(s). The European Commission plays a key role in implementing REACh legislation, determining the substances subject to authorisation and deciding whether to grant authorisation for a continued use (which is time limited up to 12 years).

In terms of manufacturing, membership of the EU has brought some benefits to the UK, for example, in the recognition on GMP standards, however, there are also potential costs, say from the imposition of REACH. In terms of FTAs, clearly the UK is able to benefit from agreements agreed by the EU but it can also be argued that the UK would have been able to negotiate improved terms outside of the EU. We investigate that in the next chapter.

45 European Commission, "China"; accessible at http://ec.europa.eu/trade/policy/countries-and-regions/countries/china/

2.5. Market Access

In terms of market access, products are launched immediately in the UK following the regulatory approval by the EMA, however in practice, for some products access through the NHS is reimbursed only following a review by the health technology agency, for example NICE in England. Where products are not assessed by NICE, say orphan products, this means products are immediately accessible to English patients. However, for most categories of product the overall picture for the UK is mixed, innovative pharmaceutical products often fail to be assessed as cost effective. Even where they are recommended by NICE this has been after a long period of assessment and the diffusion into the market is slow.[46] However, as health policy is determined at the country level, much of this is based on regulation and laws determined by the England, Scottish, Welsh and Northern Ireland governments and not by Europe.

2.5.1. The role of EU legislation

Whilst the market access framework governing pricing and reimbursement of pharmaceutical remains largely a national competence, a number of EU initiatives are shaping and influencing the way medicines get on the market and the conditions under which they reach patient.

- Market access regulations (Transparency Directive, Anti-counterfeit/Traceability Directive)
- EU initiatives to facilitate market access (EUnetHTA, EuroRapid, Moca-OMP, cross-border healthcare, Early Access schemes)
- EU competition and procurement policy (specifically parallel trade rules)

For example, this includes the development of a European database (EuroRapid) and work undertaken at the EU level on relative-effectiveness assessments (joint action 3).

Market access regulations

The existing Transparency Directive imposes conditions on the timing and clarity of the price and reimbursement process. As the UK system allows product to launch from regulatory approval and does not have a formal price setting process, the Transparency Directive has had relatively little direct impact on the UK.

Although not directly associated to market access, the Community code on medicinal products has introduced measures to protect the supply chain against falsified medicines, notably measures introduced to uniquely identify products in the supply chain. The Directive 2011/62/EU was adopted on 1 July 2011 modifying Directive 2001/83/EC to introduce additional measures to prevent the entry into the legal supply chain of medicinal products that are "falsified in relation to their identity, history or source".[47] The new measures[48] include:

46 For example, the Richards report set out the access to new medicines in different therapeutic areas.

47 European Commission (2008) Proposal for a Directive amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of medicinal products which are falsified in relation to their identity, history or source. Brussels, 10.12.2008 COM(2008) 668 final, 2008/0261 (COD)

48 European Commission – DG Health and food safety - http://ec.europa.eu/health/human-use/index_en.htm

- An obligatory authenticity feature on the outer packaging of the medicines
- A common, EU-wide logo to identify legal online pharmacies. This would make it easier to distinguish between legal and illegal online pharmacies throughout the EU
- Tougher rules for controlling and inspecting producers of active pharmaceutical ingredients
- Strengthened record-keeping requirements for wholesale distributors

This will reduce the risk of counterfeit products and therefore improve patient access to authentic products.

EU initiatives to facilitate market access

The EU has set out a series of policy initiatives over the last five years that are currently under investigation that could impact market access. This includes the development of a breakthrough designation through PRIME, European joint HTA assessment through the EUnetHTA process, early dialogue between HTA and regulators through SEED, coordinating the informational requirement of HTA and regulators through AdaptSmart. However, in many of these cases it is too early to assess the impact on market access in Europe or in the UK.

EU competition and procurement policy

An area where the EU has played a significant role over the last twenty years is the regulation of parallel trade. The impact on the UK is interesting as historically the higher prices in the UK meant it was primarily a target for parallel importation. However, in recent years, the lower prices in the UK have meant that it was also a potential source of products traded with other EU countries for some products. There is significant literature on the impact of parallel trade on market access. Our research suggests countries that are a source of parallel trade often face higher prices and reduced access than they would otherwise. This is observed in longer delays prior to launch, and the potential for shortages in some cases. Some studies have reported shortages across a range of therapeutic areas (breast cancer, osteoporosis, Parkinson's, depression, kidney disease, epilepsy) and these have been associated to parallel trade.[49] There have been concerns expressed by the Department of Health that parallel exports from hospitals are leading to shortages.[50] To mitigate this effect the UK government introduced changes to the Medicines Act.

The impact of Brexit on market access to pharmaceuticals is challenging to assess even from a theoretical perspective. Some EU initiatives clearly have improved market access, such as the development of an orphan medicine regime but it is possible that the UK could benefit from this regulation without being in the EU. Some initiatives are on-going and it is difficult to guess what will happen if the UK exited, say the Falsified Medicine Directive. In

49 The Telegraph, "Patients face drugs shortage as medicines sold abroad: inquiry launches", 22 November 2011. http://www.telegraph.co.uk/health/healthnews/8904388/Patients-face-drugs-shortage-as-medicines-sold-abroad-inquiry-launched.html. All-Party Pharmacy Group, “Report of the APPG Inquiry into medicines shortages“, www.appg.org.uk

50 Letter from Dr Keith Ridge Chief Pharmaceutical Officer to NHS Hospital Chief Pharmacists in England. 26th February 2010.

other areas, it is possible to argue that European rules reduce market access (say parallel trade rules) and Brexit could be beneficial to UK patients.

2.6. Summary

The life sciences industry is a global industry and operates globally from basic research, to product development, manufacturing and commercialisation. The life sciences industry in the UK is remarkably successful for a range of different reasons relating to its history, academic links and industrial policy. European regulation has played an important role in the evolution of the industry in Europe and in the UK and hence the UK leaving the European Union has the *potential* to have a significant impact along the value chain:

- Basic research: If the UK were to leave the EU, the access to European research funding would clearly change. This could reduce the amount of research on-going in the UK (depending on the degree to which the UK government replaced the level of funding) but it could also change the willingness of academic centres to collaborate with the UK. However, there is a counter argument that public funding at a national level is less bureaucratic and this could lead to more responsive and efficient research funding focusing on the UK's strengths. From a European perspective, this would reduce the overall investment fund, but would increase the funds available to other countries. Researchers would need to apply for a visa and there would be an additional complication in terms of hiring from outside of the UK and for UK researchers to work in the EU. However, the impact of this clearly depends on how the visa system worked in practice. It is possible that companies will lose the benefit of applying for a unitary patent that covers the UK and this will lead to the need to apply for a UK and a European patent. This will reduce cost savings from the Unitary Patent, however, it is unclear that this would reduce the incentive to undertake basic research in the UK or in Europe.

- Product development: If the UK was outside of the European Union, theoretically it would have the choice of complying with the EU clinical trial regulation, developing its own regulatory process (which would increase costs to the UK but allow it to develop its own rules) and its own rules of data protection. This could reduce regulatory costs falling on innovative companies (for example, it could have allowed the UK to avoid the impact of the first Clinical Trials Directive) and increase the attractiveness of undertaking trials in the UK. However, given that clinical trials, particularly larger Phase III trials, will inevitably be international this increases the complexity of undertaking trials in the UK and has the potential to lead to trials being undertaken elsewhere. This reduces the value of the European clinical trials rules and therefore appears to make undertaking trials in Europe marginally less attractive.

- Manufacturing and trade: Membership of the EU has brought some benefits to the UK, for example, in the recognition on GMP standards, however, there are also potential costs, say from the imposition of REACH. However, these costs could also be applied by the UK in the case of Brexit. In terms of impact on FTA with other countries, clearly the UK is able to exploit agreements agreed by the EU but it can also be argued that the UK would have been able to negotiate improved terms outside of the EU.

- Market access: The impact of Brexit on market access to pharmaceuticals is challenging to assess even from a theoretical perspective. Some EU initiatives have improved market access by encouraging innovation (such as the development of an orphan medicine regime) but it is possible that the UK could benefit from this regulation without being in the EU. Some initiatives are on-going and it is difficult to guess what

will happen if the UK exited. In other areas, it is possible to argue that European rules reduce market access (say parallel trade rules) and Brexit could be beneficial to UK patients.

In the next chapter, we draw on the experience of other countries with different relationships to the EU to determine what happens in practice.

3. Learning from the experience of Norway, Switzerland and Canada

There are no precedents for a country leaving the EU[51], so the only way to consider the impact of a change in the relationship is look at other countries and the relationship they have (which we do in this chapter) or ask different stakeholders the impact (which we discuss in the next). The challenge with using other countries is that the UK is unique and therefore any lessons need to be considered carefully. For example, it is clear from Table 1 that the UK differs in terms of size of the economy, but also relative importance of life sciences to the economy in terms of research, pharma R&D, employed and market size.

Table 1: Comparing the UK to scenario countries.

	UK	Norway	Switzerland	Canada
Economy GPD 2014 (billion EUR)	2,222	377	516	1,596
Number of high-quality scientific articles [52]	3366	126	1136	1478
Business expenditure on R&D in pharma (% of GDP)	0.3%	0.04%	0.63%	0.03%
Pharmaceutical employment	73,000	3,800	40,913	18,452
Pharmaceutical Market Value, € billion (2013)	16.6	1.6	4.1	15.1

Source: Eurostat and World Bank (GDP), EFPIA facts & figures 2015 (Pharma R&D)

Taking this into account, we consider the experience of these markets and then if these lessons are transferable to the UK. We briefly set out the overall relationship but then focus specifically on impact on life sciences along the value chain.

51 The exception discussed in much of literature is Greenland. Denmark joined in 1973, with the result that Greenland joined. When home rule for Greenland began in 1979, they voted to leave the EEC. The territory left the EEC in 1985 but remains subject to the EU treaties through association of Overseas Countries and Territories with the EU. However, Greenland is not a comparable country to the UK.

52 The Nature Index tracks the affiliations of high-quality scientific articles. The weighted fractional count (WFC) is a modified version of FC in which fractional counts for articles from specialist astronomy and astrophysics journals have been down weighted. These journals encompass a much larger proportion of the total publication output of these fields than any other field covered by the Nature Index.

3.1. Drawing from the Norwegian experience to understand the impact of EEA membership

Norway is not a member state of the European Union (EU), however, the country is closely associated with the Union through its membership in the European Economic Area (EEA), in the context of being a member of the European Free Trade Association (EFTA). The EEA agreement grants Norway full access to the EU's internal market but also guarantees the Internal Market's four freedoms[53], as well as non-discrimination and equal rules of competition throughout the area. This arrangement facilitates free movement of goods, capital, services and people between the EU and EFTA members including Norway. As a result, it is estimated by the Norwegian government that it is subject to roughly 21% of EU law.[54]

Norway has been granted participation rights in several of the Union's programmes, bodies and initiatives. This covers cooperation in areas such as research and development (discussed below), education, social policy, the environment, consumer protection, tourism and culture. It also enables the three EEA EFTA states to participate in various EU programmes. Through its EEA membership, Norway contributes €340 million a year to the EU – despite neither being a member, nor having any voting rights.

Based on our literature review and interviews there is little debate in Norway regarding relationship with the EU and therefore relatively few studies looking directly at its benefits or how this might change.

3.1.1. Basic research and product discovery.

Compared to some of European Neighbours, Norway is not considered a leading country in Europe for scientific research in healthcare or biopharmaceutical. It ranks 26/100 on the Nature Publishing Index[55], an indicator the quality of institutions for high-quality science. Although during the past ten years, health related and medical research has progressed in Norway, attracting investment from the government, charities and pharmaceutical companies, with scientists tackling some of the most common and life-threatening diseases, such as diabetes, cancer and cardiovascular disease. The government has made research and innovation one of its top priorities and aiming to be one of the most innovative countries in Europe.[56] Research and education activities is therefore an important part of Norway's cooperation with the EU.

EU research and innovation programmes

Norway has been associated to EU research and innovation programmes since 1987. This takes place through an amendment to Protocol 31 of the EEA agreement and is effective

53 The European Union's (EU) internal market, also known as the EU Single Market, is a single market that seeks to guarantee the free movement of goods, capital, services, and people – the "four freedoms" – between the EU's 28 member states.

54 Government Norway (2014) "Norway in Europe. The Norwegian Government's Strategy for Cooperation with the EU 2014-2017"; accessible at https://www.regjeringen.no/en/dokumenter/norway_in_europe/id762511/

55 The Nature Index is a unique database that tracks affiliations in research publications in a select group of scientific journals. The Index can provide an indicator of high-quality research contributions from institutions, countries, regions and disciplines. See http://www.nature.com/nature/journal/v522/n7556_supp/full/522S1a.html

56 Government Norway (2014) "Norway in Europe. The Norwegian Government's Strategy for Cooperation with the EU 2014-2017"; accessible at https://www.regjeringen.no/en/dokumenter/norway_in_europe/id762511/

retroactively to the beginning of Horizon 2020.[57] Norway was a full member of FP7 and Norwegian researchers contributed to more than 1,400 projects, receiving a total of €712 million.[58] Norwegian participants, including many SMEs, took part in the last EU programme (2007-13). In 2013, Norway confirmed their wish to take part as a full member of the new EU framework programme for research and innovation, Horizon 2020. The decision, taken at a meeting of the EEA Joint Committee allows Norwegian researchers and companies to participate on the same basis as their counterparts in the EU.[59] In return, Norway will contribute financially to Horizon 2020. Norway's contributions to the major EU programmes for research and innovation, education, and culture amounted to around €3.2 billion (NOK 26 billion at the current rate of exchange) in the period 2014–20.[60]

However, according to Director General of the Norwegian Research Council, Arvid Hallén, "the breadth and scope of the framework programme also pose major challenges to the Norwegian research sector. While many Norwegian researchers are already well established in European cooperative networks, our participation is still too narrow. We need to learn how to take even better advantage of the opportunities inherent in EU cooperation. I am quite certain that Norwegian research groups will redouble their efforts and seek to expand their participation under Horizon 2020."[61]

Norwegian companies are involved inIMI. Norway is an associated country of the IMI and is therefore part of the IMI States Representatives Group (SRG) which is an advisory group within the IMI Joint Technology Initiative and consists of representatives from Member States and Countries associated with the Research Framework Programme.[62]

Access to EU researchers and scientists

The EEA Agreement guarantees the internal market's four freedoms. Through the free movement of persons, all EEA nationals have the right to work in any other EEA state. Students, pensioners and people not in paid employment also have the right to reside in another EEA state. This means that there are no restrictions on researchers and scientist looking for a job in an EU or EEA country and these are allowed to stay in Norway even after employment has finished. Norwegian scientist may also have certain types of health and social security coverage transferred to the country in which they go to seek work.[63] People working in some occupations may also be able to have their professional

57 European Commission (2014, May 16) "Press Release: *I*celand and Norway sign up to join Horizon 2020 Brussels"; accessible at http://europa.eu/rapid/press-release_IP-14-566_en.htm

58 European Commission (2014, May 16) "Press Release: *I*celand and Norway sign up to join Horizon 2020 Brussels"; accessible at http://europa.eu/rapid/press-release_IP-14-566_en.htm

59 The Research Council of Norway (2013) "Press release: Norway says yes to Horizon 2020"; accessible at: http://www.forskningsradet.no/en/Newsarticle/Norway_says_yes_to_Horizon_2020/1253986729745

60 Government Norway (2014) "Norway in Europe. The Norwegian Government's Strategy for Cooperation with the EU 2014-2017"; accessible at https://www.regjeringen.no/en/dokumenter/norway_in_europe/id762511/

61 The Research Council of Norway (2013) "Press release: Norway says yes to Horizon 2020"; accessible at: http://www.forskningsradet.no/en/Newsarticle/Norway_says_yes_to_Horizon_2020/1253986729745

62 Innovative Medicines Initiative "Candidate and Associated Countries"; http://www.imi.europa.eu/content/candidate-and-associated-countries

63 see coordination of social security systems at http://ec.europa.eu/social/main.jsp?langId=en&catId=849

qualifications recognised abroad.[64] In 2012, 20% of academic personnel in Norway were non-Norwegian citizens (similar to the UK).[65]

Patent protection and enforcement

Since 1 January 2008, Norway has been a member of the European Patent Organisation (EPO), which mission is to grant European patents in accordance with the EPC is carried out by the European Patent Office.[66] It is therefore possible to obtain patent protection in Norway by applying for a European patent at the European Patent Office (EPO). The scope of the patent is determined by the description and claims in the granted European patent. Once the patent has been disclosed in Norway, the same regulations apply as for a national patent.[67]

3.1.2. Product development and approval regulation

A central principle of the EEA Agreement is homogeneity, which means that the same rules and conditions of competition apply to all economic operators within the EEA. To maintain homogeneity, the EEA Agreement is continuously updated and amended to ensure that the legislation of the EEA EFTA states is in line with EU internal market legislation.[68]

Pharmaceutical regulation

Norwegian regulation for pharmaceuticals is harmonised with EU regulation. I.e. regulations and directives from the EU are implemented in Norwegian law. These regulations and directives concern marketing authorisations for and distribution of pharmaceuticals, supervision of use and clinical trials. The Norwegian government participates in binding work with the EU under EMA in various committees and working groups.[69] For example, all clinical trials included in applications for marketing authorization for human medicines in the EEA must have been carried out in accordance with the requirements set out in the European pharmaceutical Directive 2001/83/EC – (Amendments: 2012/26/EU (pharmacovigilance); 2011/62/EC (community code) and others relating to advanced therapy medicinal products, market authorisation.[70]

64 see mutual recognition of professional qualifications at http://europa.eu/youreurope/citizens/work/work-abroad/index_en.htm

65 European Commission (2014) European Research Area Facts and Figures 2014 Norway - Research and Innovation EUR 26803, accessible at https://ec.europa.eu/research/era/pdf/era_progress_report2014/country_fiches/era-norway.pdf

66 European Patent Organisation (2015) “Legal foundation”; accessible at: https://www.epo.org/about-us/organisation/foundation.html

67 European Commission website (2015) “Norway - Intellectual property rights”; accessible at http://europa.eu/youreurope/business/start-grow/intellectual-property-rights/norway/index_en.htm

68 Government Norway (2014) “Norway in Europe. The Norwegian Government's Strategy for Cooperation with the EU 2014-2017”; accessible at https://www.regjeringen.no/en/dokumenter/norway_in_europe/id762511/

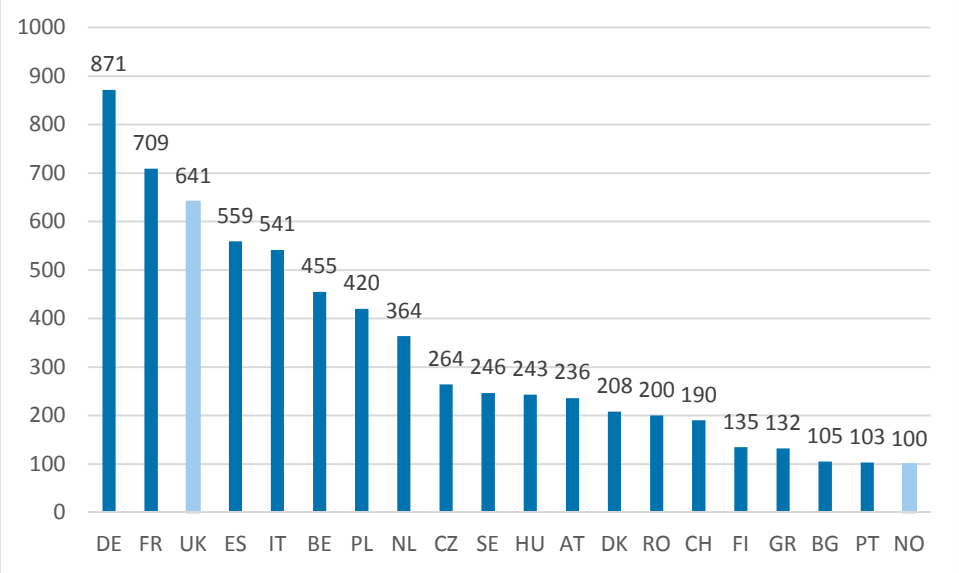
69 Norwegian Government (2009) “Norwegian regulation of pharmaceuticals is harmonised with EU regulation Article”; accessible at https://www.regjeringen.no/en/topics/health-and-care/Pharmaceutical-products/norwegian-regulation-of-pharmaceuticals-/id449522/

70 European Medicines Agency “Clinical trials in human medicines “; accessible at http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000489.jsp&mid=WC0b01ac058060676f

Clinical Trials are mainly regulated by international and national laws and the European Directive 2001/20/EC, which is fully implemented in the Norwegian Regulation relating to clinical trials on medicinal products for human use.[71]

However, as illustrated Figure 9, in Norway is not a major hub for clinical trials and only 246 trials are conducted in Norway compared to 641 in the UK.

Figure 9: Clinical trials in Europe



Source: www.clinicaltrials.gov

However, this does not mean all regulation affecting pharmaceutical gets adopted in Norway. One exception in terms of EU regulatory compliance is the Regulation on Medicinal Products for Paediatric use[72] which came into force in the EU on 26 January 2007 and which has not yet been adopted by the EEA countries.[73] In order to be applicable in the EEA, EU acts have to be incorporated into the EEA Agreement, more concretely into one of its Annexes or Protocols. These amendments to the EEA Agreement are done by means of Joint Committee Decisions (JCDs).[74] Some bottlenecks have occurred in one of the Subcommittee I discussions regarding the incorporation of the Paediatric Regulation into the EEA Agreement around whether the competence to impose fines should be given to the EFTA Surveillance Authority (ESA) or whether it should remain with the national authorities. As a result, over 9 year later, the act has not yet been incorporated into the

71 Statens Legemiddelverk Norwegian Medicines Agency "Clinical Trials"; accessible at http://www.legemiddelverket.no/english/clinical_trials/sider/default.aspx

72 Its objective is to improve the health of children in Europe by facilitating the development and availability of medicines for children aged 0 to 17 years.

73 European Medicines Agency (2007) "Paediatric Regulation"; accessible at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp

74 After an EU act has been adopted, the EFTA experts in the EEA EFTA States analyse whether the act is EEA relevant and, if so, whether any adaptations are required in the JCD for incorporation into the EEA Agreement and whether there are likely to be any constitutional requirements (see point 14 for more on constitutional requirements).

agreement. Furthermore, the Directive on standards of quality of human organs intended for transplantation was incorporated into the EEA Agreement with certain adaptations applicable to Liechtenstein. Also of note, the Pharmacovigilance Package was incorporated into the EEA Agreement and contains an adaptation text due to Liechtenstein's bilateral agreement with Austria in this area.[75]

As a member of the EEA, Norway also complies with the regulations of the EMA concerning marketing authorisations. Under the centralised authorisation procedure, pharmaceutical companies submit a single marketing-authorisation application to EMA. This allows the marketing-authorisation holder to market the medicine and make it available to patients and healthcare professionals throughout the EU on the basis of a single marketing authorisation. Once granted by the European Commission, the centralised marketing authorisation is valid in all EU Member States as well as in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway.

The Norwegian Medicines Agency (NoMA) contributes both to the assessments and to the development of new guidelines through participation in various working parties and scientific committees of EMA and participates in the EU procedures for Marketing Authorisation and has an observer status but does not get a vote. Several employees of the department are members of EU committees and working parties, and assessment tasks on behalf of the EU/EEA Community are regularly performed. NoMA actively contributes to the European Medicines Agency's Committee for pharmacovigilance, Pharmacovigilance Risk Assessment Committee (PRAC).[76] Norway also benefits from the EMA's cooperation with many of the world's largest regulatory bodies in areas such as inspections, safety of medicines and exchange of information on issues of mutual concern.

Norwegian framework for personal data protection

Norway has a comprehensive legislative regime that implements the EU Personal Data Protection Directive 95/46 EC. The EU Data Protection Directive 95/46 EC grounds allowing transfer outside of the EEA or White Listed countries have been implemented, such as where the data subject has consented or where the processing is necessary to perform a contract with the data subject. Otherwise, transferring on the basis of EU Model Clauses or the EU/US Safe Harbour certification system provides the most straightforward route to achieve compliant export. [77]

75 European Economic Area Joint Committee (2014, June 26) "Annual Report of the EEA Joint Committee 2013 The Functioning of the EEA Agreement (Article 94(4))"; http://www.efta.int/sites/default/files/documents/eea/eea-institutions/14-95798%2020140201%20Joint%20Committee%20Annual%20Report%20553025_3_0.pdf

76 Statens Legemiddelverk Norwegian Medicines Agency (2015) "Department for Medicinal Product Assessment"; accessible at http://www.legemiddelverket.no/English/about-norwegian-medicines-agency/Departments/Sider/Department-for-Medicinal-Product-Assessment.aspx

77 Norton Rose Fulbright (2014 July) "Global data privacy Director"; accessible at http://www.nortonrosefulbright.com/files/global-data-privacy-directory-52687.pdf

3.1.3. Manufacturing and trade

All major international pharmaceutical companies are represented in Norway, but only a few of them have established their own manufacturing units in the country.[78] Pharmaceutical production in Norway amounts to €745 million compared to €18,183 million in the UK.[79]

Norwegian legal framework for manufacturing

Like all EEA members Norway must comply with Directive 2003/94/EC which set out Good manufacturing (GMP) and good distribution practice (GDP) and other related aspects of the quality assurance for medicines. The European Medicines Agency plays an important role in coordinating these activities in collaboration with Member States including Norway.[80]

Trade

Norway is the EU's 5th most important import partner for trade in goods, after China, Russia, USA and Switzerland and the 7th export market for the EU, after the US, China, Switzerland, Russia, Turkey and Japan. Conversely, the EU remains the first major import and export partner for Norway, capturing 74.3% of the latter's trade.[81]

The EEA agreement grants Norway full access tariff free access to the EU's internal market and also incorporates the four freedoms of the internal market (free movement of goods, persons, services and capital) and related policies (competition, transport, energy and economic and monetary cooperation). Before Norway joined the European Economic Area, parallel imports of pharmaceuticals were not permitted. In the first year of its membership Norway adopted the EU legislation, which means parallel imports of patented pharmaceuticals became legal in 1995. The sales of parallel-imported drugs in Norway are fairly low, probably because of a fairly low price level of pharmaceuticals in Norway relative to other European countries, especially on patent-protected substances. In 2012 sales of parallel-imported drugs amounted to 3.6 percent of the total pharmaceutical sales.[82]

Norway has retained the ability to negotiate free trade agreements with other countries through the EFTA. [83] Whilst these free trade agreements with third countries secure Norwegian access to international markets and facilitate trade with partner countries, these are of little relevance to the pharmaceutical sector as Norway is not a major exporter of pharmaceuticals. As of February 2008, Norway is party to 14 bilateral investment treaties

78 Statens Legemiddelverk Norwegian Medicines Agency (2009) "The Norwegian health care system and pharmaceutical system"; accessible at: http://www.legemiddelverket.no/english/the-norwegian-health-care-system-and-pharmaceutical-system/sider/default.aspx

79 EFPIA (2015) The Pharmaceutical Industry in Figures – Key data 2015

80 European Medicines Agency "Good-manufacturing-practice and good-distribution-practice compliance"; http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000154.jsp

81 European Commission (2014) "Trade Policy Countries and regions Norway"; accessible at http://ec.europa.eu/trade/policy/countries-and-regions/countries/norway/

82 Brekke, K. R., Holmås, T. H., & Straume, O. R. (2015). Price regulation and parallel imports of pharmaceuticals. Journal of Public Economics, 129, 92-105.

83 Norwegian Government website (2009) "Norway's free trade agreements"; accessible at: https://www.regjeringen.no/no/tema/naringsliv/handel/nfd---innsiktsartikler/frihandelsavtaler/norways-free-trade-agreements/id457017/

(Chile, China, The Czech Republic, Estonia, Hungary, Latvia, Lithuania, Madagascar, Peru, Poland, Romania, Russia, Slovakia and Sri Lanka).[84] However, it is unlikely that any of these trade agreements had a major impact on the pharmaceutical sector nor on access to medicines.

3.1.4. Market Access

Market access policies such as pricing and reimbursement of medicinal products and medical devices is not harmonised on a European level, but belongs to the exclusive competence of the EU Member States. As a result, the pricing and reimbursement of pharmaceuticals is subject to very different rules across EU members and Norway is no exemption to this. There is, however, some harmonisation as regards the transparency of measures regulating the pricing and reimbursement of pharmaceuticals through the European Transparency Directive[85] as well as a number of initiatives launched by the European Commission to improve member states policies on access to medicines

NoMA assesses medications and determines which ones should be given under the general reimbursement scheme and conditions necessary for patients to access these reimbursed medicines. The Norwegian system for pricing and reimbursement is different from other countries, as these systems are largely decided at national level. HELFO, the Norwegian Health Economics Administration, is responsible for the actual reimbursement of all services, medical devices and pharmaceuticals that are covered by the NIS.[86] According to Article 11 of the EEA Agreement, Norway has the obligation to comply with the EU's so-called Transparency Directive (Council Directive 89/105/EEC) which aims to ensure the transparency of measures established by EU countries to control the pricing and reimbursement of medicinal products. The Norwegian authorities are required to adopt decisions regarding inclusion on the list of preparations within 90 days from receiving the application (cf. EU Transparency Directive 89/105/EEC). As the pharmaceuticals industry in Norway repeatedly experienced delays beyond this 90-day period, LMI filed a complaint with EFTA's surveillance authority (ESA) in December 1997.[87]

The Norwegian Drug Procurement Cooperation (LIS) performs tenders on all pharmaceuticals financed by the hospitals. All pharmaceutical suppliers, manufacturers and wholesalers are addressed and the Public Procurement Law applies. This law is in line with the European Union procurement law.

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84 Norwegian Government website (2009) "Norway's free trade agreements"; accessible at: https://www.regjeringen.no/no/tema/naringsliv/handel/nfd---innsiktsartikler/frihandelsavtaler/norways-free-trade-agreements/id457017/

85 The Transparency Directive basically provides that such measures should be based on objective and verifiable criteria. It also provides for timelines within which pricing and reimbursement decision should be taken. The European Commission issued a proposal for a new Transparency Directive in 2012.

86 PPRI (2015) "Pharma Profile Norway 2015" accessible at http://www.legemiddelverket.no/English/price_and_reimbursement/Documents/PPRI_Pharma_Profile_Norway_20150626_final.pdf

87 Legemiddelindurstrien (2001, January 1) "New LMI survey: Practice in Norway with regard to reimbursement of medicine costs"; accessible at http://www.lmi.no/english/new-lmi-survey-practice-in-norway-with-regard-to-reimbursement-of-medicine-costs-

All members of the Norwegian Association of Pharmaceutical Manufacturers also have a duty to comply with the Rules governing Drug Information as laid down by the Association. The Rules are based on the Code of practice adopted by the European Confederation of Pharmaceutical Manufacturers (EFPIA), which is the representative body for the European pharmaceutical industry and to which the Norwegian Association of Pharmaceutical Manufacturers is affiliated. The latest version of EFPIA's Code of Practice on the Promotion of Medicines was adopted by EFPIA on 5 October 2007. The code has been revised to make it fully consistent with Directive 2001/83/EC and Directive 2004/27/EC.

3.1.5. Conclusion and implications for the UK

If the UK were to negotiate a Norwegian-style relationship, the EEA agreement would enable the UK to continue to benefit from full access to the EU's internal market (although pharmaceuticals are generally tariff free regardless) and also incorporates the four freedoms of the internal market (free movement of goods, persons, services and capital) and related policies (competition, transport, energy and economic and monetary cooperation) which would guarantee access to skilled labour and research talents.

Whilst membership of the EEA comes with some level of benefits in terms of flexibility such as the ability to conduct trade deals with third countries or remain out of some key EU policies such as the common agricultural policies or the EU foreign/security policies, it can be argued that such components are little or no impact on the life sciences sector.

As seen in the above case study, as a member of the EEA Norway complies with one third of the entire EU regulation framework in general, and in fact, all (but except one) of the EU regulation which apply to pharmaceuticals. However, whilst the EEA Agreement includes provisions for the non-EU members to be consulted on new legislation, the EEA states have no right to vote in the European Council nor in the Council of Ministers or the European Parliament where national governments vote on EU legislation although it does maintain a 'right of veto'. As a result, EEA members are still be bound by EU regulations but without active involvement or influence on the legislative process.

It can be argued that given the pharmaceutical sector in Norway is relatively small, the loss of influence and active participation of the Norwegian government as part of the EU decision making process in Brussels which related to pharmaceutical is of little importance. Most pharmaceutical companies based in Norway are foreign multinationals who have a strong interest in leveraging the EU regulatory framework and having it applied to Norway. However, it can be argued that given the size and nature of the pharmaceutical industry in the UK, the loss of influence of the UK in Brussels could have a significant impact on both the legislative process in Brussels for both the EU and for Britain.

It is worth noting that whilst EU membership is often seen as complex and cumbersome, membership of the EEA also has its bureaucracy and complexities. Amendments to the EEA Agreement are done by means of the EEA Joint Committee (EEA JC) which is responsible for the management of the EEA Agreement across the 3 signatories of the agreement, namely Iceland, Liechtenstein, and Norway.[88] The JC meets six to eight times a year and decisions are taken by consensus to incorporate EU legislation into the EEA Agreement. As seen in the case of the paediatrics regulation, some bottlenecks have occurred in the EEA process and there are often important delays in the introduction of some key regulation as a result of the EEA regulation.

88 EFTA (2015) EEA Joint Committee, accessible at: http://www.efta.int/eea/eea-institutions/eea-joint-committee

EEA membership is also not without costs. Norway contributes €340 million a year to the EU – despite neither being a member, nor having any voting rights. It is unclear how this translates to the UK but one author has estimated that were the UK to leave the EU, its annual contribution through the EEA might fall to just €2 billion from the net contribution of €11.6 billion it makes at present.[89]

In terms of research and innovation, because EEA members such as Norway can have full participation in EU science programmes such as Framework 7 and Horizon 2020, there is little or no threat to the UK's relationship to the EU science programmes continuing as is if it were to join the EEA. If Britain were to leave the EU and join the EEA, it is very likely that it would be able to buy back into EU science programme participation as the EEA members have. Similarly, given the EEA membership guarantees the Internal market's four freedoms, there would not be any impact on attracting scientists or other key occupations.

It is worth noting that Norway's current economic relationship with the EU has evolved over time along with the evolution of the European Union, The EEA was established in 1994 when EFTA states which joined the EEA expressed their wish to participate in the EU's internal market without being EU members. However, it is report that EU is unhappy about the way the EEA is currently working. In a 2012 review, the Commission and the European External Action Service complained about the increasing backlog in the implementation of new EU laws by the three EEA EFTA states. By the beginning of 2014, they still had not integrated around 580 pertinent EU acts into EEA law. It is therefore questionable whether a UK member to the EEA would maintain the current framework in place or whether to would encourage the EU to renegotiate some of the terms and conditions of the EEA agreement.

3.2. Drawing from the Swiss experience to understand the impact of multiple sectoral bilateral agreements with the EU

Switzerland is not a member of the European Union. Switzerland's relationship with the EU have taken a bilateral track with the economic and trade relations governed by approximately 120 bilateral agreements. Two series of sectoral agreements, negotiated in 1999 and 2004, resulted in ten treaties that align a large portion of Swiss law with that of the EU. The 'Bilateral I' and 'Bilateral II' agreements effectively mean that Switzerland enjoys the benefits of EU member states and EEA countries on free movement of people, goods, services and capital.

This relationship has developed over a long period and began in 1960 with the establishment of the EFTA and was further developed through the signing of the Free Trade Agreement in 1972. Whilst the country appeared to move towards EU accession in May 1992: it negotiated the EEA agreement – which allows EFTA states to participate in the Union's single market – and then submitted an application for EU membership. Despite having such close ties with the EU, Swiss people were sceptical about joining and a referendum on March 2001 rejected the bid to open membership negotiations. Swiss citizens also voted against joining the EEA on 6 December 1992 and EU membership talks were consequently suspended. Since then, Switzerland's dealings with the EU have been focused on negotiating bilateral agreements on a piecemeal basis.

89 Alexander, H. (2012, July 8). "Is Norway's EU example really an option for Britain? "; accessible at http://www.telegraph.co.uk/news/worldnews/europe/norway/9383678/Is-Norways-EU-example-really-an-option-for-Britain.html

From December 2008, Switzerland has participated in the EU's Schengen area, which facilitates travel in the participating states by removing identity controls at common borders. It also partakes in the EU's Dublin agreement on dealing with asylum seekers. However, on the 9th of February 2014, the majority of the cantons and 50.3% of the electorate voted in favour of an initiative which would require immigration to be capped and limited by quotas. This has meant that Switzerland initially declined to sign the protocol covering workers from Croatia, citing the binding February 2014 referendum on curbing immigration. However, after two years, Switzerland and the European Union have now signed a deal extending the free movement of people to Croatia. But, the agreement is currently being discussed in the Swiss parliament and has not yet been ratified.[90]

Although the Swiss relationship with the EU is longstanding, there is an intense debate regarding how this might evolve in the future. There are many assessments of the benefits from this and how this might change in the future.[91]

3.2.1. Basic research and product discovery

In terms of investment in life sciences R&D Switzerland is one of the world leading economies. Pharmaceutical investment alone in R&D is over CHF 6 billion.[92] The private sector bears the cost of over two-thirds of Swiss R&D expenditure, which currently amounts to nearly 3% of GDP, or around CHF 16 billion. [93] Looking more closely, this is built on world-class academic research and international pharmaceutical companies.

It currently holds leading positions in a number of international rankings in research and innovation, or in terms of academic publications in relation to population size[94] and in terms of patent applications. In addition, Swiss academic publications are highly regarded among the international scientific community with 10 universities in the top 100 of the Academic Ranking of World Universities.[95] In 2013, 41 life science companies had their international headquarters (and 29 more their regional headquarters) in Switzerland.[96]

More than 50% of Switzerland's scientists are non-Swiss Nationals (approximately similar to the UK).[97] Under the EU-Switzerland agreement on the free movement of persons, Swiss

90 Swissinfo.ch (2016) Swiss announce unilateral safeguard clause to curb immigration, accessible at: http://www.swissinfo.ch/eng/swiss-agree-to-croatia-deal-to-save-eu-research-programme/42000888

91 AvenirSuisse (2015) Bilateralism – what else? Autonomy despite dependence

92 Interpharma (2014), "High level of research investments in Switzerland." Available at: http://www.interpharma.ch/fakten-statistiken/4510-high-level-research-investments-switzerland

93 State Secretariat for Education, Research and Innovation "Research and Innovation in Switzerland"; accessible at http://www.sbfi.admin.ch/themen/01367/?lang=en

94 The Nature Index tracks the affiliations of high-quality scientific articles. The weighted fractional count (WFC) is a modified version of FC in which fractional counts for articles from specialist astronomy and astrophysics journals have been down weighted. These journals encompass a much larger proportion of the total publication output of these fields than any other field covered by the Nature Index. Nature Index 2015 Global, accessible at http://www.nature.com/nature/supplements/nature-index-2015-global/

95 Academic Ranking of World Universities (2015)

96 KPMG (2013) European Life Sciences Cluster 2013 Report,

97 Schiermeier, Q. (2014, February 18). "EU–Swiss research on shaky ground"; accessible at http://www.nature.com/news/eu-swiss-research-on-shaky-ground-1.14733

nationals are free to live and work in the EU. Most EU and Swiss citizens are entitled, under certain conditions, to choose their workplace and residence freely within the EU and Swiss territories.[98] Restrictions only apply to nationals of Bulgaria, and Romania – who need a work permit.[99] Since the introduction of the free movement of people with the EU, the number of cross-border workers has significantly expanded in Switzerland. In Geneva, almost a quarter of the workforce is made up of cross-border workers. Each day, around 65,000 foreign workers cross the border separating Geneva from France – a figure which has doubled in the last decade.[100]

However, according to interviews public funding for research is also important. The main research funding body in Switzerland is the Swiss National Science Foundation (SNSF). With a yearly budget of above CHF 700 million, it focuses mostly on basic research and the promotion of young academics.[101] Thematic National Research Programmes amount to around 24% of SNSF's annual spending. The SNSF is well integrated in the European Research Area by its participation in numerous Joint Programming Initiatives (JPI) and ERANETs. Research in Switzerland is mostly carried out within the ten cantonal universities, the two federal institutes of technology - the Swiss Federal Institute of Technology Zurich (ETH Zurich) and the *École Polytechnique Fédérale de Lausanne* (EPFL) - as well in separate research institutes.

EU research and innovation programmes

EU funding also plays a role. Switzerland and the EU agreed on a partial association in the field of research and innovation under an "associated country" status[102]. With the Swiss receiving back more from the EU than it invests. According to a Swiss Government report, "more than 100% of the funds invested by Switzerland in research funding flowed back into the country in the form of grants for Swiss research projects. It goes without saying that participation in these programmes, which are run from Brussels, is therefore one of the priorities of Swiss science policy".[103]

During the 7th Framework Programme FP7 (2007 – 2013) in particular, Switzerland received a net investment from its participation. Researchers from Switzerland were very successful in participating in the European Research Council (ERC), which was created in 2007 as a new funding scheme for excellent individual researchers.

98 Confederation Suisse (2016), "Overview of bilateral agreements." Available at: https://www.eda.admin.ch/dea/en/home/bilaterale-abkommen/ueberblick.html

99 European Commission "Non-EU nationals"; accessible at http://ec.europa.eu/social/main.jsp?catId=470

100 SwissInfo.ch http://www.swissinfo.ch/eng/daily-migrants_cross-border-workers--a-contentious-swiss-reality/36326926

101 SwissCore website (2016) Swiss research system, accessible at: https://www.swisscore.org/swiss-knowledge/research

102 Legal entities from Associated Countries can participate under the same conditions as legal entities from the Member States. Association to Horizon 2020 takes place through the conclusion of an International Agreement.

103 Confederation Suisse (2016) "Switzerland and the European Union Federal Department of Foreign Affairs FDFA Directorate for European Affairs DEA"

- In total, 429 Swiss participations received CHF 6,461 million for healthcare related programmes. This was a net positive return on Switzerland's investments as it had contributed CHF 253 million to that sector of research.[104]
- Switzerland was ranked 5th in terms of number of ERC grants received (322 grants, € 584.5 million) after UK, DE, FR and NL. It had by far the highest success rate (23% of submitted proposals were funded). Among higher education institutions, ETH Zurich (85 grants) and EPFL (76 grants) are ranked 4th and 5th after Cambridge (126), Oxford (119) and University College London (86).

However, the relationship with the EU on support for research and development is currently being discussed. After the federal vote on mass immigration the European Commission suspended the ongoing negotiation to associate Switzerland to Horizon 2020, downgrading Switzerland as a "Third Country", not able to receive any more EU funding. This was seen as the most significant consequence of the immigration vote, for example, it was reported that "The most negative consequence was that Switzerland was excluded from the ERC, the very prestigious sub-programme of Horizon 2020, which funds Europe's best scientists with up to € 3 million per grant".[105] Since Switzerland signed the deal extending the free movement of people accord to Croatia, Switzerland has partially regain access to Horizon 2020, but only until the end of 2016.

Currently, Switzerland is associated to pillar 1 (plus Euratom/ITER and Spreading Excellence) of Horizon 2020, but not to pillars 2 and 3. The State Secretariat for Education, Research and Innovation (SERI) is funding successful Swiss participants in pillars 2 and 3 through direct payments in Swiss francs. This partial association also covers the participation in the ERC until the end of 2016. After 2016 it is possible that Switzerland will again be downgraded to a "Third country".[106]

Regarding the public private partnership, IMI, Switzerland is not a member of the IMI's States Representatives Group and is unable to provide strategic opinions to the Governing Board. However, Switzerland's companies such as Roche and Novartis can participate in IMI projects though it is unable to get funding from IMI. However, Switzerland is involved in many Innovative Medicines Initiative 2 (IMI 2) programmes.[107]

Patent application and protection

Switzerland and Liechtenstein have a single joint patent system. It can either be a national patent valid only in Switzerland and Liechtenstein, or a European patent granted under the European Patent Convention (EPC) and having a unitary character pursuant to Article 142(1) EPC. A European patent may only be granted jointly in respect of Switzerland and Liechtenstein, following a joint designation under Article 149 EPC. The agreement underlying the EU unitary patent that would be valid in participating member states of the European Union, has been signed but is not in force, as of March 2014.

104 Confederation Suisse (2015) "Swiss Participation in European Research Framework Programmes Facts and figures 2015"

105 ETZ Zurich (2015) "Switzerland's current status in the European Research Area"

106 Ibid

107 Innovative Medicines Initiative "IMI - the story so far"; accessible at http://www.imi.europa.eu/content/history

The Patent Cooperation Treaty (PCT) gives Swiss patent applicants the possibility of filing a single international application for a patent in any of the treaty member states. This international route consists of a centralized filing and search procedure. The international patent application is the subject of an international search by an authority specializing in this area, the results of which are made available to the applicant in an international search report. The applicant may opt to request an international preliminary examination, which may be considered to be an expert opinion on the application.[108]

The European Patent Convention (EPC) makes it possible to obtain protection in over 30 European states, including Switzerland and Liechtenstein, through a single application. Since European patent applications are examined for novelty and inventive step, this way leads to a fully examined patent in Switzerland. [109]

Switzerland will not be part of the "European patent with unitary effect" which will lead to a distinct reduction in patent application costs within the 25 EU Member States as national application processing costs and most of the translation costs will be eliminated.[110]

3.2.2. Product development and approval regulation

Since Switzerland is not a member of the European Union, it has its own drug regulatory authority and is not affiliated to the EMA. Pharmaceuticals are mainly regulated by the Federal Law on Medicinal Products and Medical Devices (Law on Therapeutic Products - Heilmittelgesetz) of 15 December 2000 (LTP). Based on the LTP several ordinances have been issued. The LTP and its related ordinances stipulate the conditions for obtaining a marketing authorisation and for authorisations required to manufacture, import, sell, trade and export pharmaceuticals as well as rules about the prescription, dispensing and advertising of pharmaceuticals. In many areas Swiss legislation on pharmaceuticals follows EU regulation.

Clinical trial directive

From 2010 to 2013, approximately 200 to 250 clinical trials a year were approved in Switzerland. Clinical trials is therefore a significantly smaller issue than in the UK. Shortly after the implementation of the Swiss laws, Europe also published new clinical trial regulation. While drafting its rules, Switzerland reviewed the changes in European legislations, resulting in laws that share goals such as introducing a risk-based approach for clinical trials, more streamlined and faster trial application assessment processes, and increased clinical data transparency.[111]

However, there are differences in the legislation applied in Switzerland and the EU as the ethics committee's review processes and data transparency requirements are similar but not identical. A larger difference is that the scope of the Swiss Human Research Act covers

108 IGE "Protection Abroad"; accessible at https://www.ige.ch/en/patents/protection-abroad.html

109 IGE "Protection Abroad"; accessible at https://www.ige.ch/en/patents/protection-abroad.html

110 European Council (2016), "Agreement to the European Unitary Patent." Available at: http://www.consilium.europa.eu/en/documents-publications/agreements-conventions/agreement/?aid=2013001

111 Corrado, M. E. (2014). Switzerland Guides Innovation in Clinical Trial Regulations.

a much wider range of research projects than the EU's Clinical Trials Regulation, which only covers clinical trials of medical products.[112]

Table 2: Comparison of Swiss Human Research Act and EU Clinical Trials Regulation

	Swiss Human Research Act	EU Clinical Trials Regulation
Ethics committees	Authorisation of clinical trial application	Review of clinical trial application
Multinational trials	Swiss portal is relevant for Swiss trial sites submissions	EU single portal for submission of clinical trial applications
Clinical trials for medical devices	Within the scope	Not within the scope
Research projects involving human biological materials or health-related personal data	Within the scope	Not within the scope

Source Wagner et al (2014)

Though harmonization between the EU and Switzerland are not exact, it has been argued that performing trials in Switzerland remain advantageous for sponsors due to the country's high standards of research, excellence of clinical sites, minimal bureaucracy, and even faster and effective regulatory approvals. This illustrates how small differences in regulation are unlikely to have a significant impact on location.

Swiss framework for marketing authorisation

Marketing authorisations and authorisations to manufacture, import and export pharmaceuticals are granted by the Swiss Agency for Therapeutic Products (Schweizerisches Heilmittelinstitut, Swissmedic).[113]

Swissmedics's requirements for marketing authorisation (MAA) dossier are similar to those of the EMA. Swiss applicants must hold an additional establishment license from SwissMedic in order to file an MAA. This requires setting up a quality management system (QMS) that has to be inspected and approved by SwissMedic, which takes on average six months. During this time, the pharmaceutical company cannot file an MAA. In order to save time, companies use the support of local organisation which hold the required licence.

There is an exchange of letter in place between the European Medicines Agency (EMA), the European Commission's Directorate General for Health and Food Safety (DG SANTE),

112 Niklaus Wagner, Anna Hallersten and Shayesteh Fürst-Ladani (2104) The new research rules in Switzerland versus the proposed EU Clinical trial regulation; Scrip Regulatory Affairs

113 Wnger & Vieli Ltd (2015) "Switzerland – Law & Practice"; accessible at http://www.chambersandpartners.com/guide/practice-guides/location/256/7322/1691-200

the Swiss Agency for Therapeutic Products (SwissMedic) and the Swiss Federal Department of Home Affairs (FDHA) since 10th of July 2015. The agreement allows the exchange of non-public information such as guidance and legislations, authorised or under review, both in Switzerland and in the EU in order to enhance public health protection. The arrangement supports efforts by European and Swiss regulators to improve the oversight of medicines for human and animal health. It is valid for five years and may be renewed. This will complement ongoing activities in the area of quality and manufacturing under the mutual recognition agreement between the EU and Switzerland, signed in 2002.

A number of Swiss regulatory pathways are similar but not identical to those of the centralised procedure in the EU. For example three regulatory pathways that are intended to provide opportunities and incentives for applicants in Switzerland are

- Article 13 of the Therapeutic Product Act (TPA)
- Article 5a-5d Medical Product Ordinance
- The fast track product and the simplified procedure.
- Procedure with prior notification (since 2013)

An analysis based on a selection of 25 drugs approved by the European Medicines agency in 2014 shows that products are approved much earlier in the EU than in Switzerland. As illustrated in Appendix, whilst a small number of products are approved by SwissMedic before EMA, the majority of products are approved on average 157 days after EMA approval.

This can be associated with two factors.

1. SwissMedic take longer to approval new drugs. A new report from the London-based Center for Innovation in Regulatory Science (CIRS) suggests that authorisation of medicines in Switzerland may lag behind the EMA even though SwissMedic has already improved its efficiency by using certain regulatory routes. SwissMedic came in last with a median approval time of 511 days.
2. Firms think carefully about their launch sequences and European submission is prioritised. Many companies indicated that for most products, they will file an application to the FDA, followed by the EMA and only then will they consider filing an application in Switzerland, Australia and Canada.

Orphan drug regulations

Orphans drugs are mentioned in the Swiss Therapeutic products Act. Applications for orphan designation can be based on orphan status granted by a reference authority following a comparable regulatory system (particularly the EMA). Products with orphan drug status are eligible for review under SwissMedic's simplified authorisation procedure.[114]

Swiss framework for data protection

The Swiss Federal Data Protection Act (the "DPA") is dated 19 June 1992. The DPA follows similar concepts as the Data Protection Directive. Accordingly, the European Commission

114 Swiss Medic (2016), "Questions and answers regarding the application of the administrative ordinance (ART 13, Therapeutic Product Act). Available at: https://www.swissmedic.ch/ueber/00134/00519/00520/index.html?lang=en

has found Switzerland to provide an adequate level of data protection from an EU perspective (Decision 2000/518/EC). [115]

The DPA came into force on 1 July 1993; a revised version has been in force since 1 January 2008, with some minor revisions since. A revision is currently being discussed with proposals expected by fall 2016. The changes should include those needed to comply with the to-be-revised Council of Europe Convention.[116]

3.2.3. Manufacturing and trade

Switzerland is home to many pharmaceutical companies, including very large groups, such as Novartis and Roche. The pharmaceutical industry in Switzerland directly and indirectly employs about 225,000 people.[117] It directly and indirectly contributes to 7.0% of the gross domestic product of Switzerland and contributes to 34.6% of the country's exports (in 2015).

EU legal framework for manufacturing (GMP guidelines)

There are 468 licensed pharmaceutical manufacturers in Switzerland.[118] Authorisations to manufacture, import, and trade and export pharmaceuticals are granted by SwissMedic. Applicants for manufacturing of medicinal products must be located in Switzerland (there are no restrictions on foreign ownership), and be made to SwissMedic, though they accept registration documents in the form approved by the EU.

On 22 November 2012, Switzerland was listed as the first country with equivalent standards in the manufacture of active pharmaceutical ingredients (APIs) to those of the EU. The assessment was made after Switzerland decided to apply for the "listing of third countries". This listing refers to Article 46b(2) of Directive 2001/83/EC. According to this article, "active substances shall only be imported if, inter alia, the active substances are accompanied by a written confirmation from the competent authority of the exporting third country which, as regards the plant manufacturing the exported active substance, confirms that the standards of good manufacturing practice and control of the plant are equivalent to those in the Union. Based on the decision to add Switzerland to the listing of third countries, Switzerland will not have to issue a 'written confirmation' for each consignment of active substance for medicinal product for human use imported into the EU as of 2 July 2013.[119]

The EU and Switzerland have a mutual recognition agreement in relation to conformity assessment which details the medicinal products GMP inspection and batch certification.

115 Homburger AG (2015 July) “Switzerland”; accessible at https://clientsites.linklaters.com/Clients/dataprotected/Pages/Switzerland.aspx

116 Linklaters (2015) General Data Protection Laws in Switzerland; accessible at https://clientsites.linklaters.com/Clients/dataprotected/Pages/Switzerland.aspx

117 Grass M, Mösle S, in collaboration with Polynomics (2015) The Importance of the Pharmaceutical Industry for Switzerland; A study undertaken on behalf of Interpharma

118 Swiss confederation (2011) Switzerland Pharmaceutical country profile; Published by the Swiss Federal Office of Public Health in collaboration with the World Health Organization September 2011

119 GMP Compliance (2012 December 12) "Swiss GMP Standards and Inspection Equivalent to EU”; accessible at http://www.gmp-compliance.org/enews_03421_Swiss-GMP-standards-and-inspection-equivalent-to-EU.html

This is significant as in 2014 alone, there were 420 GMP inspections, including Plasma Master File (PMF) inspections.[120]

Access to the single market (tariff and customs free trade)

Switzerland is one the main trading partners with the European Union for imports of pharmaceutical over the period 2003-2013, but with imports from Switzerland growing at a faster pace.[121] In 2015, 10.9% of the EU's pharmaceutical exports were to Switzerland while 52.1% of Switzerland's CHF 70.3bn worth of pharmaceutical exports were to the EU.[122]

The EU is Switzerland's most important partner for direct investments: Around 82% of foreign capital in Switzerland comes from the EU (2013: approx. CHF 562 billion); conversely, some 43% of Swiss direct investments abroad are in the EU (2013: approx. CHF 465 billion).[123]

Switzerland treats copyrights and trademarks as internationally exhausted but applies national exhaustion to patents. Switzerland therefore has a ban on parallel import for pharmaceuticals.

Dispute settlement mechanism (European Courts of Justice, WTO)

The nature of the bilateral agreements with Switzerland is static, given that there are no proper mechanisms to adapt the agreements to evolving EU legislation. Neither are there any surveillance or efficient dispute settlement mechanisms.

EU-Swiss negotiations for a framework institutional agreement were launched on 22 May 2014, following the adoption of the Swiss and EU mandates in December 2013 and May 2014 respectively. The negotiations were aimed at settling the problems stemming from the evolving nature of the EU acquis related to the internal market and at introducing a dispute settlement mechanism into the current bilateral treaty network. The institutional framework negotiations are crucial, because the Council of the EU is determined not to allow Switzerland any further single market access (e.g. as regards electricity) without this framework agreement. However, the negotiations have stagnated since January 2015, owing to the repercussions of the free movement crisis, and their conclusion will depend on finding a solution to this crisis. [124]

120 European Medicines Agency (2015) "Annual Report of the Good Manufacturing and Distribution Practice Inspectors Working Group 2014"; accessible at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/06/WC500188828.pdf

121 Eurostat (2013) Statistics Explained: International trade in medicinal and pharmaceutical products; Data from October 2014

122 Database "Swiss-Impex" of the Federal Customs Administration, accessed on 26.4.2016.

123 Federal Department of Foreign Affairs "Switzerland and the European Union"; accessible at https://www.eda.admin.ch/dam/eda/en/documents/publications/EuropaeischeAngelegenheiten/Schweiz-und-EU_en.pdf

124 European Parliament "The European Economic Area (EEA), Switzerland and the North"; accessible at http://www.europarl.europa.eu/atyourservice/en/displayFtu.html?ftuId=FTU_6.5.3.html

Trade with RoW - Flexibility to negotiate trade deal with others third countries

Switzerland and the EU have a free-trade area for industrial products but, unlike a customs union, they are free to determine the external tariffs in respect of third countries. [125] The conclusion of free trade agreements (FTAs) with partners outside the EU is seen as important to preserving and improving access to foreign markets.[126]

According to a government report free trade agreements with partners outside the EU has brought improved access to a market of 650 million consumers with a combined GDP of CHF 9,600 billion and has enhanced market access to fast growing economies.[127] This allows a more diversified export structure and is associated with increasing Swiss foreign direct investment in partner countries. However, we have not found any evidence that these agreements have brought significant benefits directly to the life sciences industry. It has been argued that countries like Switzerland and Norway have had difficulty negotiating free-trade deals with large emerging markets such as China and India and have struggled to protect their patents from foreign drugs companies. One example is the recent trade agreement being negotiated between India and EFTA countries (Switzerland, Norway, Liechtenstein and Iceland) which has been on the table since 2008 and according to the Swiss head of negotiations "the negotiations between India and Switzerland are going nowhere fast".[128]

Labour availability (free movement of people)

The bilateral agreement on the free movement of persons confers upon the citizens of Switzerland and of the member states of the EU the right to freely choose their place of employment and residence within the national territories of the contracting states parties.

This is conditional, however, on possession by the individuals concerned of a valid employment contract, being self-employed, or in the case of their not being in gainful employment, proof of financial independence and full health insurance coverage. The FMP provides for a phased introduction of the ground rules for the free movement of persons between Switzerland and the EU. It lays down transitional periods during which immigration can be restricted.

According to the European Commission, over 900,000 EU citizens live and work in Switzerland and many more travel through its borders on a regular basis. This is reciprocal. At the end of 2014, some 446,400 Swiss nationals were living and working in the EU/EFTA member states, while more than 1,324,400 EU/EFTA citizens were living in Switzerland. The Swiss pharmaceutical industry is composed of 65% foreign nationals (1/3rd are cross border, 1/3rd are EU and final 1/3rd are AUS/Chinese/Americans) which is facilitated by the free movement of peoples with the EU and by the independence to decide on regulations

125 Federal Department of Foreign Affairs "Switzerland and the European Union"; accessible at https://www.eda.admin.ch/dam/eda/en/documents/publications/EuropaeischeAngelegenheiten/Schweiz-und-EU_en.pdf

126 Vaterlaus S, Suter S, Fischer B (2011) The Importance of the Pharmaceutical Industry for Switzerland; A study undertaken on behalf of Interpharma

127 Swiss Confederation (2015) The Economic Relevance of Free Trade Agreements with Partners outside the EU, Federal Department of Economic Affairs FDEA

128 SwissInfo.ch; April 30, 2015, India-Swiss trade deal on ice over pharma patents, accessed on 26 May 2016 at: http://www.swissinfo.ch/eng/efta-agreement_india-swiss-trade-deal-on-ice-over-pharma-patents/41407582

for the Swiss labour market. More than 287,000 EU citizens are cross-border commuters.[129] From a Swiss industries standpoint, allowing the free movement of people has reinforced the strong economic growth characteristic of global trade since 2003.[130]

3.2.4. Market Access

Like all countries in Europe, Switzerland has its own pricing and reimbursement regulation. Switzerland does not have an institutional HTA agency such as e.g. NICE or IQWIG to assess new drugs. However, the structure and capacity for HTA is in place and cost-effectiveness and affordability are taken into account for coverage. As such Switzerland is part of the EUnetHTA project and is therefore able to leverage it to participate in EU initiatives as well as collaborate with EU countries on facilitating efficient use of resources available for HTA, creating a sustainable system of HTA knowledge sharing, promoting good practice in HTA methods and processes.[131]

Falsified medicines directive (e.g. traceability)

The European Union Falsified Medicines Directive (FMD) (2011/62/EU) was introduced in July 2011 to prevent falsified medicines from entering the legal supply chain and reaching patients. Switzerland is taking several efforts to fight falsified medicines and the research-based pharmaceutical industry in Switzerland is supporting the implementation of the FMD in Switzerland.[132] The Swiss Anti-Counterfeiting and Piracy Platform is a non-profit association with 40 members from the public sector, private enterprises, and consumer organizations. Its high profile “Stop Piracy” educational and awareness public campaigns emphasize the criminal background behind such falsification operations. In addition, the Revision of Swiss Medicines Law includes new measures relating to these issues (Art. 86/87). The imitation and falsification of medicines is clearly outlined as a criminal offence. In addition, Switzerland signed the Medicrime Convention on 23 Oct. 2011, which is the Council of Europe convention on the counterfeiting of medical products and similar crimes involving threats to public health (9). Switzerland has considered ratification, and a report by the Federal Office of Public Health (FOPH) on a Draft Implementation Act is expected during the second half of 2015.[133]

3.2.5. Conclusion and implications for the UK

The UK could follow the Swiss model of relations with the EU. The bilateral agreements give Switzerland and the EU member states mutual access to the markets in specific sectors. At the same time, this approach also guarantees Switzerland’s continued institutional independence.

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129 Federal Department of Foreign Affairs “Switzerland and the European Union”; accessible at https://www.eda.admin.ch/dam/eda/en/documents/publications/EuropaeischeAngelegenheiten/Schweiz-und-EU_en.pdf

130 Schellenbauer, P., & Schwarz, G. (2015, December 7) “Bilateralism – what else?”; accessible at http://www.avenir-suisse.ch/en/53050/bilateral-treaties-what-else/

131 Eunethta “About us”; accessible at https://eunethta.fedimbo.belgium.be/about-us

132 Kermani, F. (2015, April 14) “Evaluating the Impact of the Falsified Medicines Directive in Switzerland”; accessible at http://www.pharmexec.com/evaluating-impact-falsified-medicines-directive-switzerland-1

133 Kermani, F. (2015, April 14) “Evaluating the Impact of the Falsified Medicines Directive in Switzerland”; accessible at http://www.pharmexec.com/evaluating-impact-falsified-medicines-directive-switzerland-1

In terms of research and innovation, Switzerland is one of the leading countries in European in the field of biomedical research and as a result, it has succeeded in negotiating access to some parts of the EU research programme despite some difficulties in the negotiation linked to the acceptance of the free movement of people principle. Switzerland has also succeeded in attracting key scientists and researcher to its centres. Given the UK's similar profile in terms of science and innovation, it is not unlikely that the UK would succeed in negotiating a similar deal on research as Switzerland.

Despite some alignment on the regulatory angle, Switzerland has maintained much of its own regulatory framework for pharmaceuticals and has adapted some of its text to ensure mutual recognition of its rule through Mutual Agreements and some level of collaboration with the EU's Medicines Agency (EMA). Whilst SwissMedic's regulatory approval process has improved, medicines in Switzerland still get regulatory approval later than in the rest of Europe or the US. Should the UK follow a similar scenario, it is not unlikely that it could slip down the priority list of countries to file MA application. The UK's fragmented market access systems and reluctance to pay high prices could compound the situation, making the UK a less attractive launch market.

With respect to manufacturing and trade, the UK (like Switzerland) is a major location for pharmaceutical production with a relatively high number of manufacturing sites. Like Switzerland, trade in pharmaceuticals in the UK represent a significant source of export and having greater flexibility to negotiate trade deals with other countries could potentially represent a benefit. Although this would have to be contrasted with UK losing the benefit of EU Free Trade Agreements with other parts of the world and that individually renegotiating these deals with third countries would take years.

In terms of market access, given pricing and reimbursement procedure is largely a national competence, the UK would not stand to lose much in terms of its ability to put product on the market. Switzerland remains an active participant in most European initiatives that support market access such as EUnetHTA etc. Perhaps a significant impact of leaving the EU would be the ability to re-introduce a ban on parallel trade as a result of no longer being subject to EU competition policy. However, given the view that parallel trade can result in savings, it is not guaranteed that the UK would re-introduce such a ban should it leave the EU.

Perhaps the most important impact of the Swiss type model is the influence that the UK would lose in the legislative process. As a non-member of the EU, Switzerland has no right to participate in decisions taken at EU level. Switzerland therefore can only observe the EU legislative process and does not have the right to vote. [134] This would potentially have significant impact on the pharmaceutical industry as the UK and its policy makers have been active in driving the pharmaceutical regulatory agenda and loss of participation of bodies such as the MHRA or the department of health as part of the discussion platform in Brussels would affect both the UK industry as well as the wider European industry.

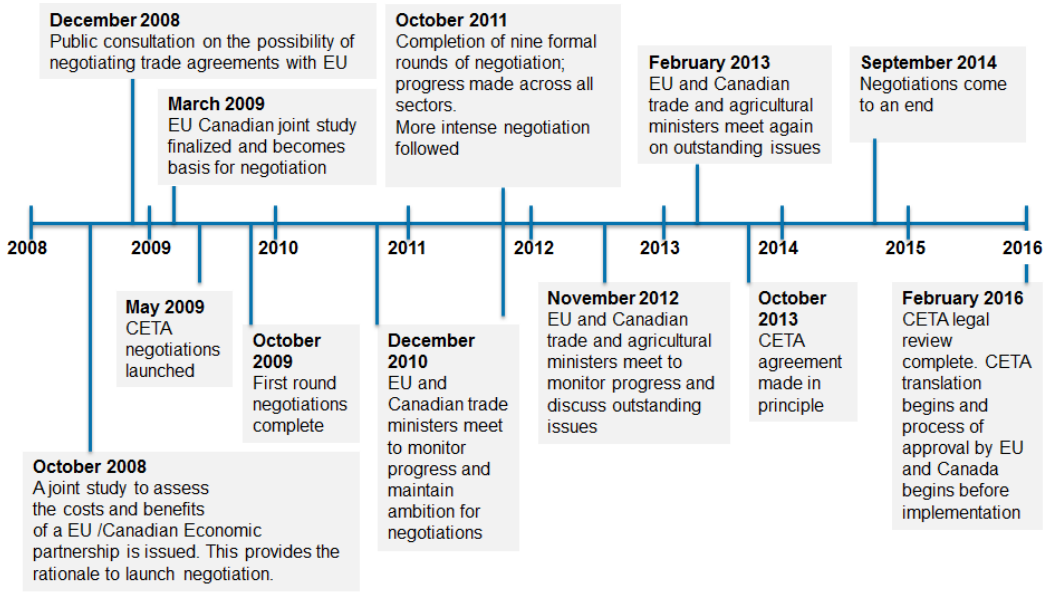
134 Federal Department of Foreign Affairs "Switzerland and the European Union"; accessible at https://www.eda.admin.ch/dam/eda/en/documents/publications/EuropaeischeAngelegenheiten/Schweiz-und-EU_en.pdf

3.3. Drawing from the Canadian experience to understand the impact of "comprehensive" FTA with the EU

Being geographically outside Europe, Canada is not a member of the European Union and yet the EU and Canada work closely together on global challenges such as the environment, climate change, energy security and regional stability throughout the world.[135] It has been discussed as a potential model for the UK, particularly, because of the Comprehensive Economic and Trade Agreement (CETA), the free trade agreement between the EU and Canada. This has been called the most "comprehensive and ambitious" free trade deal the EU has negotiated to date.[136] The objective of CETA is to increase bilateral trade and investment flows and cover a whole range of issues such as removing customs duties, end limitations in access to public contracts, open-up the market for services, offer predictable conditions for investors and also addressed illegal copying of EU innovations and traditional products.[137]

The first point to note is the length of time taken for the FTA to be negotiated. FTA negotiations such as the one with the EU (CETA agreement) took over 8 years to negotiate and has not yet been ratified.

Figure 10: Timeline for negotiating CETA



Source: CRA Analysis

The most relevant element of the CETA for the pharmaceutical and life science sector concerns the changes made by Canada on intellectual property rights of Canadian innovative pharmaceutical companies, in order to bring its intellectual property system in line with other western countries. Canada has agreed to the adoption of a patent term

135 European External Action Service: EU Relations with Canada, accessible at http://eeas.europa.eu/canada/index_en.htm

136 European Commission (2014) CETA – Summary of the final negotiating results – DG Trade – accessible at http://trade.ec.europa.eu/doclib/docs/2014/december/tradoc_152982.pdf

137 Ibid

restoration for pharmaceutical patents and an effective right of appeal under the Patented Medicines (Notice of Compliance) Regulations.[138] Beyond the IP issue, CETA had an insignificant impact on the pharmaceutical sector as tariffs had already been liberalised.

3.3.1. Basic research and product discovery

According to a survey of over 5,000 top international scientists, Canada ranks 4th in the world for the quality of its scientific research. [139] Although it has a population of less than 0.5 % of the world's population, Canada produces 4.1 % of the world's research papers and ranks 6th in the world when it comes to how often Canadian research papers are cited by other scientists.

Access to EU Research Programme and funding

An "Agreement for Scientific and Technological Cooperation between Canada and the European Community" has been in place since 1996, and it is not limited in time. As part of this agreement, Canadian based researchers are eligible to be involved in the EU research programmes (FP7, Horizon 2020) as a third country entity, however in most cases, Canadians will participate in Horizon 2020 projects without receiving funding from the European Commission. They must cover their own personnel costs and other expenses from Canadian funds. In the past, Canadian participation in Framework Programme projects has gone through an important increase in the 7th Framework Programme for Research and Innovation - FP7 (2007-2013). Canada ranks eighth among third countries involved in selected FP7 proposals. In the FP7 "Cooperation" Specific Programme, Canadians are the most active in the thematic areas of Food, Agriculture and Biotechnology; Health, Environment, and Transport. Together, Canadian researchers contributed €51 million to FP7 projects while, at the same time, they received €11 million in direct financial support from the European Commission.

Access to EU researchers and scientists

EU researchers and scientists require a work visa to work in Canada. The work visa is usually valid only for the specific job, employer and length of time stated on the permit. An immigration officer may issue a work permit after Employment and Social Development Canada (ESDC) has issued a labour market opinion confirmation letter for your job offer. A work permit will not be issued to EU citizens to come to Canada to look for work. In addition, ESDC staff in Canada and visa officers in EU cannot help EU citizens find a job.[140]

It has not been possible to identify data on people employed directly in life sciences but according to a report by the Council of Canadian Academies, during the period 1997–2010, Canada experienced a positive migration flow (0.9 per cent) with more immigrants (about 900) than emigrants (about 700). Immigrants and emigrants had comparable Average

138 Bourassa Forcier, M (2013) Canada – EU Comprehensive Economic and Trade Agreement (CETA) reached in principle: What is the impact on pharmaceutical patents? Life Sciences Bulletin: Fasken Martineau; October 22, 2013

139 Council of Canadian Academies (2012) The State of Science and Technology in Canada, accessible at http://www.scienceadvice.ca/en/assessments/completed/science-tech.aspx

140 If EU researchers and scientists intend to work in the province of Quebec, they may also need to get a Certificat d'acceptation du Québec (CAQ) from the Quebec government before a work permit can be issued. The employer must also show that hiring a foreign national to fill the position will result in a neutral or positive effect on the labour market in Canada.

Relative Citations (ARC) scores, of 1.53 and 1.57 respectively, high scores for both groups. Over the same period, Canada was able to attract seven times as many temporary foreign workers than Canadian researchers who temporarily emigrated before returning. Overall, Canada is maintaining its share of skilled workers.[141]

Patent protection and enforcement

From the industry perspective, Canada's intellectual property (IP) regime lags behind that of other developed nations and continues to be characterized by significant uncertainty and instability for innovative biopharmaceutical companies. Patent protection in Canada lasts for 20 years but Canadian Patented Medicines (Notice of Compliance) Regulations is seen as having a number of key deficiencies that weaken Canada's enforcement of patents, including the nature of patent dispute proceedings, lack of effective right of appeal for patent owners, and limitations and inequitable eligibility requirements on the listing of patents in the Patent Register.[142]

The CETA includes a chapter on Intellectual Property Rights (IPR) for pharmaceuticals. The agreement means

- pharmaceutical companies can appeal marketing authorisation decisions in Canada;
- adopts the EU regime of data protection; and
- the development of patent term restoration system ('sui generis protection') along the lines of the EU Supplementary Protection Certificate (SPC) system although Canada has a maximum protection of 2 years versus 5 years in the EU.

Overall, this means research-based pharmaceutical producers will have an improved but still not directly equivalent protection of their intellectual property in Europe and in Canada when the agreement is implemented.

In the past the Canadian patent did not hold in the EU, though there is patent protection/enforcement through WIPO and through TRIPS agreement. Thus a foreign patent may also be applied from within Canada through a treaty called the Patent Cooperation Treaty (PCT), administered by the WIPO. Under the PCT, a patent may be filed in as many as 142 member countries through a single application filed in Canada. This procedure is simpler than filing separate applications and can give you more time to raise capital, conduct market studies, etc. Only Canadian citizens and residents of Canada can file under the PCT in Canada. The application made in Canada under the PCT automatically qualifies for a normal national filing for a Canadian patent application. Canada will not be part of the EU unitary patent system.

3.3.2. Product development and approval regulation

CETA does not affect the EU and Canada adopting different regulatory and licensing requirements. In Canada, drugs are federally regulated under the Food and Drugs Act, and the Food and Drug Regulations administered by the health products and food branch within Health Canada, the federal health department. Health Canada reviews new drug

141 The state of science and technology in Canada. (2012). Ottawa: Council of Canadian Academies.

142 PhRMA (2016) Pharmaceutical Research and Manufacturers of America, Special 301 submission 2016

submissions for the purposes of safety, efficacy and quality of manufacture, and issues marketing authorisations – known in Canada as notices of compliance (NOC).

Clinical trial regulation

Canada has its own clinical trial regulation which has been revised in 2001 to strengthen protection for clinical trial participants. Health Canada also developed a national inspection program to verify that clinical trials conducted in Canada comply with these regulations, which were designed to protect the participant's safety and to generate high-quality clinical data. Indeed, Canada boasts one of the world's shortest clinical trial approval timelines (30 days or less), and its medical community and facilities meet the highest international standards.[143] Drug sponsors seeking approval to conduct Phase I-III trials must submit a Clinical Trial Application (CTA) to Health Canada. (Some sponsors depend upon their clinical trial partners to complete the CTA).[144]

As in most countries, Canada has adopted the "Guidelines for Good Clinical Practice" developed by the ICH which defines an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. This means Canada rules are similar to the EU. However, there is no intention for Canada to share a clinical trial authorisation process with the EU or share the clinical trial portal.

Product approval regulation

The European Medicines Agency cooperates with the Health Products and Food Branch of Health Canada on regulatory issues and international medicine inspections. The Agency and Health Canada exchange information on pre- and post-authorisation applications, including issues of major public-health interest, such as extensions of indications and important safety concerns that may have an impact on the use of a medicine.

Like Switzerland, drugs are approved later in Canada than in the US or the EU. A recent study published in the New England Journal of Medicine (NEJM) shows that the average time taken by Health Canada (HC) to approve a drug product was 409 days, compared to 366 day for the European medicines Agency (EMA) and 322 days for the US FDA.[145] As shown in the appendix, a CRA analysis based on a selection of 25 drugs approved by the European Medicines agency in 2014 shows that products are approved much earlier in the EU than in Canada with an average delay of 144 days.

3.3.3. Manufacturing and trade

Canada's pharmaceutical sector is composed of companies developing and manufacturing innovative medicines and generic pharmaceuticals, as well as over the counter drug products. Annual domestic pharmaceutical manufacturing production is valued at $7.7 billion as of August 2014 with a declining compound annual growth rate of 2.5 percent since

143 Pharm-Olam (2014). "Clinical Trials in Canada A Primer for Sponsors. "http://www.pharm-olam.com/sites/default/files/poi-clinical-trials-whitepaper_canada.pdf

144 Ibid

145 Downing, N. S., Aminawung, J. A., Shah, N. D., Braunstein, J. B., Krumholz, H. M., & Ross, J. S. (2012). Regulatory review of novel therapeutics—comparison of three regulatory agencies. New England Journal of Medicine, 366(24), 2284-2293.

2008.[146] In 2014, the manufacturing portion of the sector employed 26,300 people and over the last 5 years employment has fallen by 6.3 percent.[147] In 2014, €1,273 million worth of pharmaceutical products were exported from Canada to the EU (4.6% of all Canadian exports to the EU) while there was €3,564 million worth of pharmaceutical products were imported from the EU to the Canada (11.3% of all EU imports to the Canada).[148]

Regulatory framework for manufacturing (GMP guidelines)

As part of Mutual Recognition Agreement (MRA) between Canada and the European Economic Area, the European Medicines Agency and Health Canada have also signed a mutual recognition agreement to improve activities around good manufacturing practice (GMP) inspection information. Canadian companies exporting or importing drugs/medicinal products to/from any EEA-EFTA countries may benefit from specified GMP exemptions provided by the MRA as listed in the Canadian GMP Guideline.[149]

Access to the single market (tariff and customs free trade)

CETA removes 99% of customs duties and other obstacles for business although pharmaceutical products were already excluded from tariffs.[150] However, most of the progress on trade does not relate to life sciences as related tariffs were reduced or eliminated before the CETA. Rather liberalisation is being made on agricultural products, where the EU and Canada will eliminate 93.8% and 91.7% of tariff lines respectively.

CETA has created a framework to resolve any future disagreement**s** that may occur between EU and Canada about the interpretation and implementation of the Agreement. It applies to most areas of the agreement. The system is intended as a last resort should the parties fail to find a solution by other means. It proceeds along a fixed set of procedures and time-frames. Should parties fail to reach an agreement through formal consultations, they can request the establishment of a panel, made up of independent legal experts.

As an alternative to formal dispute settlement mechanism, the EU and Canada also set rules that will allow for mediation to tackle measures that adversely affect trade and investment between EU and Canada. This can be used on a voluntary basis.[151]

Trade with RoW - Flexibility to negotiate trade deals with other third countries

Unlike a country within the EU, Canada does have the freedom to negotiate FTAs with third countries and Canada has concluded free trade agreements with more than 40 countries. As illustrated below, FTA negotiation can take several years. As shown in Table 3, the

146 Government of Canada website (2015) The Canadian Life Science Industries: Biopharmaceuticals and pharmaceuticals industry profile; accessible at: https://www.ic.gc.ca/eic/site/lsg-pdsv.nsf/eng/h_hn01703.html

147 Ibid

148 Europe Commission (2006) “European Union, Trade in goods with Canada.“ Directorate-General for Trade. http://trade.ec.europa.eu/doclib/docs/2006/september/tradoc_113363.pdf

149 Government of Canada (2013) Agreement on Mutual Recognition Between Canada and the European Community accessible at: http://www.international.gc.ca/trade-agreements-accords-commerciaux/agr-acc/other-autre/mra-eu.aspx?lang=eng

150 "European Commission Directorate-General for Trade." EU-Canada Comprehensive Economic and Trade Agreement (CETA). Web. 29 Mar. 2016. <http://ec.europa.eu/trade/policy/in-focus/ceta/>.

151 "EU-Canada Comprehensive Economic and Trade Agreement (CETA)." European Commission Directorate-General for Trade. Web. 29 Mar. 2016. <http://ec.europa.eu/trade/policy/in-focus/ceta/.>

shortest FTAs (Peru and Costa Rica) took a minimum of 2 years whilst some other FTA negotiations such as the one with the EU (CETA agreement) took over 8 years to negotiate and have not yet been ratified.

Table 3: Average negotiation time for Canadian FTA with third countries

	ought into force	gotiations started	ber of years taken
Canada-Korea	01-Jan-15		9
anada-Honduras	01-Oct-14	21-Nov-01	13
anada - Panama	01-Apr-13	29-Oct-08	4
Canada - Jordan	01-Oct-12	20-Feb-08	5
nada - Colombia	15-Aug-11	07-Jun-07	4
Canada - Peru	01-Aug-09	07-Jun-07	2
Canada - EFTA	01-Jul-09	09-Oct-98	11
nada - Costa Rica	01-Nov-02	30-Jun-00	2

Note: It should be noted that some bilateral agreements that took the least time to complete were also agreements with the least commercial significance in terms of bilateral trade (e.g. Peru. Costa Rica, Panama).

Source: CRA analysis

The EU trade policy sets the direction for trade and investment in and out of the EU. The EU is involved in the negotiation of international trade treaties representing all 28 member states. This allows the EU negotiate more comprehensive access and conditions for trade and investment through free trade agreements with third countries. Comparing the Canadian FTA with Korea (CKFTA) with the EU-Korea Free Trade Agreement (FTA) – see appendix; we observe that the Canadian FTA focuses more of tariff elimination while the EU FTA focused more on non-tariff barriers like regulatory and transparency guidelines and included a chapter on IPR which addresses the current asymmetry in the level of protection in the EU and in Canada.

3.3.4. Market Access

Pricing and reimbursement

Like all European Countries, Canada has its own process for regulating the pricing and reimbursement of innovative pharmaceuticals. Canada does not influence the EU legal framework on market and patient access. However, given the important synergies in terms of policies objectives on pharmaceutical pricing and reimbursement policies, Canada does participate in some EU initiative on market access. One example of this is the EUNetHTA

project[152] where Canada's Coordinating Office for Health Technology Assessment (CCOHTA) is involved in some EUnetHTA Project such as Project WP2 (Communications), Project WP6 (HTA and Health Policy) and Project WP8 (System to support HTA).[153] Canada also has established links with relevant organisations to enhance scientific cooperation on HTA with Europe such as through the collaborating with HTAi, a global scientific and professional society for all those who produce, use, or encounter HTA.[154]

Competition policies

Though Canada has different competition policies from the EU, in 1999, Canada and the EU signed the EU/Canada Competition Cooperation Agreement. The agreement provides for reciprocal notification of cases under investigation by either authority.

Whilst the policy of regional exhaustion permits parallel trade within Europe, Europe has not adopted International exhaustion which means that parallel trade with countries outside Europe is not permitted. European Countries therefore cannot re-import prescription medicines from Canada.

3.3.5. Conclusion and implications for the UK

The free trade deal between the EU and Canada is attracting growing interest as a possible template the UK could follow for its relationship with the EU after Brexit.

In the area of research and innovation, under a Canadian type bilateral agreement model, the UK would have less access to the EU research programme and associated funding than it currently enjoys. Whilst Canadian research centres has been actively involved in EU research projects and benefited from collaboration opportunities on EU projects, Canada is not directly involved in projects such as the IMI which benefits more specifically to the life science research base and pharmaceutical companies alike. However, given the importance of the UK science base in Europe, it is not unlikely that the UK would be able to negotiate greater levels of access to ongoing EU research programmes than Canada has.

The Canadian model would not require the UK to accept the free movement of people. However Canada has struck a deal with the EU to facilitate the temporary movement of skilled professionals such as scientists and researchers. The UK could potentially adopt this approach. Research shows that under this current framework, Canada has remained an attractive place to conduct scientific research and has been able to attract seven times as many temporary foreign workers and has succeeded in maintaining it's attractiveness in a highly competitive, global research environment.[155]

Under a bilateral agreement, the UK would not be bound by EU regulation and could develop its own regulatory framework for pharmaceuticals. Given the UK is currently fully

152 EUnetHTA was established to create an effective and sustainable network for HTA across Europe – we work together to help developing reliable, timely, transparent and transferable information to contribute to HTAs in European countries.

153 EUNetHTA website: EUnetHTA involvement: HTAi, Canada ; accessible at: http://www.eunethta.eu/organisation/htai-canada

154 EUNetHTA website: EUnetHTA involvement: HTAi, Canada ; accessible at: http://www.eunethta.eu/organisation/ccohta-canada

155 The state of science and technology in Canada. (2012). Ottawa: Council of Canadian Academies.

compliant with the EU regulatory standards, it is unlikely that the UK would develop regulations that are significantly different from its current EU standard although over time some differences in regulatory standards may emerge, and these may constitute some barriers to trade in the long term. Like Health Canada, the MHRA could negotiate a collaboration programme with the EMA which would include some exchange of information on pre- and post-authorisation applications, including issues of major public-health interest, however, the MHRA would not be guaranteed to participate in the ongoing efforts and the initiative of the EMA such as international collaboration and other EMA projects (early dialogue, fast track process etc).

In terms of access to the single market, whether or not the UK has full access to the single market would make little difference to trade flows for medicines. Even before CETA, Canada enjoyed tariff free access to the European Market for industry products such as pharmaceuticals so this is unlikely to be an area of significant concern to the pharmaceutical industry. The UK would lose the benefit of EU Free Trade Agreements with other parts of the world. Experience of CETA suggests that a bespoke UK-EU trade agreement would be complex to negotiate and would indeed take many years not because of issues affecting the life sciences industry but it would still be affected by them. This could mean several years of uncertainty with key businesses badly damaged. Until all of the issues are resolved for every sector affected by the FTA, the FTA does not come into force, meaning that Life Sciences is hostage to the more problematic issues facing other sectors. This could discourage foreign direct investment flows and in the long term discourage companies for locating their activities in the UK.

4. Learning from life science industry stakeholders

As set out in the introduction it is unclear what the exact relationship that the UK would have with the EU following a decision to leave the EU. Although, the experience of other markets is valuable, the UK is different to these markets, with the result that this only provides some insight and guidance. In this chapter, we bring together the evidence from case studies and insights from interviews with a range of life science stakeholders[156] who were asked to consider the hypothetical impact a Brexit would have on the their organisation along the value chain under the 3 different scenarios.

4.1. Basic research and product discovery

It was generally agreed across all interviews that the UK is one of the world's leading scientific nations by a range of measures, both in terms of fundamental and applied research and this would continue under all scenarios. As pointed out by the UK House of Lords Science and Technology Select Committee report on Brexit, "It is irrefutable that the UK's research excellence was established long before the inception of European integration in 1952".[157] However, many respondents argued that the EU plays a crucial role in promoting the leadership of the UK in science. Based on our interviews, there were four areas where Brexit could affect the life sciences industry's ability to conduct research and develop new products:

1. The provision of collaborative schemes and programmes which foster participation in shared pan-European research project;
2. The provision of funding for research and innovation;
3. Ensuring researcher mobility;
4. The ability to file patents and ensure patent protection in an efficient manner.

4.1.1. Collaboration

According to the interviews, probably the most detrimental impact to UK science following a Brexit would be on the international leadership currently held by UK academic centres. Interviewed academics highlighted that most coordination roles are undertaken by universities and that any reduction in EU collaborations would damage the UK's reputation as an excellent manager of multinational projects. The vitality of UK academic institutions, especially those outside of the golden triangle[158] that rely on the UK's reputation as a

156 CRA interviewed academics, clinical research organisations, SMEs and pharmaceutical companies. The interviewees are listed in the appendix.

157 Science and Technology Committee (Lords) Relationship between EU membership and UK science inquiry

158 The Golden Triangle refers to the universities in the Oxford, Cambridge and London area. Mullins, J (2005), "England's golden triangle- New Scientist 20 April 2005. Available at: https://www.newscientist.com/article/mg18624962-800-englands-golden-triangle/

leader of science to attract good exchange of people, ideas and funding would then suffer.[159,160]

Theoretically, restricted access to EU collaborative programmes will create barriers to UK-EU partnerships but should not necessarily hinder collaborations entirely. But, this theory had little resonance in the interviews conducted with academic researchers who indicated that the set-up of collaborations are very resource intensive, often requiring resources and capacitates that UK academics simply do not have. The legal and contractual frameworks provided in EU collaborative programmes are therefore critical to encouraging the flow of science between the UK and the EU.[161] In the long run, we heard from interviews that the UK life sciences industry will see reduced IP generation (as IP is often produced by collaboration leaders), weakened research clusters and fewer biotech start-ups.[162,163]

Interviewed SMEs indicated that without the likes of IMI, the ability to collaborate with EU institutions becomes immeasurably more difficult such that this would erode the scientific ecosystem of UK start-ups. The ability to join consortium of scientists as part of EU funding project was seen as core their ability to maintain the development of innovation as well as attract scientist to local biotech clusters.

We found a consistent view from those interviewed from large pharmaceutical companies. They reported that it is highly likely that UK scientists will be less able to participate in formal EU collaborations and for academic scientists, this could be detrimental. However, even if the UK left the EU, the ability to collaborate with EU scientists will not change for big pharmaceutical companies. Companies indicated that the UK's participation in the EU Research and innovation framework is not a necessary prerequisite to European collaborations for large pharmaceutical companies who tend to use other channels to foster international collaboration on clinical research. While some interviewed companies expressed that they would be disappointed in the restricted access of formal EU collaborations like IMI, large companies currently have more offers to work in consortiums than the resources to fill those offers. These companies are confident that they will adapt to continue collaborations with the EU, and more so with the rest of the world although it was acknowledged that fewer companies would be able to participate in IMI projects (given the current IMI rules only allow 30% non EU contributions, meaning not all EFPIA companies would be able to contribute).[164]

159 House of Lords (2016), "EU membership and UK science – 2nd Report of Session 2015-2016." Available at: http://www.publications.parliament.uk/pa/ld201516/ldselect/ldsctech/127/127.pdf

160 Moreschalchi et al (2015), "The evolution of networks of innovators within and across boarders: Evidence from patent data." Available at: http://www.sciencedirect.com/science/article/pii/S0048733314001905

161 Interview with UK university

162 Interview with UK university

163 Porter, M., "Clusters and the New Economics of Competition", Harvard Business Review, November–December 1998

164 IMI (2012), "Rules for participation in the IMI JU collaborative projects." Available at: http://www.imi.europa.eu/webfm_send/486

4.1.2. Funding

In terms of funding, limited or restricted access to EU research and innovation programs would have a much greater impact on academic researchers and SMEs than on big pharmaceutical companies according to the interviews.

It was pointed out that the importance of EU funding was not uniform and some UK universities get up to 20% of their research funding from the EU, from programs such as Horizon 2020 and Marie Curie Fellowships.[165,166] As such, in the event of a Brexit, negative implications would surface within 12 months. According to interviewed research organisations, should access to funding from Horizon 2020 be suddenly curtailed, research organisations would need to discontinue research as they are unlikely to have sufficient financial reserve to continue employing researchers. Indeed, academic researchers who commonly have 12 month work contracts, and the UK science industry are likely to suffer.[167]

It was also indicated that EU Structural funds are particularly important in areas of the UK where the life sciences industry is less developed, like Wales and Scotland. In Wales, the Swansea University Institute of Life Sciences research facility (£12.8 million from the EU) and Aberystwyth University have both benefited from the European Regional Development Fund (a European Structural Fund that seeks to support innovation and research development across the EU).[168]

As described in chapter 2, the EU provides an extra funding mechanism to UK SMEs through access to the European Investment Fund, the European Investment Bank and the ERDF.[169] Interviewed SMEs reported that these EU funding sources have been critical for the development and expansion of biotech SMEs. For example, the UK investment fund "Imperial Innovations Group" obtained £30 million from the EIB to invest in biotech and therapeutic sectors.[170] In turn, Imperial Innovations has invested in UK based SMEs like Oxford Immunotec, PsioOxus Therapeutics and Circassia.[171] Particularly for SMEs outside the investment popular English Golden Triangle, we heard that EU Structural funds are of major importance. It was nevertheless pointed out that access to EU funding is incredibly bureaucratic and often difficult to access.

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165 Ratcliffe R (20150, "Quality of European Commission (2016), "Marie Skłodowska-Curie actions research fellowship programme."threatened by cuts." Available at: http://ec.europa.eu/www.theguardian.com/higher-education-network/2015/jan/16/quality-of-european-research/mariecurieactions/apply-now/how-to-apply/index_en.htm-threatened-by-cuts

166 Interview with UK university

167 Interview with UK university

168 Haines, L & Nicholl, A (2015), "EU membership: benefits and challenges for Wales." Available at: http://www.jillevans.net/eu_membership_benefits_and_challenges_for_wales.pdf

169 European Commission (2014), "European Regional Development Fund." Available at: http://ec.europa.eu/regional_policy/en/funding/erdf/

170 Imperial Innovations (2015), "Innovations obtains further £50m loan facility from EIB to strengthen UK biotec and life science investment." Available at: http://www.imperialinnovations.co.uk/news-centre/news/innovations-obtains-further-50m-loan-facility-eib-/

171 Imperial innovations (2016), "Investment Portfolio". Available at: http://www.imperialinnovations.co.uk/ventures/portfolio/

As a result, some biotech SMEs indicated whilst they benefited from EU funding, this represented a small portion of total funds raised (10-20%). It was suggested that the ability to access difference sources of finance directly from capital markets was more vital to fast growing biotech firms. It was stressed that access to private equity financed was highly connected to the stability of financial markets and the integration of the UK with the European Union. Funding from the EU FP7 has serveed as a signal for other investors (like angel investors as a result of the due diligence performed by such programmes shows they are of value). As a result, whilst UK based biotech SME have not benefited direct from EU funds (as set out in Chapter 2), the flow of EU funding to the UK has supported access to capital for these firms.

Large pharmaceutical companies indicated that restriction to EU funding would have a small effect on the research and product discovery sections. Interviewed companies suggested that there would be little direct effect on the company led research as these often rely on private funding. However, if UK academic researchers reduce their scope of research due to the restricted or lack of EU funding, then big pharmaceutical companies might become less inclined to partner with UK research organisations and may instead seek partner organisations that have access to EU funding.[172] In this case, the UK life sciences industry would suffer as a whole.

4.1.3. Ensuring researcher mobility

A sizable proportion of UK's pharmaceutical research is conducted by EU nationals and is made possible by the free movement of people's agreement within the European Union.[173] Taking away this freedom and implementing restrictions was seen as having a negative impact for all stakeholders, and particularly for academic researchers and SMEs. As we mention in Chapter 2, 15% of all academic staff in UK universities are from other EU countries.[174] Currently the UK is an attractive location for scientists from the EU based on the ease of immigration. We heard that this flexibility helps the UK attract talent and ensures quality in research which is beneficial for academia and SMEs.[175] According to the interviews, if this freedom is restricted, and the ease of relocation and travel becomes more difficult and the breadth of career opportunities shrink for EU researchers themselves but also for members of their families (e.g. spouse, children). As a result, interviewed academics and SMEs suggested that young researchers would become less inclined to move to the UK.[176] Biotech SME stressed that they rely heavily on the ability to draw on the "best and brightest" expert scientists from across the EU and attract a scientist based with multicultural background. While interviewed parties recognized the possibility to recruit EU researchers through visa processes, both academic researchers and SMEs highlighted these processes could be extremely cumbersome and administratively costly to manage (there would be additional cost and human resource implications, one SME estimated the

172 Interview with large pharmaceutical companies

173 Cressey, D. (2016, February 4). "Academics across Europe join 'Brexit' debate"; accessible at http://www.nature.com/news/academics-across-europe-join-brexit-debate-1.19282

174 Universities for Europe (2016), "Universities and the European Union – common myths and misconceptions." Available at: http://www.universitiesforeurope.com/register/Pages/myth-busters.aspx#collapse1

175 Interview with academic researcher and SME

176 Interview with UK based pharmaceutical company

need for one additional human resource employee). [177] Therefore, the general conclusion from an academic and SME perspective was that in the short and long term, the quality of life science research would suffer.

In the large pharmaceutical companies interviewed, we heard that more than 50% of all non-UK employees were European and these European employees fall across business functions, including but not restricted to science. For these companies, the impact of restricted free movement of people within the EU is less significant than what we have described for academia and SMEs. While the additional visa system will undoubtedly add a new level of complexity and cost to acquiring talent from the EU, the interviewed UK pharmaceutical companies were confident that the required foreign talent would still be accessible. These companies would simply pay and absorb the additional cost for recruitment of EU talent or in the event that the UK might relax some of its non EU immigration laws (increasing immigration quotas for non EU foreigners for example), simply turn to fill in talent gaps with non EU foreigners. [178]

There was widespread consensus that over the long term, the overall attractiveness of the UK as a base for world-class science would diminish for EU nationals if there was restriction in the free movement of people. In this case, the quality of UK science would suffer and large pharmaceutical companies indicated a risk of employment drain to Europe, where there is a greater degree of mobility.

4.1.4. Patent enforcement

As discussed in Chapter 2, there are two EU regulations that affect patent enforcement. The SPC, which extends patent term for a maximum of five years is recognized to incentivize innovation and the forthcoming European Patent Convention (EPC) provides advantages across the UK life sciences industry in terms of cost savings (only one patent application for Europe) and simplification of patent application processes. However, in the interviews conducted, we heard that the expected impact of being outside the EU on the ability to apply for SPCs was minimal. At present, the original patent holder of the product with EU marketing authorisation is eligible to apply for the SPC suggesting that UK patent holders would still have the opportunity to use this provision. In addition, being outside of the EPC was seen to have insignificant impact on researchers and companies who would continue filing patents in geographic areas deemed necessary, irrespective of the cost and process.[179]

From the interviews conducted, it emerges that the impact of a potential Brexit for stakeholders within research and discovery is significantly more negative for the UK life sciences industry than for the European life sciences industry.

177 Interview with academic researcher and SME

178 Interviews with large pharmaceutical companies

179 Interviews with academic researchers, SMEs and large pharmaceutical companies

Table 4: Summary of the impact of Brexit on components of basic research and product discovery from the perspective of the UK and European life sciences industry

	Impact on life science industry in the UK	Impact on life science industry in Europe
Access to EU research programme		
Outside collaborative research platform		
No access to R&D and other EU Funding		
Limited researcher mobility		
Patent filing and enforcement		
No access to EPC and unitary patent		

Legend

	Minor impact	Some impact	Significant impact	Major impact
Positive impact				
Negative impact				

4.1.1. Conclusion on impact of Brexit on research and product discovery

We examine the impact of Brexit according to the different scenarios. The expected impact on research and product discovery is much less significant if the UK were to resume a relationship with the UK through EEA membership than if the UK were to fully break from the EU or be associated by bilateral agreements.

EEA Membership

Should the UK join the EEA, few differences are expected from the current UK EU status in terms of collaborative research aside from a potential change in the patent enforcement framework. Drawing from the experience of Norway, although the UK would not be an EU member, it would have full access to Horizon 2020 funding and collaboration.[180] EEA membership requires compliance to the EU internal market rules which means that there is free movement of people.[181] Therefore, in terms of the EU funding and collaboration

180 Horizon 2020 (2016), "Non-EU partners: international cooperation in Horizon 2020." Available at: http://www.horizon2020.lu/Toolbox/FAQ/Non-EU-Partners

181 The European Union's (EU) internal market, also known as the EU Single Market, is a single market that seeks to guarantee the free movement of goods, capital, services, and people – the "four freedoms" – between the EU's 28 member states.

provisions, which interviews indicated were critical to the basic scientific research, an EEA membership model for the UK poses little threat. The only key difference is around the patent filing and enforcement system. Norway is currently not a member of the EPC and this therefore suggest that an EEA membership model would not create harmonisation with the EU patent system.[182] However, considering that the exclusion from the EPC was not considered by interviewed stakeholders to have a significant impact on life sciences research and product discovery, an EEA membership is able, to a large extent, to maintain the status quo of scientific research in the UK.

Bilateral agreement

Unlike the EEA membership, the damaging effects of bilateral agreements on UK basic research is dependent on the specifics of the negotiated agreement. However, it can be expected that access to EU funding will be limited, whether partially (as in the Swiss situation) or completely (Horizon 2020 funds are not directly available to Canadian participants).[183] In this case, while the lack of access to funding will more quickly and acutely be felt by UK academia and SMEs, UK research as whole can be expected to suffer long term, as the reputation of UK research diminishes.[184]

Specifically, the restrictions to EU funding would give rise to a funding gap, which the UK government could fill using EU science contributions. If the UK followed the Swiss approach and closes the funding gap using public resources, there would be little impact on UK scientific research. However, given that current UK public investment in research is 0.55% GDP (lower than the average of other advanced countries 0.8%)[185], interviewed stakeholders had little confidence that additional public funds would be allocated to science and instead expected the UK science base and competitive attractiveness to suffer.

The arrangements around the free movement of people will vary based on the negotiated agreement (Swiss bilateral agreements are currently based on a free movement of people while the Canadian CETA is not). Where the free movement of people faces restriction, a negative impact is expected for the UK academic researchers and SMEs. If the UK left the EU and restricted the free movement of people, the UK would likely face a similar situation as the Swiss. It has been argued the current Swiss environment has a negative impact on the life sciences industry.[186] While the Swiss official figures on IP and international collaborations appear to be constant even after the EU restriction on Horizon 2020 participation, it is important to remember these figures are pre restriction on Horizon 2020 participation and does not accurately reflect the current situation. Anecdotally, the Swiss life sciences industry is suffering, as research projects are suspended because of a lack of Horizon 2020 (although we could not find any quantitative evidence to support this).

182 Francks & Co, (2016), " European Patent Convention Patents" Available at: http://www.franksco.com/services/patents/european-patent-convention

183 European Commission (2015), "Canada – Country Page." Available at: http://ec.europa.eu/research/participants/data/ref/h2020/other/hi/h2020_localsupp_canada_en.pdf

184 Interview with Swiss company

185 Universities for Europe (2016), "Universities and the European Union – common myths and misconceptions." Available at: http://www.universitiesforeurope.com/register/Pages/myth-busters.aspx#collapse1

186 Scientist for EU.

It is likely that there would remain a considerable level of collaboration with the EU as the UK is a large market and has a good knowledge base. However, it is expected that the EU would only need to collaborate with the UK on the top 5% of research topics (and the EU would leave the French and German universities to compete with UK). The UK could negotiate some bilateral R&D agreements (with France, Germany etc.) but these would be at a low level, only ensuring that the EU universities can fill in key skills gaps from the UK.

Finally the impact of patent processes that are divergent to the EPC (the Canadian scenario) is considered minimal. In fact, independence from EU patent processes, as demonstrated by the Swiss experience, could be beneficial in creating an environment that is more favourable to companies.[187]

Full Break

Under a full break, the UK is likely to have no direct access to Horizon 2020 and this will therefore prevent access to both EU funding but also to the collaborative research programme. Should this happen, the UK would need to establish other ways to ensure its scientists can collaborate with other countries outside the EU platforms. In this situation, the ease of and funding for collaborative research decreases, particularly after the transition period and a relocation of research to mainland Europe is likely.[188] Nonetheless, given the excellent academic reputation of the UK, which predated EU membership[189], not all collaborations with Europe will fall away; former Eastern bloc countries (Romania, Bulgaria) would still seek to work with the UK.[190]

In addition, the additional restriction on free movement of people and the separate patent process that accompanies a full break from the EU, the life science research sector would lose some of its attractiveness and in the long run see significant damage to basic scientific research. Many stakeholders indicated that this scenario is likely to be very damaging for UK research and product discovery in general and lead to significant disinvestment in scientific and clinical research in the UK. We summarise our conclusions in Table 5 below.

187 Up until recently when the Swiss joined the EPC, the Swiss had the independence to ensure favourable patent environment for companies by introducing incentives such as the orphan drug incentive. Francks & Co, (2016), "European Patent Convention Patents" Available at: http://www.franksco.com/services/patents/european-patent-convention; Ladani, SF (2012), "Succeeding in Switzerland's regulatory environment for pharma- similarities and differences compared with the EU." Available at: https://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwioyqav7PnLAhVBXRQKHcsCDrwQFggfMAA&url=http%3A%2F%2Fwww.sfl-services.com%2Fmedia%2F8T4PB7W9%2FSRA_Nov_Succeeding_in_Switzerland.pdf&usg=AFQjCNF8yWAMr5tdzFm2Emf3NUGVDKmDgA&bvm=bv.118443451,d.ZWU

188 Our interview highlighted a similar experience with Genetically Modified Organism research which once banned from the EU, relocated to Switzerland. Vrieze JD (2013), "Switzerland creates secure test site for GM crops." Available at: http://www.sciencemag.org/news/2013/02/switzerland-creates-secure-test-site-gm-crops

189 Interview with large pharmaceutical company

190 Interview with large pharmaceutical company

Table 5: Impact of Brexit on basic research and product discovery under the 3 "Brexit" scenarios from the perspective of the UK and European life sciences industry

	Impact on life science industry in the UK	Impact on life science industry in Europe
EEA Membership	 Full access to EU research programme but some loss of credibility	No impact- UK remains competitor for EU research programme funding
Bilateral agreements	 UK likely to have "associated country" status to EU research programme UK universities and SMEs lose funding and coordinator role	No impact- as an "associated country", UK remains competitor for EU research programme funding
Full Break	 No access to EU research programme, few collaboration opportunities with EU countries and important loss of credibility as science leader in Europe	 Reduced opportunity to access UK science and research

4.2. Product development and approval regulation

It was widely agreed that the single regulatory framework has brought significant benefits to pharmaceutical companies. Particularly, the harmonised assessment of safety, efficacy and quality assessment by the EMA simplifies the process of marketing authorisation. It was also recognised that the interpretation of some EU regulations have been considered "red tape" for UK pharmaceutical companies.

4.2.1. Product development regulation

Looking at clinical trials, the EU clinical trials regulation provides greater freedoms in conducting clinical trials and makes the investment decisions around clinical trials in Europe much easier. Should the UK leave the EU then companies might decide to exclude the UK in the Phase III studies (especially clinical trials for rare diseases) and focus on the EU, which provides a much wider population base.[191]

As the UK has traditionally been an attractive location to conduct clinical trials in Europe thanks to the strength of its teaching hospital centres in London and other major cities across the UK, the quality and experience managing trial programmes and the capacity to undertake large trials efficiently, all companies indicated that Phase I clinical trials are

191 BioIndustry Association (2016) House of Commons Science and Technology Select Committee inquiry: EU regulation of the life sciences submission – March 2016

unlikely to be affected given the UK has a strong clinical research base (and that Phase I trials are often undertaken in a single location). However, many respondents argued that the track record of the UK for Phase III clinical trials is not good enough to attract companies to conduct trial in the UK, especially if the undertaking clinical trials in the UK requires separate clinical trial approval.[192,193] We heard it is not unlikely that Phase II and Phase III trials would progressively be conducted elsewhere. Initially, the impact would not be too great as operation of Phase III trials are not bound by geography. However over time, as the UK provides only a small percentage of the patient population base in comparison to the EU, Phase II and Phase III trials may migrate to mainland Europe.

From the interviews conducted, it was acknowledged that the data protection framework is useful for facilitating clinical trials but is not a deciding factor for clinical trial location or investment. Indeed, we heard that even if the UK left the EU, the new UK data protection framework is not expected to deviate from the EU framework drastically as the current Data Protection Act has been in operation for 18 years (since 1998). However, a Brexit would mean that the UK industry, through the Information Commissioner's Office (ICO) would lose influence on future data protection legislations. Also, should the EU find that the UK's national data protection framework is not sufficient, then companies would face greater costs and complexities in negotiating the use and sharing of data outside of the UK to EU member states.

4.2.2. The centralised authorisation procedure

Should the UK withdraw from the centralised process, interviewed pharmaceutical companies highlighted that the authorisation process in the UK is likely to become delayed as the MHRA will need to re-authorise all existing licenses that have been granted by the EMA. In addition, the UK would become a lower market access priority and access to medicines could be delayed. Whist many companies aim to launch globally, the typical submission sequence being the FDA (USA), EMA (European Union), PMDA (Japan), then other countries like Canada and Switzerland based on market size. Invariably, under this model, the UK as a separate market apart from the EU would be sequenced as lower priority (of course contingent on the size of the market and the reviewing time of the agency). In order to remain a priority market for launch and to minimise the launch delays, the UK agency would have to do a quicker assessment. Some companies estimated an expected launch delay of 6 months in the UK (dependent on the size of the market, the type of medicine; it was suggested that oncology products would see such a delay). If the UK authorisation process was made more complex, one company noted the possibility of negative decisions regarding their decision to launch, although this would only affect formulations rather than new drugs.

The role of the MHRA

If the UK takes on national marketing authorisation processes this would make business in the UK more complicated (unless the same regulations as the EU are taken). It was pointed out that none of the alternative EU relationships (Norwegian, Swiss and Canadian) provide any real advantage/simplifications in comparison to the current marketing authorisations system under EU membership.

192 Interview with large pharma company

193 Interview with UK contract research organisation

The UK has also been particularly active and involved in shaping the EU regulatory framework and effective in influencing EU regulation that impacts the life sciences sector. The MHRA has been able to exploit its reputation, leadership and expertise to positively influence the EU medicines regulatory regime. As an example, it was noted that on the recent Base Erosion and Profit Shifting (BEPS) initiative, the UK, finding itself in the minority of international opinion, brokered a compromise deal with Germany which was tabled and then accepted by the OECD.[194]

Location of EMA

If the EMA left the UK this could affect some of the activities conducted in the UK. Respondents acknowledged that the geographical proximity to the currently location of EMA in London is not particularly important for many companies and that a change in the location of the EMA would not have a massive impact on companies operations. Currently, a number of both UK and US based companies hold a substantial number of regulatory staff in the UK but this is not strictly linked to the location of the EMA in London.

Nonetheless, it was acknowledged that the presence of EMA in London also has significant advantages in terms of attracting regulatory expertise to the UK. If the UK were to leave the EU and EMA were to relocate to another European country, then in the long term, it is not unlikely that some companies might progressively shift regulatory employment to that new location. It was acknowledged that this would not necessary change a company's investment or employment decisions in the short term. However, in the long term, if the EMA moved to an attractive location post Brexit, it is not unlikely that regulatory expertise would migrate to another location which is closer to the regulatory decision making agency.

Pharmacovigilance

However, it was also pointed out that Brexit could bring advantages in terms of regulation. One company suggested that the current EU legislation around paediatrics and pharmacovigilance is particularly burdensome. A Brexit would give the UK freedom to change these regulations for the better (for example, the pharmacovigilance rules could look at more than just safety outcomes). A few respondents have argued that the UK could better handle certain legislation (such as the data protection regulation) to make them more favourable for the life sciences industry. However, it was also argued that the UK would need to ensure that pharmacovigilance is accounted for nationally (the submission for adverse events is currently done on a pan European basis). Companies could be faced with a more complex system and data requirements for pharmacovigilance in the UK.[195] This would be costly for companies but regulatory experts did not expect this separate process to have any implications for patient safety. Overall, however, it was noted that European regulation had become more sympathetic to innovation and these benefits would be small.

194 BIA House of Commons Science and Technology Select Committee inquiry: EU regulation of the life sciences BioIndustry Association submission – March 2016

195 BIA (2016), "House of Commons Science and Technology Select Committee inquiry: EU regulation of the life sciences- Bio Industry Association Submission." Available at: http://www.bioindustry.org/document-library/bia-response-eu-regulation-of-life sciences/?utm_campaign=6927631.

We summarise the impact on key changes in the product development regulation and marketing approval process on the UK and European life sciences industry in Table 6 below. We conclude that the UK life sciences industry will suffer from a Brexit, more so than the European life sciences industry who will continue to benefit from the harmonised EU regulations on product development and approval.

Table 6: Summary of the impact of Brexit on components of product development and approval from the perspective of the UK and European life sciences industry

	Impact on life science industry in the UK	Impact on life science industry in Europe
Product development regulation		
UK outside the EU Regulations for clinical trial subjects		
UK outside the EU clinical trial framework		
UK outside the EU Data protection framework		
Centralized authorization procedure		
UK outside EMA single MA procedure		
UK outside EU Orphan Drugs Incentive programme		
UK outside pharmacovigilance regulation		

4.2.3. Conclusion on impact of Brexit on product development

The level of disruption following a Brexit would depend on whether the UK remained part of the European regulatory framework. If not, the UK will have to resume separate authorisations, which would lead to substantial delays and a duplication of processes.

EEA Membership

If the UK were to join the EEA, it could still be possible to remain under the EMA's umbrella, as demonstrated by Norway and Iceland. The MHRA would take part in the EMA marketing authorisation assessment such that the MHRA accepts all EMA approvals. Under EEA, membership it is likely that the UK will continue to comply with EMA decisions (much like the Norwegian approach where Norway, as part of the EFTA complies with EU medicines approval, remain involved in the EMA committee and recognises all EMA procedures). It was pointed out that the UK is akin to Norway in that it has given up its sovereignty to the EU for a long time ago (20 years of collaboration thus far, Norway does this by way of the EFTA agreement) so the UK is unlikely to suddenly desire to derive an entirely separate

process from the EMA. Such an arrangement should be plausible given the EU should be keen to keep the UK involved, given their reputed expertise. In this case, the level of disruption for pharmaceutical companies who seek UK regulatory approval would be minimal.

Bilateral agreement

Under a bilateral agreement, the UK would not be bound by EU regulation and would need to develop its own regulatory framework for pharmaceuticals. Given the UK is currently fully compliant with the EU regulatory standards, it is unlikely that the UK would develop regulation that are significantly different from its current EU standard although over time some differences in regulatory standards would no doubt emerge.

Another option for marketing authorisation is to follow the Canadian or even Swiss lead and conduct an entirely separate marketing authorisation process lead by the MHRA. It was stressed by most companies that there would not be many advantages for the UK to develop market authorisation processes highly divergent from the EMA. However, this independence from the EMA process gives the MHRA a chance to attract priority filings in the UK by having a more rapid approval process (for chemical entities for example). However, our interviews with companies in Switzerland confirmed that, with regards to market authorisation, SwissMedic is on average slower than the EMA in terms of evaluation, taking 511 days (median time approval), suggesting that in reality, a more rapid approval process is a difficult feat to achieve.[196] Respondents felt that in reality, a national MHRA process would mean additional cost and administrative burden to collect and present data to UK requirements and a likelihood to deprioritise filings in the UK.

It's also very likely that should the UK disconnect itself from the centralised procedure, that the EMA would relocate its UK headquarters to another country within the EU in the event of Brexit. This is discussed in the next chapter.

Full Break

In terms of regulatory framework, the situation under full break would not differ significantly from that scenario above. However, it is likely that the MHRA would benefit from even less interaction with other regulatory agencies and is less likely to collaborate with EMA and other bodies. We summarise our conclusions in Table 7 below.

196 News Center Watch (2015), "FDA fastest in granting new drug approvals among major regulators including EMA, TGA, Health Canada." Available at: http://www.centerwatch.com/news-online/2015/02/02/fda-fastest-in-granting-new-drug-approvals-among-major-regulators-including-ema-tga-health-canada/

Table 7: Impact of Brexit on product development and approval regulation from the perspective of the UK and European life sciences industry

	Impact on life science industry in the UK	Impact on life science industry in Europe
EEA Membership	 Loss of influence of EU regulatory framework	 Some loss of regulatory expertise from UK. European regulatory framework likely to be more conservative without UK
Bilateral agreements	 Some regulatory alignment and mutual recognition expected but: More difficult for biopharmaceutical SME to conduct multinational clinical trials Market launch strategy is severally affected and long timeline to get products approved	 Some regulatory alignment and mutual recognition expected but: Large multinational companies move CT to other countries in EU Companies face extra cost of MA approval
Full Break	 No regulatory alignment between UK and EU Significant barriers for SMEs to develop products and significant additional costs to get MA approval outside UK	 No regulatory alignment between UK and EU More difficult for pharma to develop products and significant additional costs to get MA approval outside UK

4.3. Manufacturing and Trade

Interviewed stakeholders agreed that the relationship between the UK and Europe on manufacturing and trade is heavily influenced by EU membership. In particular, the EU provides a uniform legal framework for manufacturing and a large base of labour availability, both of which are advantageous for the UK life sciences industry. It was also recognised that there are aspects of trade that are less affected by EU legislation, such as tariffs and customs for finished pharmaceutical products and the availability of a EU dispute settlement mechanism.

4.3.1. EU legal manufacturing framework

Currently, the UK complies with the EU Common Directive on Good Manufacturing Practice (GMP) for human medicinal products.[197] For UK manufacturing companies, we heard that the EU GMP is of great value; companies need only to understand and comply with a single set of manufacturing, which facilitates a reliable supply chain. Not only so, as part of the

197 European Commission (2016), "EudraLex- Volume 4 Good manufacturing practice (GMP) Guidelines." Available at: http://ec.europa.eu/health/documents/eudralex/vol-4/

EU, the UK has the opportunity to influence legislation around manufacturing.[198] Interviewed stakeholders noted that the EU GMP simplifies the navigation required to conduct trade and provides trade partners with assurance of quality, which increases trade and incentivises investment in the UK.[199]

In the case of a Brexit, the UK would no longer automatically have its manufacturing practices recognised by the EU. This would not only damage the reputation of UK manufactured products and discourage trade but also drastically increase the cost of manufacturing practice assessments and disrupt supply chains (multiple surveys from multiple EU nations creates great barriers for manufacturing). We heard from a few companies that this could increase the number of times UK manufacturing sites were assessed to as many as 27, once for each member state.[200] The UK would also lose its voice in the EU decision making process and have no influence in shaping the future of manufacturing guidelines. In the event that the UK leaves the EU, the UK pharmaceutical industry would want to ask MHRA to lobby to keep the mutual recognition as there is no advantage for the UK to start from scratch (even Canada and the Swiss maintain this mutual recognition).

In terms of UK trade to the EU, there would be additional costs to ensure compliance to the EU GMP which would materialise as a disruption in the flow of UK goods to the EU, damaging the UK's trade reputation and inadvertently discouraging foreign investment into the UK.

4.3.2. Access to the EU single market (tariff and customs union)

One of the four freedoms of the EU is free trade which means that the trade all finished products are free of any tariffs or customs and this benefit extends to pharmaceutical products.[201] All respondents agreed that while in principle that access to the EU single market is useful for trade, it was also added that tariffs and customs for pharmaceutical products are more generally governed by the WTO "zero-for-zero initiative" which eliminates tariffs for WTO member countries (including the EU).[202] However, it was pointed out that this may hinder the free flow of intermediate manufacturing good such as APIs and other products. This could increase the cost of manufacturing certain products.

4.3.3. Trade agreements with countries outside of the EU

With regard to the rules for negotiating trade agreements, the EU currently negotiates with non EU member countries as a single entity, on the behalf of the UK and the UK cannot freely negotiate trade deals with third countries. Our respondents highlighted several advantages for the UK under this arrangement. First, through representation by the EU in trade negotiations, the UK gains in economic power in negotiation processes and has a

198 Interviews with UK large pharmaceutical companies

199 Interview with Swiss based pharmaceutical company

200 Interview with UK based companies

201 European Commission (2016), "The European Single Market." Available at: http://ec.europa.eu/growth/single-market/index_en.htm

202 Office of the USTR (2016), "Pharmaceuticals." Available at: https://ustr.gov/issue-areas/industry-manufacturing/industry-initiatives/pharmaceuticals

greater chance of arriving at deals that are beneficial for the UK. [203] Again because the EU presents a large economic market (27% of the global pharmaceutical sales while the UK represents only 3%)[204], countries wish to undertake trade deals with the EU; as illustrated by on-going negotiation on Transatlantic Trade and Investment Partnership with the US. Finally, the UK can rely on the EU to negotiate trade agreements on their behalf, reaping cost and administrative efficiencies.

Were the UK to leave the EU, we heard differing views on the potential impact but it remained clear that there can be both advantages and disadvantages. On the one hand, lack of EU membership allows the UK freedom to undertake its own trade agreements which could be useful in ensuring that the entire make up of a trade agreement was tailored to benefit the EU (for example, if IP was important for the UK, it could ensure that IP would be protected in trade agreements). However, many companies stated that the UK would lose economic power and therefore negotiation power. Many recognised that trade deals would be expected to take much longer to complete. Furthermore, while the UK is a major economic power within the EU, the UK would be less attractive than the EU as a trade partner; considering the TTIP example, the US would be much more interested in having access to the EU single market than only in the UK. As such, the UK would risk being left out in important trade deals.[205]

4.3.4. Labour availability

Should the UK leave the EU, respondents suggested that the ability for the UK to attract talent for manufacturing and trade would suffer as it is not unlikely that potential EU employees would seek relocation to geographies that do not require complex visa processes. Pharmaceutical companies also highlighted that as the labour base for the UK reduces, the cost of labour recruitment and labour will rise, which could ultimately affect the final cost of pharmaceutical products and negatively impact patient access to medicines.[206]

Smaller Biotech SMEs indicated that the issue of labour availability and attracting individuals from across the EU was vital to their business. Based on the interviews with biotech SMEs a significant proportion of their staff came from the EU countries. It was stressed that any restriction on the free movement of people with the rest to the EU was a strong concern to them as it would jeopardize their ability to put the “right person in the right job” and benefit from the best brain in Europe. It was also indicated that should visa requirements be introduced for EU nationals, this would represent significant complexities which would have a significant cost impact on small companies. This would not prevent them from hiring EU national but would significantly decrease their attractiveness on the international scene. It was also indicated that it would be much more difficult to obtain the same level of skills and expertise if it were to draw from UK nationals only.

203 Interview with UK based pharmaceutical companies

204 BIA (2016), “House of Commons Science and Technology Select Committee inquiry: EU regulation of the life sciences- Bio Industry Association Submission.” Available at: http://www.bioindustry.org/document-library/bia-response-eu-regulation-of-life sciences/?utm_campaign=6927631.

205 Interview with Swiss based pharmaceutical company

206 Interview with UK based pharmaceutical company

4.3.5. Investment decisions

The UK is one of a number of possible global locations (EU and RoW) which is often considered by pharmaceutical companies for new or expanded manufacturing facilities. Some companies indicated that EU membership per se is unlikely to be a major consideration for such major investment decisions in the medium to short terms. Investment decisions are more driven by assessment of factors such as business criticality, site/location capabilities, transport logistics, skills availability, employment costs, taxes and & other local factors.

Table 8: Summary of the impact of Brexit on components of manufacturing and trade by the UK and European life sciences industry

	Impact on life science industry in the UK	Impact on life science industry in Europe
UK outside the EU GMP regulatory framework		
Restricted access to the EU single market		
UK outside the EU trade policy (UK negotiate its own trade deal)		
Restricted immigration (no access to free movement of people)		
Impact on investment decisions		

4.3.6. Conclusion on impact on manufacturing and trade

EEA membership

We heard from interviews that EEA membership would have little impact on the current state of affairs for manufacturing and trade compared to today. EEA membership retains the mutual recognition of the GMP inspections, the free movement of people, and access to the European legal dispute mechanisms such that the UK would still be able to benefit from these EU provisions.

EEA membership would however allow the UK greater freedom to undertake its own trade agreement which could be useful in ensuring that the entire make up of a trade agreement was tailored to benefit the EU (for example, if IP was important for the UK, it could ensure that IP would be protected in trade agreements). Left outside the EU negotiating table, it would need to configure its own trade relations with the likes of the US, Canada and the rest of the EU. However, the benefit of conducting individual trade deals was nuanced by Norwegian and the Swiss respondents who indicated that trade deals have not brought substantial benefits to the pharmaceutical companies.

Bilateral agreements

The impact of Brexit on manufacturing and trade would depend largely on the type of agreement that the UK would be able to negotiate both in terms of mutual recognition of manufacturing regulations and arrangements as well as in labour flow. Drawing from the lessons from Switzerland and Canada, both countries have negotiated a mutual recognition of conformity and quality control with the EU, the EEA, EFTA states and Canada. This mutual recognition saves the pharmaceutical industry significant costs and it is not unlike that the UK would be able to negotiate such deals.

Both Canada and Switzerland, like Norway have retained the ability to negotiate their own trade agreement. However, as described above, the value of negotiating such deals needs to be put into context. In Canada, the trade negotiation between EU and Canada became a very low priority when the EU-US Trade negotiations (TTIP) started. It was also pointed out that in the case of Canada, although the CETA does improve IP provisions in Canada, there is no explicit link between IP and competitiveness of the industry investment. The industry suggested that improving IP in Canada would help companies attract R&D to Canada. In Switzerland, Swiss Companies have been able to voice the pharmaceutical industry's need for IP to the Swiss government who have then prioritised IP in FTAs, for example with India (which also explains why the FTA has not yet been signed). [207] The disadvantages of the current Swiss-EU relationship is that there is no automatic inclusion in EU treaties (for example TTIP does not automatically include Switzerland and the Swiss would need to initiate a bilateral agreement).

The UK pharmaceutical industry would need to work closely with the UK Government and with the EU to develop the new trade, regulatory and many other agreements required. This activity would be conducted at the same time as every sector of UK commerce and public society would be conducting similar discussions to inform and influence agreements and would dominate dialogue with Government for many years during which time uncertainty of the future would be a major concern to business. It was also pointed out that negotiating trade deals take a significant amount of time and this could lead to considerable disruption of business activities. The EU-Canada agreement, for example, has taken seven years to negotiate and is still not in force. Whilst the UK has currently fewer differences with the rest of the EU to address in such a deal, it remains likely that a UK-EU agreement could require the agreement of all 27 of the remaining EU and renegotiating a similar deal could potential take many years. This could mean several years of uncertainty with key businesses badly damaged.

In terms of labour availability and being able to access foreign nationals, this is likely to be a key aspects of the UK's new relationship with the EU as immigration "remains a major concern" politically. An OECD report suggest that "After Brexit, immigration is likely to be restricted more significantly". Respondents argued that this could have two broad effects:

1. It was widely agreed across all stakeholders interviewed that the restriction of immigration could have a significant negative impact on the pharmaceutical industry in terms of their ability to attract talent as well as put the "right person in the right job".

207 Patnaik P (2014), "Swiss-Indian trade deal: bitter pill to swallow." Available at: http://www.swissinfo.ch/eng/big-pharma_swiss-indian-trade-deal--bitter-pill-to-swallow/38013218.

2. Secondly, drawing from the experience of Switzerland, restriction of immigration could jeopardise the ability of the UK to negotiate bilateral agreements with the EU such as access to the EU research programme. In this case, pharmaceutical companies would suffer in talent recruitment and also the ability to export (greater barriers to trade).

Some companies indicated that they have very important exposure to foreign employees and this would increase costs.

Full Break

If the UK opted for a full break in terms of trade arrangement and simply relied on WTO rules, this would likely have significant effects on the pharmaceutical industry due to mutual recognition of manufacturing but not on tariffs.

It is not unlikely that with a full break scenario would be associated with stricter immigration policies along with strong conditions for bringing foreign nationals to work in the UK. As highlighted above, this would have serious consequences on the industry's ability to remain competitive in the medium to long term.

Table 9: Impact of Brexit on Manufacturing and Trade from the perspective of the UK and European life sciences industry

	Impact on life science industry in the UK	Impact on life science industry in Europe
EEA Membership	 Full compliance with EU GMP framework UK would need configure its own trade relations with other countries and likely to lose negotiating power to ensure strong IP agenda	 Wider industry loses UK government as leverage in trade negotiation. EU is now small market and has less weight in trade negotiation
Bilateral agreements	 Few Biotech SME have significant manufacturing activities which reduces exposure to changes in GMP regulation and trade deals UK would need configure its own trade relations with other countries and likely to lose negotiating power to ensure strong IP agenda. Loss of UK negotiating power to ensure strong IP agenda	 Wider industry loses UK government as leverage in trade negotiation. EU is now small market and has less weight in trade negotiation
Full Break	 Lack of mutual recognition of GMP standard could cause issues Possible tariff on intermediate good for manufacturing	 Lack of mutual recognition of GMP standard could cause issues Wider industry loses UK government as leverage in trade negotiation

4.4. Market Access

Considering that market access processes are conducted nationally and not at the EU level, many companies did not see EU membership having any significant impact on market access and their ability to launch products.

4.4.1. Pricing and reimbursement

Whilst it was acknowledged that the EU Transparency directive is currently helpful in ensuring transparency of the pricing and reimbursement process, it was suggested that this does not have a significant impact on the UK and little would change with regards to reimbursement delays.

It was however suggested that the UK's fragmented market access system and reluctance to pay high prices and recognise innovation could compound the situation, making the UK a less attractive launch market in the long term. Whilst it was recognised that uptake of innovation is not directly associated with EU membership, some respondents indicated that the EU has exerted some positive pressure on the UK to adopt new drugs and that it is likely that the UK is likely to become less innovation friendly if it left the EU. For example, one company indicated that if the UK did not reimburse it new innovative drug and continues to demonstrate a repeated trend of not rewarding innovation, then it would consider conducting its research elsewhere and ultimately the company might choose to invest elsewhere in innovation friendly countries.

International reference pricing (IRP)

In the current system, the UK is referenced by a large number of countries in the IRP network. Right now, the UK has a relatively high list price which is important for company's price setting strategy which makes the UK a priority market. However, if the UK exited the EU, then this could be an opportunity to reduce medicine (given the current DoH shortfall in recuperation of pharmaceutical rebates). In this case, some companies indicated that may downgrade UK in its launch priorities. However, the opposite can be argued, and this will depend on the economic performance and political priorities post Brexit and is therefore difficult to predict.

Market access initiatives

The UK plays a key role in initiatives like early dialogue, adaptive pathways, international collaboration on HTA (EUNETHA) and the like. A Brexit could jeopardise the UK's participation in pan-European projects. To the extent some of these are intended to speed up patient access to innovation this could be detrimental.

If the UK were not able to participate in these initiatives, these initiatives would most likely continue. However, the UK might lose out on the benefits of collaboration if participation was restricted. It was however highlighted that the ability to participate in the EU initiatives set to facilitate market access is useful but to date, companies have observed that these initiatives have not had much impact on the local market access process. There is a broad consensus that if there was restricted access to these EU initiatives on market access in the event of a Brexit, there would be no significant impact on market access conditions in the UK.

Drawing from the Swiss experience, Swiss administration has made an attempt to be part of these initiatives such as EUNetHTA but is not a full member. Some Swiss respondents

indicated whilst Switzerland is involved in EUNetHTA as an associated member, the initiative is not in line with their interests (lengthens the process) and therefore participation in EU initiatives on market access are not necessarily advantageous.

EU's Public Procurement framework

EU directives on public procurement cover tenders that are expected to be worth more than a given threshold. This framework is designed to achieve a procurement market that is competitive, open, and well regulated. It was indicated that EU regulations around public procurement is not an important concern for pharmaceutical companies and if the UK were to pull out of such a framework, this would be unlikely to affect companies' ability to market its products.

4.4.2. Compliance to the EU competition policy

In the case of Brexit, activities in the UK would no longer be subject to European Competition law and the EU would lose its jurisdiction over the UK. However, as is required under the current membership rules, the UK has national laws that mirror EU provisions and these will still apply so Brexit is unlikely to alter the fundamentals of competition regulation in the UK.

Competition and antitrust law

In terms of competition and antitrust law regulation, companies indicated that a potential down side of Brexit is dual investigations by both the UK Competition Authority and the European Commission. If the European Commission launches an investigation into alleged breaches of competition law, national member's states cannot investigate the same allegations. Post-Brexit this will no longer be the case in the UK so cross border infringements could face investigations by both the Commission and the CMA, with each authority having the power to impose substantial fines.

On mergers an EU filing will no longer cover UK merger control law so this may lead to increased costs, time and burden on some deals where a filing with the CMA is required in addition to the EU.

The biggest potential difference would be in the area of state aid. Under EU rules the Member States cannot provide assistance to national industries. If the UK is no longer a member of the EU this may give greater flexibility to the UK Government to provide support to UK businesses. However, given the priorities of other industries the benefits to the life sciences industry was seen as weak.

Parallel trade

It was acknowledged that parallel trade at the moment is detrimental for pharmaceutical companies (and ultimately patients). If the UK were independent of EU regulations on parallel trade like the Swiss or Canadian situation, then the industry would find this beneficial. However, some respondents expressed some doubts as to whether this would effectively happen given this has brought some saving to the NHS. However, given the situation with PPRS receipts and shortfall in rebates linked to purchase from other countries in Europe, there is a possibility that the government would want to restrict parallel trade. Some companies indicated that a potential restriction on parallel trade is not necessarily favourable as it could affect the reliability of supply chains.

4.4.3. Falsified medicines directive (e.g. traceability)

In terms of the EU regulations on product security such as the falsified medicines directive. Most companies confirmed that the EU falsified medicines directive brought value to companies as it served the benefit of harmonising product security requirements which will help reduce costs as the packaging of the drugs could be made similar across Europe. This would be at risk following Brexit.

We summarise the impact on key changes in the market access landscape for the life sciences industry in the UK and EU in Table 10 below.

Table 10: Summary of the impact of Brexit on components of market access from the perspective of the UK and European life sciences industry

	Impact on life science industry in the UK	Impact on life science industry in Europe
Pricing and reimbursement regime		
Involvement in market access initiatives		
Competition and antitrust law		
Possibility to received State Aid		
Possibility to ban parallel trade		
Compliance with Falsified medicines directive	Assuming UK industry will comply with FMD regardless	

4.4.4. Conclusion on market access

EEA membership

As discussed above, pricing and reimbursement remains a national decision and the UK has a well-defined system for pricing and adapting new drugs which differs from that of other EU member states. This is not expected to change in the event of a "Brexit" should the UK decide to join the EEA. As highlighted in chapter 2, Norway has its own system for pricing and reimbursement which is different from other countries, as these systems are largely decided on national level. The UK would continue to be subject to some level of compliance with transparency of measures regulating the pricing and reimbursement of pharmaceuticals through the European Transparency Directive[208] as well as a number of

208 The Transparency Directive basically provides that such measures should be based on objective and verifiable criteria. It also provides for timelines within which pricing and reimbursement decision should be taken. The European Commission issued a proposal for a new Transparency Directive in 2012.

initiatives launched by the European Commission to improve member states policies on access to medicines include the falsified medicines directive. Under the framework of the EEA, the UK would also need to continue to comply with the EU competition policy. As such, an alternative relationship with the EU would not have much of an impact the market access strategy of life sciences companies.

Bilateral agreements

As above, under the framework of a bilateral agreement with the EU, pricing and reimbursement would continue to remain a national decision. However, the UK would no longer be subject to the EU transparency directive which means that potentially, timeline for approving drugs for reimbursement could slip beyond the 180 days' timeframe. However, as the UK system allows products to launch from regulatory approval and does not have a formal price setting process, the Transparency Directive has little direct impact on the UK.

The UK plays a key role in market access initiatives like early access programs, EUNetHTA or adaptive pathways and Brexit could clearly jeopardize the UK participation in pan-European projects intended to speed up patient access to innovation although it was stressed that this would not necessarily have significant business impact on the industry as whole as these initiatives would be likely to carry on without UK participation.

With the European Commission losing its jurisdiction over the UK, its powers of investigation would no longer extend to business premises in the UK and Companies' corporate headquarters based in the UK could no longer be subject to a physical raid by the Commission. The CMA, the UK Competition Authority, would instead be the relevant authority and it is an active authority and has extensive powers of investigations This may lead to increased costs, time and burden on some deals where a filing with the CMA is required in addition to the EU.

However, in the area of state aid, if the UK is no longer a member of the EU this may give greater flexibility to the UK Government to provide support to UK businesses which could bring some benefits to companies experiencing cyclical difficulties.

Perhaps one significant impact of leaving the EU would be the ability to introduce a ban on parallel trade as a result of no longer being subject to EU competition policy. However, there is no guarantee that the UK would re-introduce such a ban should it leave the EU.

Regarding compliance with additional regulation such as the Falsified medicines directive (e.g. traceability), the UK would no longer need to comply with such regulation. However, it has been argued that an important part of the investment to complying with the requirement of the regulation have already been made in the UK. It is therefore unlikely that the UK would chose not to comply with such standards. In fact, Swiss companies have indicated that Switzerland will be complying with the FMD. In fact, they indicated that if the EU-CH bilateral were nullified due to the restriction on immigration, then Swiss companies would need to provide additional documentation for products (for example, provide inserts in different languages etc.) which would be burdensome and add to product supply costs.

It is therefore unlikely that a move towards a bilateral agreement would bring about significant changes in the market access landscape in the UK.

Full break

In terms of market access, conditions under a full break scenario would be no different from the above "Bilateral agreements" scenario. We summarise our conclusions in Table 11 below.

Table 11: Impact of Brexit on pharmaceutical market access from the perspective of the UK and European life sciences industry

	Impact on life science industry in the UK	Impact on life science industry in Europe
EEA Membership	No change to P&R system or compliance with regulation	No change to P&R system or compliance with regulation
Bilateral agreements	 Possibility benefit from state aid	No change
Full Break	 Possibility benefit from state aid	No change

4.5. Summary table

Table 12: Implications of a change in UK relationship for activities along the value chain

Trade model	Characteristic	Basic Research	Collaboration	Product development	Regulatory Approval	Manufacturing & Trade	Market Access	Overall assessment
EEA like member model	• Full access to EU single market • Free movement of people • Full access to EU R&I framework (HR 2020) • Full adoption of EU regulatory framework • Conduct its own trade deals (outside EU negotiating platform)	 Little impact- Full access to EU research programme. UK science base risks losing leadership role	No impact- Full access to EU research funds & collaborative programme	 EU Clinical Trials Directive Standards & Conditions Some loss of influence over regulatory framework	 Applications continued to be processed by EMA. Some loss of influence of regulatory framework	 Full compliance with EU GMP framework UK likely lose negotiating power to ensure strong IP agenda	No change to P&R system or compliance with regulation	 Limited impact but loss of influence over future of regulation
Bilateral treaties model	• Likely to have access to EU single market • Some restriction on free movement of people but visa waver prog for scientists • "associated country" status to EU R&I framework • Own regulatory framework but some regulatory alignment expected • Conduct its own trade deals (outside EU negotiating platform)	 UK universities lose funding and coordinator role More limited access to major EU science progs.	 SME lose funding and but keep ability to collaborate.	 More difficult for biopharmaceutical companies to conduct multinational clinical trials	 Companies face extra cost of MA approval Separate regulatory approach (even based on consistent approach) will lead to regulatory delay	 UK would need to ensure mutual recognition of GMP standard UK likely lose negotiating power to ensure strong IP agenda	 Possibility to ban parallel trade and benefit from state aid Delay in regulatory approval would delay access (for some products) & loss of influence on wider policies affecting market access	 Some added complexities to pharmaceutical operations but no direct business risk

Full break: WTO model	• WTO general trade & tariff principles apply • WTO dispute resolution mechanisms • Framework for bilateral treaties • No access to EU research programme, • Little or no regulatory alignment between UK and EU • MHRA would likely set EMA / FDA compatible standards & issue UK product licenses	 Loss of credibility as science leader in Europe UK funding does not replace EU funding	 Reduced opportunities to collaborate and no platform/mechanism to join research consortium (e.g. IMI) - weakened research clusters and fewer biotech start-ups	 No regulatory alignment between UK and EU Significant barriers for SMEs Reduction in clinical trial activity	 Additional costs and time to get MA approval outside UK Likely delays in approval and access to medicines	 Lack of mutual recognition of GMP standard but outside of REACh UK would need configure its own trade relations with other countries and likely to lose negotiating power to ensure strong IP agenda	 Possibility to ban parallel trade and benefit from state aid Delay in regulatory approval delays access & loss of influence on wider policies affecting market access	 Makes operation of pharmaceutical companies significantly more complex This model might open up greater flexibility for UK policy but benefits are modest

5. The transition

We now turn to assessing the impact that the transition period would have on the life science industry in the UK and in Europe more broadly. Even where commentators disagree on the benefits or costs of Brexit most agree that a vote to leave the EU would lead to a period of uncertainty during the transition period with negative economic consequences. The length of transition is unknown:

- It is likely that the UK would attempt to negotiate with the EU a UK specific agreement and Article 50 assumes a two year period.
- Even if the UK chooses the full break, this is likely after a period of negotiation.
- Experience of CETA suggests that a bespoke UK-EU trade agreement could be complex to negotiate and would indeed take many years. A government document which sets out the complex process for withdrawing from the EU concludes that this "could lead to up to a decade or more of uncertainty".[209]
- Experience of Switzerland suggests a series of bilateral agreements are often spread over many years.

It seems reasonable to conclude that there would be considerable uncertainty over the first two years and potentially for 5-10 years. This was confirmed by our respondents in our interview. After conducting 30 interviews, it is also clear that there is no consensus on the scenario that is most likely to occur and in reality, independent of whether the UK follows a model closer to Canada, Switzerland or Norway, there were a series of questions relevant for investment decisions where the answer is currently unknown:

1. Will the UK continue to have access to EU collaborative programmes and funding? If access is immediately restricted, will the UK government fill in the funding gap and create a new collaborative platform to assist with the setting up of UK-EU collaborations?
2. If the UK science base is uncertain (due to potential restriction in immigration, access to EU funding, collaborations), will companies that list on UK markets during the transition period be able to attract investment, specifically FDI?
3. To what extent will the UK restrict the free movement of people during the transition period and subsequently? Will we see scientists and researchers immediately exiting the UK or difficultly in attracting scientists to the UK?
4. What will happen to the UK clinical trials approval process (will there be access to the clinical trial portal)? Will the UK still be a good place to undertake clinical trials during the transition period? Will the application process for undertaking clinical trials in the UK be similar to that in Europe?
5. Will the other countries recognise GMP inspections undertaken in the UK or will this require inspections from an EU country? Will EU requirements on manufacturing, such as REACh, apply in the UK?

209 Kingsley Napley (2016) Brexit for startups: cutting red tape or cutting off life support? The process for withdrawing from the European Union, HM Government (2016).

6. Will regulatory approval for the UK market become more challenging during the transition process and in the new UK process?
    a. How quickly will it take MHRA to develop its own application process? Will there be a delay in approvals?
    b. Would the MHRA immediately re-access all existing products with EMA marketing authorisation?
    c. Would the MHRA marketing authorisation process significantly diverge from the EMA marketing authorisation process and timeframe?
    d. Will the UK be able to continue influencing developments/ initiatives in the EMA – adaptive pathways?

There are a number of areas where this uncertainty could have significant implications for activities along the industry value chain today.

5.1. Impact on industry

In terms of any industry, economic theory suggests that firms are likely to reduce or postpone irreversible investment as uncertainty increases and there is a plethora of literature that demonstrates this point.[210] For example, uncertainty of inflation rates has a negative impact on R&D investment in OECD countries.[211] In fact the negative impact of uncertainty, such as those arising from political shocks, extends beyond the scope of investments into hiring and trade.[212,213,214] Studies show investment decisions of manufacturers are negatively correlated with levels of uncertainty, as companies were trying to raise savings to prepare for a potential deterioration of business conditions.[215] Moreover, uncertainty makes firms less sensitive to other conditions in the business environment like demand and prices. [216]

Life sciences is unusual in that, investment occur periodically, in terms of the location of research hubs, clinical trial programmes and manufacturing plants, but the life cycle of the product is over twenty years, so decisions need to take into account long-term consequences. These findings are therefore even more likely to apply to the pharmaceutical industry where investment in R&D is higher than most other sectors,

210 Stein et al. (2013) "The Effect of Uncertainty on Investment, Hiring, and R&D: Causal Evidence from Equity Options". http://www.public.asu.edu/~lstein2/research/stein-stone-uncertainty.pdf

211 Costamagna, R (2015), "Inflation and R&D investment." Available at: http://www.cairn.info/revue-journal-of-innovation-economics-2015-2-page-143.htm

212 Baker, Scott and Nicholas Bloom (2011). "Does uncertainty drive business cycles? using disasters as natural experiments". NBER Working Paper 19475.

213 Bloom, Nicholas (2009). "The impact of uncertainty shocks". Econometrica 77(3), pp. 623--685.

214 Handley, Kyle and Limao, Nuno (2012), "Trade and Investment under policy uncertainty: Theory and Firm Evidence", NBER working paper 17790.

215 Korean Development Institute (2005), "The impact of uncertainty on investments: Empirical evidence from manufacturing firms in Korea." Available at: https://faculty.washington.edu/karyiu/confer/sea05/papers/lee_hy.pdf

216 Bloom, N (2013), "Fluctuations in uncertainty." Available at: https://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwiRwoDHzLvMAhVMCcAKHf_NCA8QFgghMAA&url=https%3A%2F%2Fwww.aeaweb.org%2Farticles%3Fid%3D10.1257%2Fjep.28.2.153&usg=AFQjCNE4stQUkM9cr4J5nsEBghJCeRWP1A&bvm=bv.121070826,d.ZGg

investments have long duration (often decades) and are often specific to particular products or technologies. A study of Korean pharmaceutical companies on the Korea Listed Company Association found that when companies faced financial risk they become increasingly conservative in their R&D investments.[217] It is not just the market environment that has an effect on investment. For the choice of clinical trial locations in Europe, Gehring et al 2013 found the ease of clinical trial approval was the dominant determinant for the choice of clinical trial location.[218]

The relationship between regulatory uncertainty and investment in R&D has been analysed in many papers. It is useful to note that the impact can be immediate and have a particular large effect on smaller companies:

- Grabowski and Vernon (1978) employ a regression model to analyse the effects of regulation on the pharmaceutical industry. They find that increased stringency and compliance uncertainty due to regulatory delay resulted in a decrease in the market innovation of new drugs. In essence, regulation caused drug innovation to concentrate in larger, multinational firms that were better able to deal with the regulatory costs.[219]
- Hauptman and Roberts (1987) use regression models to examine the effect of increased stringency of social regulation on young firms in the biotechnology industry, and they find that the resulting compliance uncertainty reduced market innovation—especially that of advanced technology products—but that innovation rebounded after several years.[220]
- Thomas (1990) uses a regression analysis to examine the gradually increasing stringency of FDA regulations from 1962, using the United Kingdom as a baseline for regulatory stringency. He finds that market innovation fell substantially in smaller pharmaceutical firms but larger firms were unaffected.[221]
- Golec et al. (2005) show that policy uncertainty surrounding price controls can reduce market innovation well before the regulation is in effect. They also show that regulation may not reduce market innovation per se, but rather it may change the nature of innovation. Their study uses the Clinton Administration's proposed 1993 Health Security Act (HSA) as a natural experiment to study the effect of proposed drug price controls on biotech and pharmaceutical firms. They find that the mere proposal of the

217 Lee M & Choi M (2015), "The determinants of research and development investment in the pharmaceutical industry: focus on financial structures." Available at: http://www.sciencedirect.com/science/article/pii/S2210909915300187

218 Gehring,M et al (2013), "Factors influencing clinical trial site selection in Europe: the survey of attitudes towards trial sites in Europe (the SAT-EU study)." Available at: http://bmjopen.bmj.com/content/3/11/e002957.abstract

219 Grabowski, H. G., J. M. Vernon, and L. G. Thomas. 1978. Estimating the Effects of Regulation on Innovation: An International Comparative Analysis. Journal of Law and Economics 21(1): 133-163.

220 Hauptman, O., and E. B. Roberts. 1987. FDA Regulation of Product Risk and Its Impact Upon Young Biomedical Firms. Journal of Product Innovation Management 4(2): 138-148.

221 Thomas, L. G. 1990. Regulation and Firm Size: FDA Impacts on Innovation. RAND Journal of Economics 21(4): 497-517.

HSA reduced firm R&D spending by about $1 billion and caused firms to cut back on clinical trials.[222]

Applying these findings to the life science industry in the UK suggests that the uncertainty in the larger economic environment that stems from the transition phase as the UK redefines its relationship with the EU will be hugely detrimental. As described below, we found that interviewed stakeholders had consistent views.

- **Impact on business strategy:** Both large pharmaceutical companies but also biotech SME indicated that predictability of the future regulatory environment is key their long-term planning and investment strategy. Respondents highlighted that the uncertainty associated with a change in both the clinical trial framework and the marketing authorisation regulation could have significant impacts on their future product launch strategy and ongoing business development. One example of this was provided by a small biotech SME with a product which has just received an orphan drugs designation by EMA and benefiting from the EMA's fast track approval process. It was stressed that losing access to the EU fast track regulatory approval process and the uncertainty associated with the future product approval process could significantly increase cost of regulatory compliance and alter both the European launch strategy and the ability of the product to gain rapid access to market. This has repercussions on the company's investors who have adopted a "wait and see" attitude which is already impacting the company's long term business strategy. In reality, the location of the company does not affect its eligibility for the EMA Priority Medicines fast track initiative (PRIME) but the uncertainty created by the Brexit debate is already affecting investment decisions.[223]
- **Limit ability to retain current staff or attract new talents:** Leave or remain, it is unlikely that the UK would immediately 'pull up the drawbridge' for EU nationals to work in the UK, however, in the interim, Brexit may well make the UK a less attractive place to move for skilled EU workers.[224] As indicated in chapter 4, there is concern that Brexit may reduce the size of the talent pool and make it even more difficult to find people with the required skills. It was suggested that for current EU nationals living or working in the UK, the level of uncertainty around future immigration policies could lead to staff reconsidering their medium to long term plan to remain in the UK. One interview with an academic research centre already indicated that some researchers from other EU countries have already been turning down place for fixed-term research positions, due to the length of time and the uncertainty around Britain's future immigration policy. Similarly, there are concerns within small businesses such as research based biotech SMEs that current EU national might consider moving back to their home countries. It has also been argued that many larger companies could begin to temporarily shift work outside the UK during the transition period. This is already taking place in Switzerland, primarily as a result of uncertainty over access to the EU market. Research

222 Golec, J., S. Hegde, and J. Vernon. 2005. Pharmaceutical R&D Spending and Threats of Price Regulation. Working Paper. National Bureau of Economic Research, Cambridge, MA.

223 EMA (2016), "PRIME – Priority Medicines." Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac05809f8439

224 https://www.kingsleynapley.co.uk/news-and-events/blogs/eu-referendum-blog/brexit-for-startups-cutting-red-tape-or-cutting-off-life-support

programmes will move to EU-based sites and current expansion within the UK would likely decline at least in the short term.[225]

- **Limit opportunities to take part in collaborative research**: Our interviews indicated opportunities for university and biotech SMEs (as well, but to a less extent large pharma companies) to engage in collaborative research is perhaps the most significant benefit that EU membership affords science and research in the UK. Some academic research centres and biotech SMEs who are involved in joint research products have expressed their concerns that during the transition period, their ability to take part in large European research consortiums might reduce or be limited as a result of the uncertainty associated with the UK's future status in the UK. This will limit their ability to lead and coordinate large European research projects which are currently being considered.
- **Create a "wait and see" attitude toward investment decisions:** The period between the vote and the EU exit would be extremely turbulent in terms of investment and that the uncertainty associated with the Brexit debate has greatly destabilized capital markets and the ability of small firms to access sources of finance. As highlighted by the governor of the Bank of England, Mark Carney, the prospect of British exit is "the biggest domestic risk to financial stability because, in part, of the issues around uncertainty." Biotech SME who rely heavily on access to capital expressed their concerns on the existing concerns that these periods of uncertainty would likely impact stock prices; especially for UK based companies. Data from accountant EY has shown that the share price would likely fall and the implications of this would limit the number of future IPO's. In fact, evidence shows that for the first quarter of 2016 the total raised through IPOs slumped to £1.6bn, down from £4bn in the last quarter of 2015 as a result of the sluggishness in the market has been put down to volatility and the uncertainty associated with the fast approaching referendum over Britain's continued membership of the European Union.[226] Large pharmaceutical companies indicated that Brexit would not have any "knee jerk" impact on their investment decisions. Most companies indicated that they do not believe that EU membership is not the deciding factor for pharmaceutical investment into the UK. However, companies indicated that it is expected that a potential Brexit would least a period of uncertainty of around 5-10 years which would be highly destabilising even for large businesses.

There is conflicting evidence of whether signing new FTAs will increase FDI. Looking at the experience of the Singapore-US FTA, which saw an overall increase in the exports of Singaporean pharmaceuticals to the US market three years after the implementation of the FTA, it appears that there was an influx of investment into pharmaceutical production and research facilities by multinational companies after the FTA.[227] However, a study by Oxfam also found no evidence that the FTA between US and Jordan has had a positive impact on

225 Scientist for EU

226 City AM (2016) Brexit vote puts brakes on City's huge IPO boom, cutting the amount raised by by almost 75 per cent since the last quarter of 2015, Tuesday 29 March 2016 04:54 GMT, accessible at http://www.cityam.com/237648/brexit-vote-puts-brakes-on-citys-huge-ipo-boom-cutting-the-amount-raised-by-by-almost-75-per-cent-since-the-last-quarter-of-2015

227 Nanto, D (2008), "CRS Report for Congress: The US-Singapore Free Trade Agreement: effects after three years" Available at: https://www.fas.org/sgp/crs/row/RL34315.pdf

FDI by drug companies.[228] Considering that there is some evidence that FTAs will increase FDI, the impact of the transition period is of concern for the UK life sciences industry.

5.2. Impact on EMA and regulatory process

The transition to Brexit will directly impact the environment for companies undertaking activities in the UK but will also have an impact on the European activities. It seems reasonable to assume that most of EU regulation will be unchanged. The impact on the macroeconomy could clearly have a significant impact on other European countries and therefore on the attractiveness of investing in Europe. This will affect all sectors, so we do not focus on this issue. Instead, the area of most concern according to our interviews was the impact on the EMA.

In the event of the UK leaving the EU, the EMA would have to relocate out of the UK because EU institution agencies cannot be located outside the Union's borders.[229] There are a number of issues that are relevant for considering the impact of this move:

- **Disruption during the physical move:** The EMA was founded in 1993 by the European Commission and first operated in 1995, suggesting the set up process took at least 2 years.[230,231]
- **The loss of staff:** As of April 2016, there were 885 staff members at the EMA. Staff are from all EU member states, with French, Italian, Spanish and British being the most common nationalities (Figure 11).[232] According to the EMA, of the 79 named senior members of staff in their operational functions, approximately 10% hold British nationality.[233] Any change in location involves a loss of key staff. There are not robust estimates of the proportion but a look at the impact of within country relocations clearly suggests that the impact on loss of staff and costs for retention incentives will be

228 Oxfam. All Costs, no Benefits: How TRIPS-plus Intellectual Property Rules in the US–Jordan FTA Affect Access to Medicines. Oxford, Oxfam Briefing Note, March 2007. The Oxfam study examined the Jordanian pharmaceutical market since the US-Jordan FTA came into effect in 2001. It stated that there had been "nearly no foreign direct investment by drug companies into Jordan since 2001 to synthesize or manufacture medicines in partnership with local generics companies."

229 In the event that post Brexit the UK joined the EEA it would then be eligible for membership of the European medicines regulatory network, through its national agency, the MHRA. However prima facie it appears unlikely even in this case that it would prove acceptable to the EU Commission and member states to allow the Agency to remain in an EEA country.

230 EMA (2016), "EMA About us." Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000235.jsp&mid=

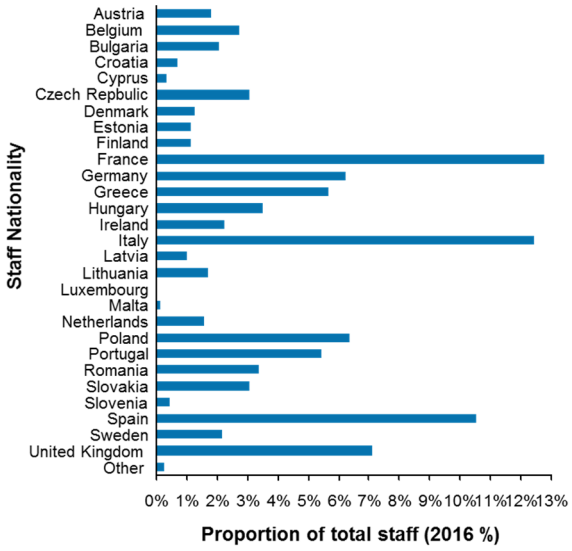
231 European Commission (2016), "Authorisation Procedures for medicinal products." Available at: http://ec.europa.eu/health/authorisation-procedures_en.htm

232 EMA (2016), "Recruitment at the EMA". Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/08/WC500170475.pdf

233 These are the MHRA CEO acting as the UK representative in the EMA management board; the Head of Procurement and Contract Office; the Head of Quality – Human Medicines; the Head of veterinary medicines; the Head of Pharmacovigilance; the Head of stakeholders and communication; the Head of online and corporate design; the head of Personnel, the Head of learning and development, the head of corporate support. As seen in EMA (2016), "Who we are." Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000112.jsp&mid=WC0b01ac0580028a43

significant.[234] The experience of the British Broadcasting Company relocation within the UK, from Greater London to Salford suggests a large proportion of staff was lost in this within country relocation - 62%.[235]

Figure 11: EMA staff composition – by nationality



Source: EMA

- **The loss of capacity to undertake reviews:** As set out in Chapter 2 the UK is the most common rapporteur for reviews, involved in nearly 15% of all reviews.
- **Loss of experience:** The location of EMA in London has built up regulatory expertise to the UK. Fernand Sauer, the first executive director of the EMA indicated that, "it would be a big shock for the entire authorization process in Europe, because the U.K. provided some of the best experts over the years – sometimes a bit difficult but also very good, and helped create a good mix of experts." Many companies recognised that the location of EMA in London has brought a pool of resources for assessment increasing confidence that the assessments are done fairly and efficiently.

Finally, many of the industry respondents also believed that the UK played a significant role in shaping EMA policy in an innovation friendly manner. This would be diminished affecting the future evolution of the EMA.

In conclusion, the reputation and expertise of the EMA is now well established, relocation after a sensible long-term transitional period should not constitute a serious threat to continuing to grant timely access for innovative medicines to all EU markets. However, in the transition it is possible that this leads to delays. For example, if this reduced the capacity

234 Forsythe AJ (2015), "Relocating – but how can we keep our staff?" Available at: https://next.ft.com/content/0aa55da6-b05b-11e4-a2cc-00144feab7de

235 National Audit Office (2013), "The BBC's move to Salford – Report by the Comptroller and Auditor General presented to the BBC Trust Finance Committee 10 April 2013." Available at: https://www.nao.org.uk/wp-content/uploads/2013/05/10143-001_The-BBCs-move-to-Salford.pdf

of the EMA to review products in line with loss of UK capacity, this could result in a delay of 2-3 months for two years.[236]

236 For example, in 2014, the EMA approved 82 products with an average length of process of 210 active days. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/01/WC500180149.pdf

Appendix

Table 13: Interviews conducted

Organisation type	Name
Pharma trade association	• ABPI • Interpharma Switzerland • LMI (Norway) • Innovative medicines Canada • BIA
Pharma companies with HQ in Switzerland	• Roche • Biogen • Novartis
Pharma companies with large investments in the UK	• Eli Lilly • UCB • Janssen • GlaxoSmithKline • AstraZeneca • Pfizer
Contract Research Organisation	• Orion
University staff	• Universities UK • University of Oxford
SME Biotech	• European Biotechnology Network • Redx Pharma Plc (Cheshire) • Neem Biotech (Wales) • Magnus Lifescience (London)
Charities involved in funding R&D	• Cancer Research UK

Table 14: Comparing Regulatory Approval by EMA vs SwissMedic

Drug Name	EMA Approval	SwissMedic Approval	Time difference between EMA & SwissMedic (days)
Scenesse	22 December 2014	Not approved	-
Cyramza	19 December 2014	29 October 2015	+ 314
Rixubis	19 December 2014	22 May 2014	**-211**
Duavive	16 December 2014	02 April 2015	+ 107
Lynparza	16 December 2014	14 January 2016	+ 394
Moventig	12 August 2014	08 July 2015	+ 330
Trulicity	21 November 2014	06 May 2015	+ 166
Vargatef	21 November 2014	Not approved	-
Brimica Gen-uair	19 November 2014	Not approved	-
Duaklir Genuair	19 November 2014	Not approved	-
Rezolsta	19 November 2014	Not approved	-
Harvoni	17 November 2014	16 December 2014	+ 29
Imbruvica	21 October 2014	10 November 2014	+ 20
Zydelig	18 September 2014	22 January 2015	+ 126
Xultophy	18 September 2014	12 September 2014	**-6**
Abasaglar	09 September 2014	09 July 2015	+ 303
Triumeq	09 January 2014	08 January 2015	+ 364
Velphoro	26 August 2014	22 January 2015	+ 149
Daklinza	22 August 2014	26 June 2015	+ 308
Vizamyl	22 August 2014	not approved	-
Nerventra	19 August 2014	not approved	-
Reasanz	08 May 2014	not approved	-
Translarna	31 July 2014	not approved	-
Nuwiq	24 July 2014	not approved	-
Gazyvaro	23 July 2014	10 June 2014	-43
		Average delay (days)	**+156**

Source: CRA Analysis

Table 15: Comparing Regulatory Approval by EMA vs Health Canada

Name	EMA	Canada	Time difference between EMA & Health Canada (days)
Scenesse	22 December 2014	Not approved	
Cyramza	19 December 2014	16 July 2015	209
Rixubis	19 December 2014	30 September 2014	-80
Duavive	16 December 2014	23 October 2014	-54
Lynparza	16 December 2014	Not approved	
Moventig	12 August 2014	02 June 2015	294
Trulicity	21 November 2014	10 November 2015	354
Vargatef	21 November 2014	25 June 2015	216
Brimica Genuair	19 November 2014	Not approved	
Duaklir Genuair	19 November 2014	02 April 2015	134
Rezolsta	19 November 2014	19 June 2014	-153
Harvoni	17 November 2014	15 October 2014	-33
Imbruvica	21 October 2014	17 November 2014	27
Zydelig	18 September 2014	27 March 2015	190
Xultophy	18 September 2014	not approved	
Abasaglar	09 September 2014	01 September 2015	357
Triumeq	09 January 2014	09 October 2014	273
Velphoro	26 August 2014	not approved	
Daklinza	22 August 2014	13 August 2015	356
Vizamyl	22 August 2014	not approved	
Nerventra	19 August 2014	not approved	
Reasanz	08 May 2014	not approved	
Translarna	31 July 2014	not approved	
Nuwiq	24 July 2014	23 October 2014	91
Gazyvaro	23 July 2014	25 November 2014	125
		Average time difference	144

Source: CRA analysis

Table 16: EU-Korea Free Trade Agreement vs EU-Korea Free Trade Agreement

	Canada-Korea Free Trade Agreement	EU-Korea Free Trade Agreement
Pharmaceuticals	63 percent of tariff lines will be duty-free and all remaining tariffs will be eliminated within five years (current duties of up to 8 percent).	90.5 percent of tariff lines will be duty-free and all remaining tariffs will be eliminated within three years (current duties of up to 6.2 percent for korea and 0% for EU).
Medical devices	Upon the Agreement's entry into force, 88 percent of tariff lines will be duty-free. Tariffs on diagnostic/laboratory reagents, medical apparatus parts, thermometers—current duties of up to 50 percent—will be eliminated within 10 years.	Upon the Agreement's entry into force, 74.3 percent of tariff lines will be duty-free and all remaining tariffs will be eliminated within seven years
Guidelines	Promotes the use of internationally accepted standards and quality management system guidelines in regulating medical devices and pharmaceutical products to facilitate safe bilateral trade in those products	introduce stronger transparency rules for Korea's regulatory system in general and, in particular, for its pricing and reimbursement
patents	In line with Canada's current regime, including criteria regarding patentability and exclusions from patentability.	

Source: CRA analysis