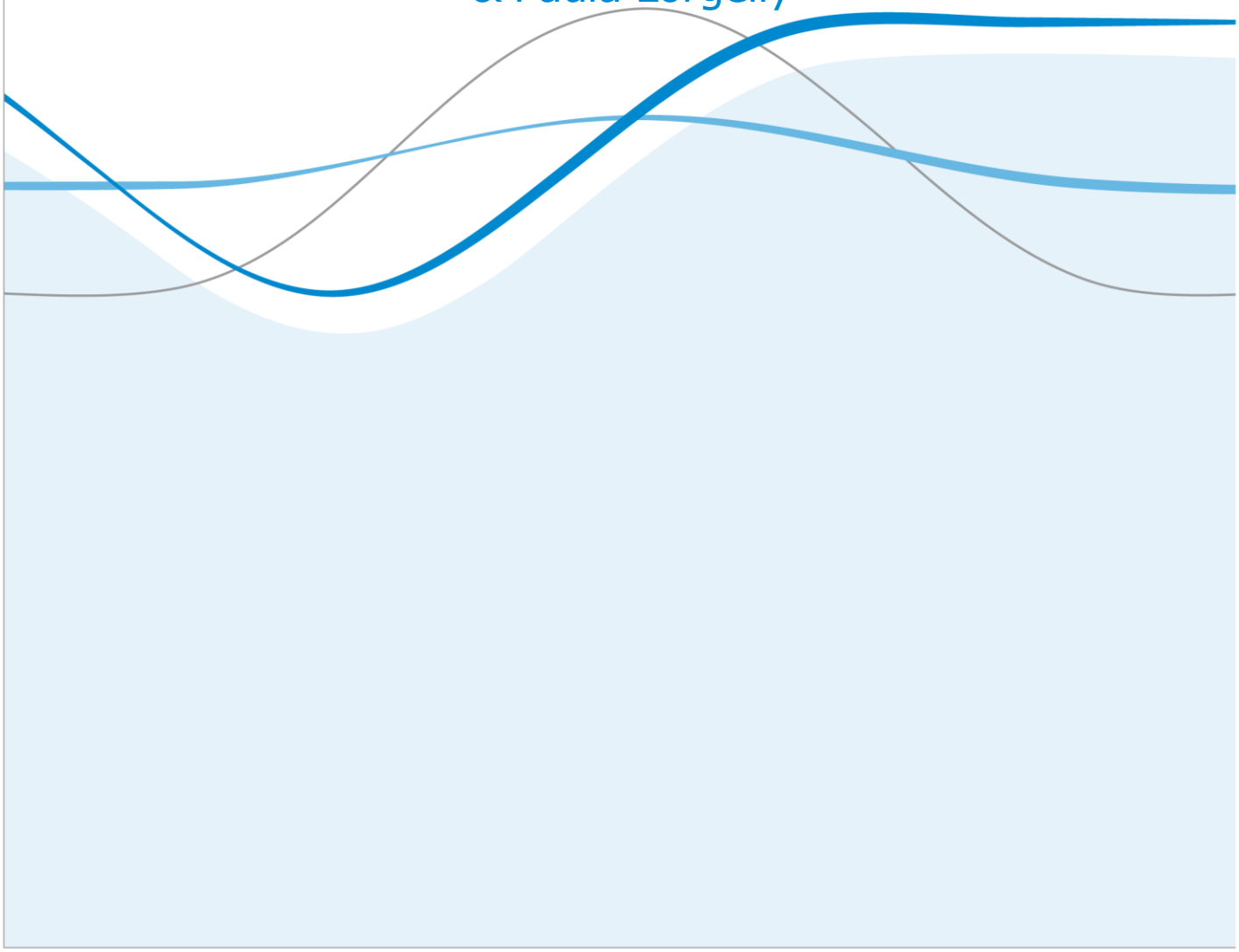
Office of Health Economics Consulting

Executive Consulting Report

Public Health and Economic Implications of the United Kingdom Exiting the EU and the Single Market

November 2017

Francois Maignen, Mikel Berdud, Grace Hampson & Paula Lorgelly



Public Health and Economic Implications of the United Kingdom Exiting the EU and the Single Market

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About This Report

This report was commissioned by the Association of the British Pharmaceutical Industry (ABPI) and the BioIndustry Association (BIA) to provide important evidence for the ongoing policy analysis into the implications of the UK leaving the European Union.

OHE Consulting would like to thank the project Steering Committee for guiding the scope of the project, and for providing useful feedback and support across the various analyses that have been undertaken.

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ABBREVIATIONS

API	Active Pharmaceutical Ingredient
Brexit	United Kingdom's withdrawal from the European Union
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
CMO	Contract Manufacturing Organisation
CMDh	Co-ordination group for mutual recognition and decentralised procedures for human medicinal products
COMP	EMA Committee for Orphan Medicinal Products
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
EU27/EEA	The remaining 27 member states of the European Union plus the non-EU members of the EEA following the withdrawal of the UK from the EU and the EEA.
EudraVigilance	EU data processing network of individual case safety reports of adverse drug reactions
FTA	Free Trade Agreement
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
MFN	Most Favoured Nation
MHRA	Medicines & Healthcare products Regulatory Agency
MRA	Mutual Recognition Agreement
NCA	National Competent Authority
NIBSC	National Institute for Biological Standards and Control
OMCL	Official Medicines Control Laboratories
PASS	Post-Authorisation Safety Study
PDCO	EMA Paediatric Committee
PRAC	EMA Pharmacovigilance Risk Assessment Committee
QP	EU Qualified Person (for batch release)
QPPV	EU Qualified Person Responsible for Pharmacovigilance
UK	United Kingdom
WTO	World Trade Organization

EXECUTIVE SUMMARY

The consequences of the exit of the United Kingdom (UK) from the European Union (EU) and from the Single Market on public health will be highly dependent on:

- the terms of trade deals agreed between the UK and the remaining countries of the EU and the European Economic Area (EU27/EEA);
- the extent to which the UK will be involved in EU public health activities;
- the time given to companies to adapt to any legal obligations and regulatory changes;
- the transposition of relevant EU Regulations (e.g. orphan medicinal products, clinical trials, paediatric medicines, advanced therapies and small and medium-size enterprises) into UK law.

This report explores the sensitivity of the various public health and economic impacts to different combinations of regulatory and trade agreements according to the following scenarios (whereby the impacts of the different scenarios are cumulative).

Scenario 1: The Medicines and Healthcare products Regulatory Authority (MHRA) remains fully involved in EU27/EEA public health activities; the UK negotiates free trade agreements (FTAs) with the EU.

Public health and economic consequences are minimal for the EU27/EEA and the UK due to full cooperation in public health activities and free trade agreements.

The cost of Brexit for both a large UK-based pharmaceutical company and a large US-based pharmaceutical company in year 1 is assumed to be negligible in this scenario.

Scenario 2: The MHRA implements a standalone regulatory system and negotiates agreements with the EU that cover inspections of quality and manufacturing processes (not the releases of batches); the UK negotiates FTAs with the EU.

There could be a **reduction in the number of submissions and/or delays in submissions of marketing authorisation** applications in the UK for new medicinal products:

- 45% of marketing authorisation applications submitted to the EMA during 2013-2015 had not been submitted to all three third countries (Australia, Canada, and Switzerland) by the end of 2016.
- Applications that were submitted to the third countries faced delays in submission of two-three months (median), and in 5-15% of cases the delay was greater than one year.

Delays in the detection and management of new signals could lead to public health impacts in both the EU27/EEA and the UK:

- Delays could be up to five months, based on analysis of communication between EMA and non-EU authorities.
- The UK has detected the greatest number of signals of all member states since 2012; the EU27/EEA will therefore lose direct access to the UK's expertise in this area (and vice versa).

In terms of **post-authorisation safety**:

- The UK contains the highest number of centres for the conduct of pharmaco-epidemiology studies.
- The UK is also the country in which the highest number of post-authorisation safety studies (PASS) are conducted.
- Both the UK and the EU27/EEA face the loss of expertise and centres for the conduct of these types of studies.

Delays in communicating both emerging risks and crisis management could also result in delays in regulatory action in both the UK and the EU27/EEA. Coupled with inefficient coordination due to the duplication or divergence of requirements, this could impact on the management of public health threats like pandemic influenza.

Where marketing authorisations holders (MAH) are based in the UK, these would need to be **transferred or duplicated to a MAH in the EU27/EEA**. The same applies for MAHs based in the EU27/EEA being transferred or duplicated to the UK. The cost of this transfer process to a "typical" global pharmaceutical company (assuming 600 products need to be transferred) is estimated to be £19m.

Testing and release of batches would no longer be recognised between EU27/EEA and the UK. This would imply an implementation cost for a typical company of £13.6m to duplicate batch testing and release facilities and have them in both the EU27/EEA and in the UK. Note that there is little added value for this increase in cost.

The **cost of Brexit** for a large UK-based pharmaceutical company in year 1 is estimated to be £45.2 million (£42.2 million implementation; £2.9 million annual maintenance) in this scenario.

The **cost of Brexit** for a large US-based pharmaceutical company in year 1 is estimated to be £64.63 million (£54.9 million implementation; £9.73 million annual maintenance) in this scenario.

Scenario 3: The MHRA implements a standalone regulatory system and negotiates agreements with the EU that cover inspections of quality and manufacturing processes (not the releases of batches); trade cooperation is regulated by WTO most favoured nation (MFN) agreements.

In addition to the consequences outlined above, there could be **shortages of medicines** due to changes in trade and parallel trade between the UK and the EU27/EEA.

The **UK is a major importer, manufacturer and batch certifier of medicinal products in the EU**:

- The UK hosts the second highest number of good manufacturing practice (GMP) sites and manufacturing sites;
- The UK hosts and the third highest number of sites involved in batch certification in the EU;
- The impact of no mutual recognition of batch release would thus be substantial for the EU27/EEA and the UK.

Customs delays resulting from the absence of customs agreements could result in **major changes to the supply chain of medicines** manufactured in the UK, with subsequent

impacts on costs for businesses. It is likely that the absence of customs and trade cooperation between the UK and the EU27/EEA could create delays and disruption in the supply chain of medicines and contribute to an increased frequency of medicines shortages. Notably, sites conducting importation of immunological (i.e. vaccines) and blood products (i.e. human blood derived medicinal products) are disproportionately located in the UK compared with the rest of the EU.

There will also be costs to companies associated with **changes to the supply chain** that are necessary due to the loss of free trade agreements, as well as tariff measures and non-tariffs measures, irrecoverable value added tax, and brokers' fees. Estimated costs for additional duty for a typical company are in the region of £23.5m annually.

The cost of Brexit for a large UK-based pharmaceutical company in year 1 is estimated to be £72.6 million (£42.2 million implementation; £30.4 million annual maintenance) in this scenario.

The cost of Brexit for a large US-based pharmaceutical company in year 1 is estimated to be £72.43 million (£54.9 million implementation; £17.53 million annual maintenance) in this scenario.

Scenario 4: No public health cooperation between the MHRA and the EU27/EEA; trade cooperation regulated by WTO MFN agreements.

In addition to the consequences outlined above, the absence of an MRA may **complicate the certification of manufacturing, importation and distribution sites** (e.g. the MHRA would face a sudden additional inspection workload, and different GMP inspection regimes could result in different findings).

The cost of Brexit for a large UK-based pharmaceutical company in year 1 is estimated to be £86 million (£49.6 million implementation; £36.4 million annual maintenance) in this scenario.

The cost of Brexit for a large US-based pharmaceutical company in year 1 is estimated to be £101.03 million (£62.9 million implementation; £38.13 million annual maintenance) in this scenario.

Final comments

In summary, if comprehensive agreements (FTA and mutual recognition agreements) cannot be negotiated, public health impacts will be felt in terms of reduced availability of medicines in the UK (45% of marketing authorisation applications were not submitted to all three third countries in our analysis); delays of two to three months or more for marketing authorisation applications to be submitted in the UK; delays of up to five months in signal detection and management for pharmacovigilance in the UK and the EU27/EEA; delays in the management of crises and public health threats in the UK and the EU27/EEA, and shortages of medicines in both jurisdictions. If FTAs are not in place by March 2019, companies will face tariff measures and non-tariff measures (including delays) which could lead to medicines shortages in the UK and the EU27/EEA.

Our analysis has broadly assumed that these scenarios, and therefore their impacts, will apply from March 2019. In reality, in the absence of a clear signal from Government about the exact nature of any transition period post March 2019, companies may be forced to plan for the 'worst case' (i.e. Scenario 4) and some of the costs that we have identified may be incurred in advance of this deadline.

Finally, we have identified impacts on public health (focusing on delays in marketing authorisation; supervision and pharmacovigilance; crisis management and medicines shortages) and costs to pharmaceutical companies. There are many other areas likely to be affected that have not been assessed here, such as transparency initiatives for the results of clinical trials, prices of medicines, or the long term implications for the competitiveness of the UK as a life sciences base. These are important issues but were not within the scope of this study.

1. INTRODUCTION

Following the referendum on the withdrawal of the United Kingdom (UK) from the European Union (EU), the UK government triggered Article 50 of the Treaty of the European Union procedure in order to withdraw both from the EU and the Single Market (commonly known as Brexit). Brexit will mean changes to the established relationships between the UK and the EU covering the development, authorisation and supervision of medicines, as well as trade between the UK and other EU member states. Such changes are likely to have a significant impact on public health in both the UK and the remaining 27 countries of the EU and the non-EU members of the European Economic Area (EU27/EEA). Pharmaceutical companies will have to comply with the new legal requirements associated with the withdrawal, which will not be without cost. The purpose of this report is to identify, and where possible quantify: (i) the likely effects on public health in both the UK and the EU27/EEA; and (ii) the economic consequences for pharmaceutical companies.

The impact of Brexit will be highly dependent on the nature of any agreement resulting from the negotiations between the UK and the EU27/EEA, and the extent that the UK is involved in the future EU public health activities related to the authorisation and supervision of medicines for human use (including but not limited to the European Medicines Agency (EMA) and to the decentralised procedures activities). At the time of writing (October 2017) these relationships are not yet defined. As such, the consequences of Brexit were assessed according to various scenarios. The scenarios are described in Section 2.1 of this report.

1.1. Public health implications

The public health impacts considered within this report are those which will arise due to legal and regulatory changes associated with Brexit, relating to the development, authorisation and supervision of medicinal products for human use in the UK and the EU27/EEA. These issues were identified in the Health Committee's inquiry and annexed to the letter from MP Dr Sarah Wollaston to the Health Secretary of State Rt Hon Jeremy Hunt (Wollaston, 2016) (see the Technical Annex for more details). Specifically, we analysed the following:

- Possible delays in marketing authorisation for medicines;
- The effects on supervision activities and pharmacovigilance, specifically signal detection and the conduct of Post Authorisation Safety Studies (PASS);
- Incident and crisis management;
- Public health threats (such as pandemic influenza);
- Possible medicines shortages;
- The supply of medicines as a result of changes to trade and supply chains.

We sought to consider the effects of each of these consequences for the EU27/EEA as well as the UK.

1.2. Economic implications for pharmaceutical companies

In order to identify and measure the economic consequences of Brexit from the perspective of pharmaceutical companies we considered costs associated with:

- Changes to the supply chain, such as:
    - batch testing for products imported into the EU from third countries;

    - batch release of products to be distributed and used in the EU;
    - new import and export procedures between the EU27/EEA and the UK.
- Post-authorisation procedures and pharmacovigilance, such as:
    - the need for a Qualified Person for Pharmacovigilance (QPPV) in both the UK and the EU27/EEA[1];
    - reporting requirements for adverse reactions in the UK and signal detection activities;
    - resources for post-authorisation activities and procedures.

These key areas were identified through discussion with a steering committee and refined through a set of interviews with key representatives from the pharmaceutical industry.

1.3. Scope of the study

The scope of our analysis was determined by a project steering committee. The steering committee prioritised the specific impacts to be analysed as part of this study, but these should not be considered to be the only implications of Brexit for public health and pharmaceutical companies. The specific effects on orphan and paediatric medicines, as well as impacts on Health Technology Assessment activities and parallel regulatory-Health Technology Assessment advice, transparency initiatives for the results of clinical trials and prices of medicines are also important, but were not within the scope of this project. There will also be a significant impact on regulation - such regulatory changes are not the primary focus of this research, but given their importance, we provide a review of the key points in the Technical Annex.

The analysis in this report covers small and medium-size enterprises as well as major multinational pharmaceutical companies. The analysis is not limited to branded pharmaceuticals and includes the impact on generic medicines wherever possible.

1.4. Structure of this report

This report is based on a series of individual analyses undertaken to assess the potential impacts of Brexit according to various scenarios. The main body of this Executive Report focuses on the methods for developing the scenarios (Chapter 2), and on the impacts under each scenario (Chapter 3). The methods and results for each of the individual analyses are generally not scenario specific, and as such are confined to the Technical Annex.

[1] The EU legislation foresees that the holder of a marketing authorisation in the EU has permanently and continuously at his disposal the services of qualified persons (QP). The first QP is responsible for ensuring that each individual batch has been manufactured and checked in compliance with laws in force in the member state where certification takes place, in accordance with the requirements of the marketing authorisation (MA) and with Good Manufacturing Practice (GMP) (Article 4 of Directive 2001/83/EC). The second QP is the EU responsible person for pharmacovigilance (QPPV) who is responsible for the quality system and the pharmacovigilance activities of the marketing authorisation holder (Article 104(3)(a) of Directive 2001/83/EC).

2. METHODS

2.1. Scenarios

The impact of Brexit will be highly dependent on any trade deals agreed between the UK and the EU27/EEA and the extent to which the UK is involved in EU public health activities. In the absence of certainty around the form that these relationships will take, it was necessary to conduct our analyses against a range of possible scenarios. Each scenario was constructed with varying combinations of the various possible trade agreements and levels of public health cooperation. The scenarios are *not* intended to represent outcomes of the Brexit negotiations that are considered to be likely, appropriate, or acceptable. Instead, the scenarios have been constructed to explore the sensitivity of the various public health and economic impacts (identified in sections 1.1 and 1.2) to different combinations of regulatory and trade agreements.

The trade scenarios were informed by:

- The speech given by the UK Prime Minister at Lancaster House in January 2017;
- Two key reports from the House of Lords: Brexit trade in goods (European Union Committee, 2017) and Brexit the options for trade (European Union Committee, 2016);
- Discussions with representatives from industry, the Department for Exiting the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA);
- Information on EU trade agreements (obtained from the European Commission Directorate General Trade (DG Trade) website[2]).

The public health cooperation scenarios were based on:

- The current processes and procedures described in the EU legislation and in the implementing texts published in Eudralex[3];
- Existing Mutual Recognition Agreements (MRAs) negotiated between the EU and third countries (EMA, 2017);
- Discussions with representatives from industry, the Medicines and Healthcare products Regulatory Authority (MHRA), and EFPIA;
- The working assumptions made by the EMA: at the time of writing (October 2017), the EMA are working on the assumption that the UK will become a third country from 30 March 2019.

Four scenarios were developed in collaboration with the project steering committee. These scenarios reflect a wide range of levels of cooperation: from a full level of cooperation on public health and trade (Scenario 1) to a complete absence of cooperation (Scenario 4).

Scenario 1: Full cooperation between the MHRA and the EMA on public health; negotiation of a Free Trade Agreement (FTA) (tariffs and customs) between the UK and the EU27/EEA; adoption (within a transition period) of the existing FTAs negotiated between EU and third countries.

[2] http://ec.europa.eu/trade/index_en.htm [Accessed July 2017].
[3] http://ec.europa.eu/health/documents/eudralex_en [Accessed July 2017].

Scenario 2: Public health cooperation between the UK and the EU27/EEA via the referencing of EMA scientific opinions by the MHRA for the authorisation and supervision of medicines by the MHRA and negotiation of MRAs for inspections covering the quality and manufacturing procedures;[4] negotiation of an FTA (tariffs and customs) between the UK and the EU27/EEA; adoption (within a transition period) of the existing FTAs negotiated between EU and third countries.

Scenario 3: Public health cooperation between the UK (MHRA) and the EU27/EEA and MRAs as described above; trade cooperation regulated by the WTO MFN agreements (tariff and non-tariff barriers); no adoption of the existing EU FTAs within the transition period.

Scenario 4: No public health cooperation between the UK (MHRA) and the EU27/EEA (i.e. no MRAs); trade cooperation regulated by the WTO agreements (tariff and non-tariff barriers); no adoption of the existing EU FTAs within the transition period.

The scenarios are summarised in Table 1~~Table 1~~. Further detail is given in the Technical Annex. Note that these scenarios were considered to apply from the end of negotiations: Day one of Brexit on 30 March 2019.

2.2. Potential impacts under to each scenario

Various analyses were then undertaken to explore the potential impacts of Brexit under each scenario. These analyses were based on analysis of various datasets and expert interviews; detailed methods and results can be found in the Technical Annex. The results section (Chapter 3) of this report summaries the impacts under each scenario by drawing together the results of these individual analyses.

[4] The EU has signed mutual recognition agreements (MRAs) with third-country authorities concerning the conformity assessment of regulated products. Such agreements contain a sectoral annex on the mutual recognition of GMP inspections and batch certification of human and veterinary medicines. MRAs allow EU authorities and their counterparts to rely on each other's GMP inspection system, share information on inspections and quality defects, and waive batch testing of products on import into their territories. A description of these agreements is published on the EMA website at the following URL http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001843.jsp&mid=WC0b01ac058005f8ac (accessed on 14 September 2017).

Table 1: Plausible public health and trade scenarios used to assess the impact of Brexit

	Scenario 1	**Scenario 2**	**Scenario 3**	**Scenario 4**
Public Health Cooperation	**Full cooperation between the MHRA and the EMA on public health.**	**The MHRA would implement a standalone regulatory system; manufacturing procedures would be covered by a MRA (excluding the recognition of batch release).**	**As for Scenario 2.**	**The MHRA would implement a standalone regulatory system; Manufacturing procedures would not be covered by an MRA.**
Clinical development of medicines	The UK remains aligned with the EU on clinical trial regulations. The MHRA would be involved in all EMA pre-authorisation activities.[5]	The UK remains aligned with the EU on clinical trial regulations.	As for Scenario 2.	As for Scenario 2.

[5] These pre-authorisation activities are described in the Technical Annex.

Manufacturing and supply chain	Inspections (GMP, GCP), certificates of compliance and the release of batches would be mutually recognised. The qualified person must be located in the EU27/EEA but would rely on testing procedures conducted in the UK. The UK would perform quality controls for the official release of batches (e.g. for biological medicinal products) on behalf of the EU27/EEA.	Inspections (GMP, GCP) and certificates of compliance would be covered by MRAs but batch testing and release would not be recognised and would have to be conducted by the QP, in the EU27/EEA. The UK would *not* perform quality controls for the official releases of batches (e.g. for biological medicinal products) on behalf of the EU27/EEA.	As for Scenario 2.	In addition to Scenario 2 impacts, certificates (GMP, GCP) and periodical inspections would not be mutually recognised.

Authorisation/ supervision of new products via the centralised procedure	MHRA fully involved in EMA evaluation and supervision activities including full membership of all the EMA scientific committees for human medicines and their working groups and CMDh. This would also cover decisions related to the CAT, CHMP, COMP, PDCO and PRAC committees. The core activities, documents and persons involved in the maintenance activities of the holders of a marketing authorisation could be located either in the EU27/EEA or in the UK (e.g. EU QPPV).	MHRA would implement a standalone regulatory system and would issue its own authorisations. However, MHRA would perform a targeted assessment following CHMP / CMDh opinion. The core activities, documents and persons involved in the maintenance activities of the holders of a marketing authorisation should be located in the EU27/EEA (and, for UK approval, in the UK).	As for Scenario 2.	The MHRA would issue marketing authorisations and conduct post-authorisation activities via an independent standalone procedure.
Authorisation of new medicinal products via the national procedures	MHRA would be fully involved in the decentralised and mutual recognition procedures in full cooperation with the CMDh.	Scientific opinions of the CMDh would also be referenced by the UK, followed up with a targeted assessment.	As for Scenario 2.	The MHRA would issue marketing authorisations and conduct post-authorisation activities via an independent standalone procedure.

Access to the EU IT public health network	The MHRA would be fully connected to the EU IT network, including access to EudraVigilance.	MHRA would not retain access the EU IT network including EudraVigilance.	As for Scenario 2.	As for Scenario 2.
Trade agreements	**FTA (tariffs and customs) between the EU and UK; transitional adoption[1] of the existing EU FTAs**	**As for Scenario 1.**	**UK has no access to the single market: trade cooperation regulated by the WTO agreements (tariffs); no transitional adoption of the existing EU FTAs.**	**As for Scenario 3.**
Parallel trade	Persistence of the parallel trade of medicinal products between the UK and the EU27/EEA.	As for Scenario 1.	Disappearance of the parallel trade of medicines between the UK and the EU27/EEA.	As for Scenario 3.

Abbreviations: CAT: Committee for Advanced Therapies; CHMP: Committee for Medicinal Products for Human Use; CMDh: Co-ordination group for mutual recognition and decentralised procedures for human medicinal products; COMP: Committee for Orphan Medicinal Products; EMA: European Medicines Agency; EU: European Union; FTA: Free trade agreement; GCP: Good clinical practice; GMP: Good manufacturing practice; IT: information technology; MA: marketing authorisation; MHRA: Medicines & Healthcare products Regulatory Agency; MRA: Mutual recognition agreement; PDCO: Paediatric Committee; PRAC: Pharmacovigilance Risk Assessment Committee; UK: United Kingdom; WTO: World Trade Organization.
Notes: [1]'Transitional adoption' refers to adoption of the FTAs within the transition period.

3. RESULTS

3.1. Public health impacts of Brexit

The four scenarios are associated with increasing public health impacts as the level of cooperation both from a trade and public health perspective decreases across the scenarios (from Scenario 1 to Scenario 4). The consequences are summarised in Table 2 and described in further detail below.

Table 2: Possible public health impacts of Brexit according to the scenarios

	Scenario 1	**Scenario 2**	**Scenario 3**	**Scenario 4**
Public Health Cooperation	**Full cooperation between the MHRA and the EMA on public health.**	**The MHRA would implement a standalone regulatory system; manufacturing procedures would be covered by a MRA (excluding testing and release of batches).**		**The MHRA would implement a standalone regulatory system; Manufacturing procedures would not be covered by an MRA (excluding testing and release of batches).**
Submission of marketing authorisation applications and authorisation of new medicines	Impacts mitigated by involvement of the MHRA in activities of the EMA scientific committees.	Delays in submissions of marketing authorisation applications for new medicinal products of two-three months (median seen in third countries). In addition, some products might never be authorised in the UK because of lack of any marketing authorisation submission (45% of applications had not been submitted to all three reference countries following submission to the EMA, at the time of our analysis).		

	Scenario 1	**Scenario 2**	**Scenario 3**	**Scenario 4**
Signal detection and management	No impacts.	Delays in the detection of new signals in the UK and EU27/EEA between one and two months (due to the loss of connection of the MHRA to the EU information technology public health network including EudraVigilance). Delays in the management of new signals (between two and five months) due to the absence of direct communication between MHRA, EU27/EEA regulatory authorities and other non-EU authorities (e.g. Food and Drug Administration, United States). The UK has detected the greatest number of signals of all member states since 2012; this expertise will no longer be directly and immediately available to the EU27/EEA. The same is true of the availability of EU27/EEA experience to the UK.		
Post-authorisation safety studies	No impacts.	Both the UK and the EU27/EEA face the loss of expertise in their respective Regulatory networks and a loss of resources for the conduct of PASS. The UK contains the highest number of centres for the conduct of pharmaco-epidemiology studies (35; 22%). The UK is also the country in which the highest number of PASS are conducted (164; 50%).		
Emerging risks and public health threats (pandemic influenza)	No impacts.	Delays in communication in case of emerging risk or crisis management situations resulting in delays in regulatory action. Inefficient coordination linked to the duplication or divergence of requirements in case of public health threat (e.g. pandemic influenza).		

	Scenario 1	**Scenario 2**	**Scenario 3**	**Scenario 4**
Shortages in medicines	No impacts. Assuming that the FTA allows for the parallel trade of medicines between the UK and the EU27/EEA.	Possible shortages of medicines (in the UK for the products manufactured in the EU27/EEA and in the EU27/EEA for the products manufactured in the UK) linked to the absence of mutual recognition of the batch release between the UK and the EU27/EEA.	Consequences as described in Scenario 2 plus: Disappearance of the parallel trade of medicines between the UK and the EU27/EEA. Our analysis confirms the UK as a major importer and exporter of pharmaceutical products. The UK imports around 54% of its pharmaceuticals from Germany, the Netherlands and Belgium and exports 48% of its medicines to Germany, the Netherlands and France. Customs delays and/or tariff measures that complicate the movement of this quantity of products between the UK and the EU27/EEA could have substantial implications for public health in both jurisdictions.	Consequences as described in Scenarios 1-3 plus: The shortages could be further aggravated by the additional hurdles linked to the absence of an MRA between the UK and the EU27/EEA.

Abbreviations: EU27/EEA: The remaining countries of the EU and the European Economic Area; EU; European Union; MRA: mutual recognition agreement; PASS: post-authorisation safety study; UK: United Kingdom.
Notes: See Table 1 and the Technical Annex for more detail on the scenarios.

3.1.1.Public health consequences associated with Scenario 1

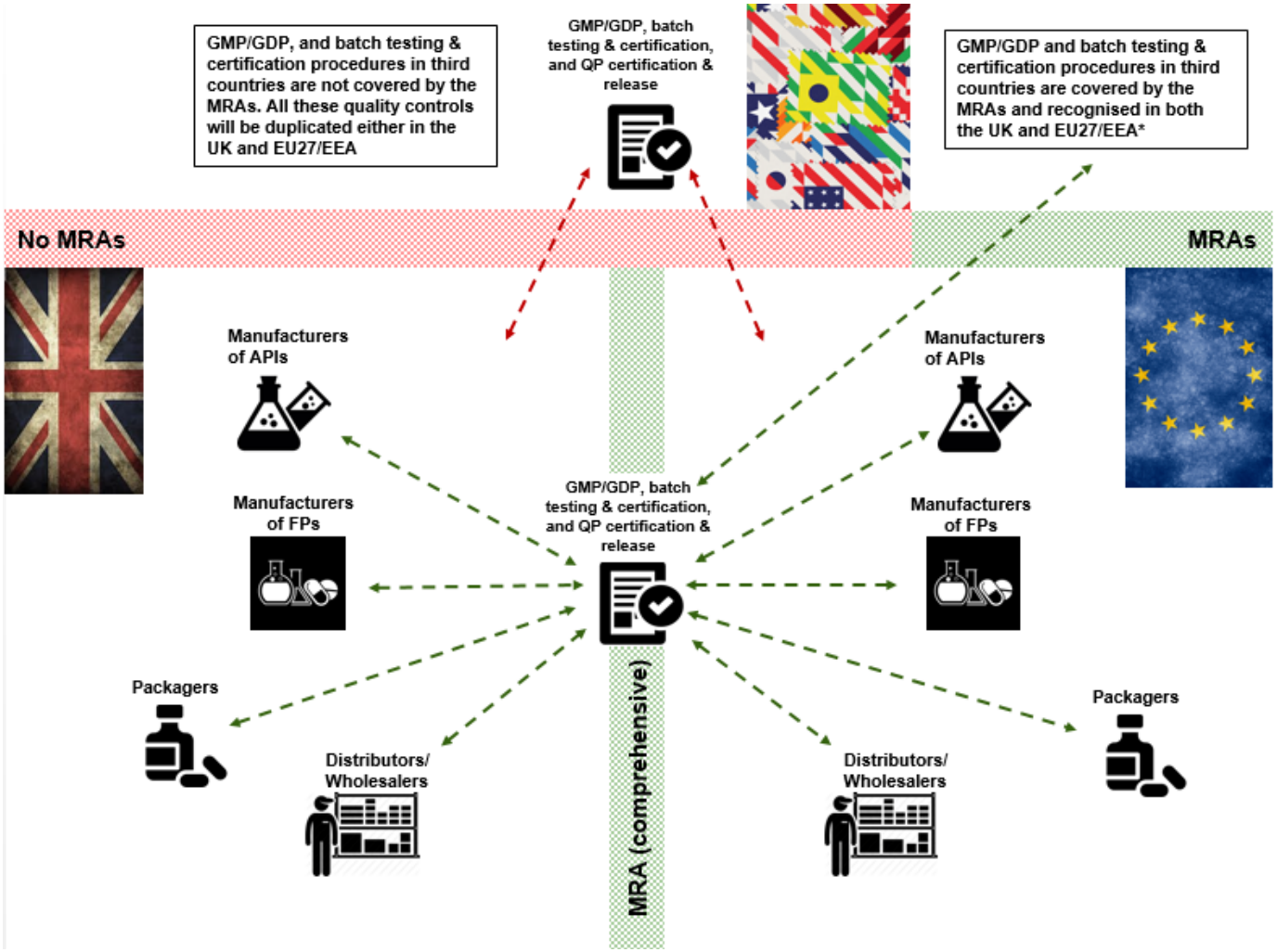
We assume that impacts on centrally authorised products, supervision and pharmacovigilance activities, crisis management and public health threats are minimal in Scenario 1, due to the direct involvement of the MHRA in EU public health activities.[6]

In addition, given that the inspections and releases of batches conducted either in the EU27/EEA or in the UK would be mutually recognised, no changes to the supply chain will be required. Figure 1 and Figure 2 show the regulatory clearance and quality controls and the UK-EU27/EEA trade relationship under Scenario 1 respectively.

In this scenario we assumed that the role of parallel trade would not change following Brexit. Although we note that this a strong assumption, the legality of parallel imports will depend on the terms of the FTA negotiated between the UK and the EU27/EEA (Bart, 2008; Mukhopadhyay, 2016). Therefore, under this scenario we would not expect to observe medicines shortages resulting from the loss of the freedom of circulation of goods between the UK and the EU27/EEA.

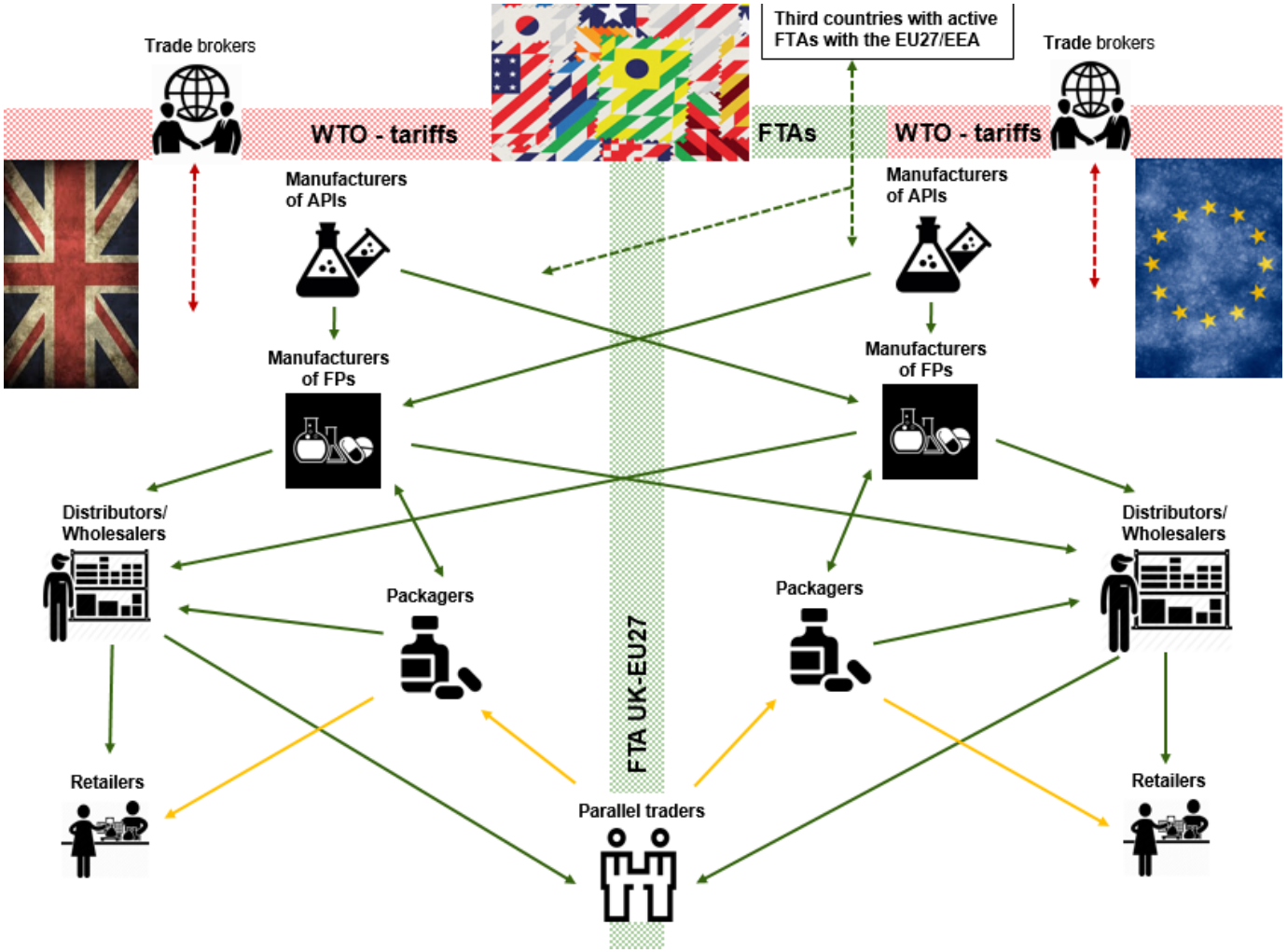
[6] Scenario 1 was designed to minimise the public health consequences of the withdrawal of the UK from the EU, and as such we have assumed that the full involvement of the MHRA in the activities of the EMA scientific committees would mitigate all public health impacts. This assumption was made for simplicity and to provide a reference point against which the other scenarios could be compared (as noted in Section 1 of this report, the scenarios are not intended to represent outcomes of the Brexit negotiations that are considered to be likely, appropriate, or acceptable. Instead, the scenarios have been constructed to explore the sensitivity of the various public health and economic impacts to different combinations of regulatory and trade agreements). Whilst it is correct that the public health impacts are likely to be much reduced compared to the other scenarios, in reality Scenario 1 would still involve underlying legal changes that *could* produce some of the impacts that are described in later scenarios (for example delays in the submission of marketing authorisations), albeit to a lesser extent.

Figure 1: Regulatory clearance and quality controls under Scenario 1



Notes: GMP and GDP certifications and inspections as well as batch certificates issued by manufacturers are mutually recognised. Batch certificates issued by manufacturers will be mutually recognised between the UK and the EU27/EEA as well as all batch testing and release activities performed by the National Competent Authorities of either the UK or EU27/EEA. For a more detailed explanation of this diagram see the Technical Annex.
*Countries with which the EU has currently active MRAs are Australia, New Zealand, Canada, Japan, Israel, Switzerland and the US.

Figure 2: UK-EU27/EEA trade under Scenario 1



Note: Solid green lines reflect trade between the UK and the EU27/EEA as well as economic flows between intra-country supply chain stakeholders. Solid yellow lines reflect parallel trade between countries of the EU27/EEA and the UK under the FTA. Dashed green lines reflect trade between the UK/EU27/EEA countries and countries with which the EU has FTAs. Dashed red lines reflect trade under WTO rules with no established FTA. For a more detailed explanation of this diagram see the Technical Annex.

3.1.2.Public health consequences associated with Scenario 2

Regulatory impacts

Under this scenario, changes to the current regulatory procedures governed by EU Regulations (orphan, paediatric, advanced therapy medicinal products, registration and supervision of clinical trials, support to small and medium size enterprises) may be anticipated unless these Regulations are transposed in internal law in the repeal bill. See the Technical Annex for further details.

Centrally authorised products

For the products that are currently authorised in the EU (those that received a marketing authorisation via the centralised procedure between 1995 and July 2017):

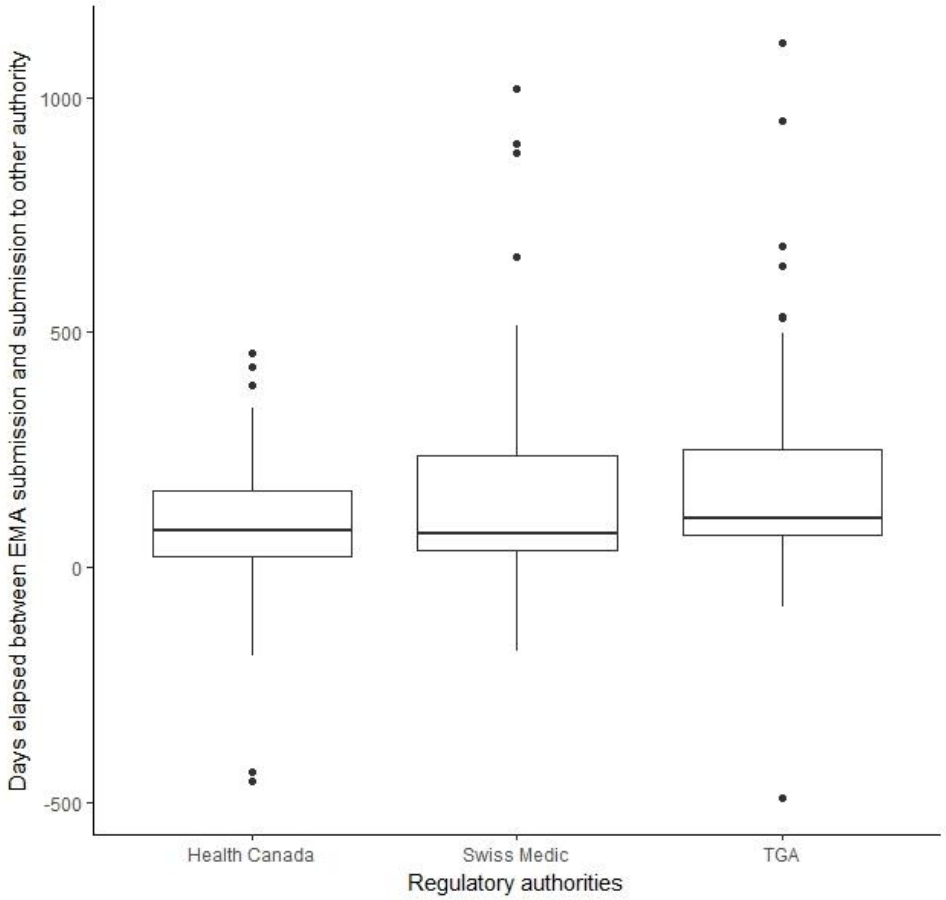
- The effect for the UK is that a transposition into UK law will have to be performed for 978 medicinal products which received a marketing authorisation via the centralised procedure between 1995 and July 2017.
- The effect on the EU27/EEA is that the marketing authorisation holder will have to be transferred from a UK holder to a EU27/EEA-based holder for over one third of these products (361; 37%).

For the products which will be authorised after the withdrawal of the UK, Scenario 2 could lead to a lack of submissions and delays in submissions of marketing authorisation applications compared to Scenario 1:

- The median lag of submission could be 2-3 months (based on existing submission delays in third countries for centrally authorised products containing a new active substance – see Figure 3). Note that this is shorter than other estimates reported in the literature (Campbell 2017; Fahy and Hervey 2017; Gulland 2017a; Gulland 2017b; Hatswell 2017; Tryl 2016);
- 5-15% of applications could be submitted more than a year after the EU27/EEA submission;
- Some products might never be authorised in the UK because of lack of any marketing authorisation submission (45% of applications had not been submitted to all three reference countries following submission to the EMA at the time of our analysis[7]);
- The MHRA would face a sudden increase in workload in procedures involving human medicinal products, this increased workload could subsequently increase the assessment timelines.

[7] No marketing authorisation application was submitted in any of the three countries in 15 instances (15% of the products), and an application was submitted in only one or two of these countries in an additional 30 cases. See Technical Annex for more details. Data correct up to the end of 2016 for all products submitted to the EMA during 2013-2015. We acknowledge that some applications may have been submitted during 2017, or may be submitted in future. In these cases they will represent delayed submissions rather than non-submissions.

Figure 3: Boxplot of the distribution of the marketing authorisation submission gaps (days), 2013-2015



Source: Centre for Innovation in Regulatory Science. Note one outlier submitted to Health Canada 5103 days before the EMA is not shown.

Supervision and pharmacovigilance activities

The loss of access to the EU IT network of public health, including EudraVigilance, could mean that detection and management of some new safety signals of public health relevance could be delayed both in the UK and in the EU27/EEA.

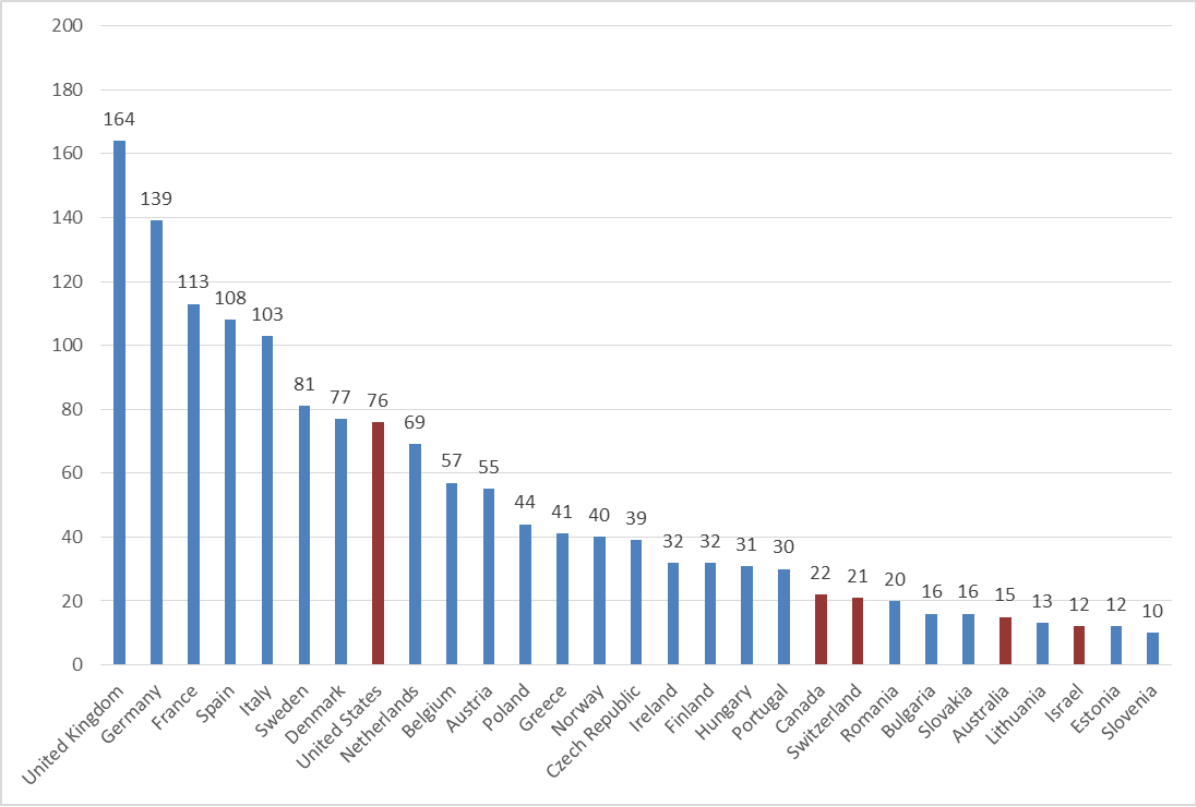
Since the implementation of new EU legislation on pharmacovigilance in July 2012, 364 signals have been detected, prioritised and assessed by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). Of these, 186 (51%) were identified by EU member states (the others were via the EMA), 39 of which (21%) were identified by the MHRA. The MHRA was the leading member state in terms of number of signals detected and discussed by the PRAC (see Technical Annex).

We estimate delays of two to five months for detection, and two to five months for publication of recommendations relating to safety signals under Scenario 2, based on existing delays with third countries (see Technical Annex). These delays could apply to the UK and/or the EU27/EEA, depending on where the signal is originally detected. The high proportion of signals detected by the UK's MHRA indicates that the impact could also be significant for the EU27/EEA. Under this scenario, the UK will have lost access to EudraVigilance, the ability to detect new signals in the UK will also depend on the reporting requirements of Individual Case Safety Reports and suspected unexpected serious adverse reactions to the MHRA after Brexit.

We assume that the withdrawal of the UK from the EU is also likely to induce delays in the exchange of safety information relating to incidents associated with the use of medicinal products (e.g. quality defects, pharmacovigilance information) and consequently result in delays in the management of these incidents in the future. We also highlight that the UK would have to negotiate public health (confidentiality) arrangements for the exchange of information concerning these signals with regulatory agencies from third countries like the Food and Drug Administration in the United States. The EU27/EEA already has these in place.

The UK is the country which contains the highest number of EU centres of pharmaco-epidemiology (35; 22% of 161). These centres include pharmacoepidemiology resources that are used globally (see Technical Annex). The UK is also the country in which the highest number of PASS are conducted; nearly 50% of PASS (164 out of 331) were conducted in the UK (see Figure 4). This confirms the strength of the UK in active pharmacovigilance activities and thus demonstrates that there will be public health implications for the EU27/EEA as well as the UK under Scenario 2.

Figure 4: Number of PASS included in the risk-management plans of products (authorised in the EU) conducted in the different countries worldwide



Source: European Medicines Agency, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance register. For more details see the Technical Annex. Note: bars corresponding to the EU countries are in blue. The bars corresponding to the non-EU countries are in red. The countries in which less than 10 studies are conducted are not included in the graph.

Scenario 2 is also likely to lead to some duplication of work, and/or possible divergence of requirements, in particular for the following activities and procedures:

- The establishment of the pharmacovigilance system and the creation and maintenance of a pharmacovigilance master file separately in the EU27/EEA and in the UK;

- The reporting requirements and signal detection activities supported by EudraVigilance and the UK equivalent;
- The submission of Periodic Safety Update Reports and risk-management plans; and
- The conduct of pharmacovigilance inspections.

Concerning the specific function of QPPV, Scenario 2 may pose problems for pharmaceutical companies that will need to either relocate or recruit additional adequately qualified and experienced persons who will be able to assume these functions. As of the 15th May 2017, 153 QPPV were located in the UK out of 1,205 EU QPPV across the EU. It is also anticipated that companies may have to have two different qualified persons at their disposal, one person located in the EU27/EEA and one person in the UK. This situation will complicate and may slow down the pharmacovigilance communication channels within the companies and therefore, consequently possibly delay the communication with EU27/EEA and UK regulatory authorities.

Scenario 2 could also result in differences and divergences in the scientific assessments concerning new signals, emerging risks and public health threats, regulatory procedures such as periodic safety update reports and PASS, and pre- and post-authorisation procedures. Expert interviewees emphasised that convergence of requirements would be important for minimising the burden for companies. We suggest that convergence is also important from a public health perspective, to ensure relevance of PASS across different countries.

Incident and crisis management

In terms of emerging risks or crisis management, it is likely that the UK would be excluded from the EU Regulatory Network Incident Management Plan under Scenario 2. This could lead to delays in communication around crisis management between the EU27/EEA and the UK, leading to delays in regulatory action in the EU27/EEA. Based on the number of referral procedures and Class 1 recalls seen in recent years, it would appear (see Technical Annex) that the EMA may use the incident management plan on average 9-10 times a year. Delays in communication, and therefore management, or these signals could therefore have important implications for public health in both the EU27/EEA and the UK. This said, should the risks be serious, we assume that the EMA would also make a public announcement.

Public health threats (pandemic influenza)

The EMA supports global efforts to respond to existing and emerging public health threats. Inefficient coordination could also have further public health effects if a public health threat (e.g. pandemic influenza) were to arise (see Technical Annex for a discussion of this issue). As above, should the risks be serious, we assume that the EMA would also make a public announcement.

Shortages of medicines

In this scenario we assumed that the role of parallel trade will not change following Brexit, although we note that this will depend on the terms of the FTA negotiated between the UK and the EU27/EEA. Therefore, under this Scenario we would not expect to observe medicines shortages resulting from the loss of the freedom of circulation of goods between the UK and the EU27/EEA.

However, the loss of mutual recognition of the release and official release and testing of batches could introduce some important disruptions in the supply chain of medicines and in particular for biological medicinal products, especially if companies are not given sufficient time to relocate their testing facilities. The relocation or duplication of the batch release facilities (i.e. testing, official release, QP certification) both in the UK and in the EU27/EEA could introduce disruptions in the supply chain of medicines and lead to shortages, in particular during the implementation period when companies are in the process of relocating these facilities in the UK and in the EU27/EEA after 30 March 2019. Our analysis (see Technical Annex) suggests that:

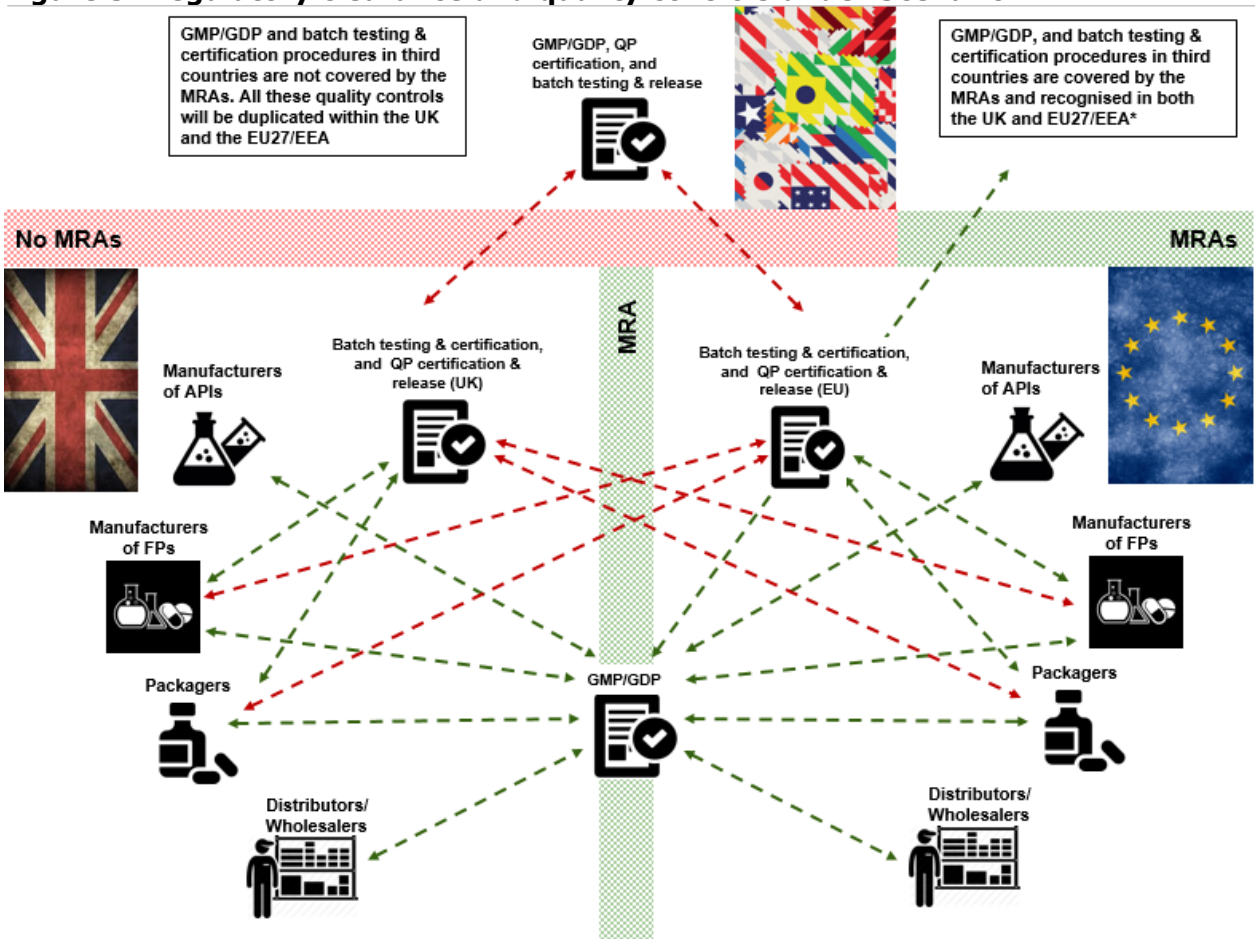
- Batch release facilities will have to be established in the EU for 96 (10% of 978) centrally authorised products;
- Batch release facilities will have to be established in the UK for 754 (77%) centrally authorised products;
- 128 centrally authorised products (13%) have batch release sites located both in the UK and in the EU27/EEA;
- The UK hosts the third highest number of sites involved in batch certification operations (231 sites), after France (321) and Germany (302);

Figure 5 from the perspective of an UK based manufacturer of finished pharmaceuticals, shows that there could also be implications for the following stakeholders within the supply chain that might further exacerbate issues with supply:

- Manufacturers of finished pharmaceuticals: batch testing, and QP certification and batch release facilities would have to be established in the EU27/EEA for the official batch release of finished products exported from the UK. The company must also retain batch testing facilities and a QP within the UK for batch testing and release within the UK market. Batch testing methods and release facilities are thus duplicated.
- Packagers: The QP should confirm compliance with national requirements for parallel importation and EU rules for parallel distribution. The QP must certify that any repackaging for parallel trade purposes of a batch already released has been performed in compliance with the marketing authorisation specifications and good manufacturing practice (GMP). Under Scenario 2 the QP doing the review of the repackaging must be located where the repackaging is completed (UK or EU27/EEA).
- Parallel traders: Repackaging (e.g. language, labelling) carried out on a batch already released must be reviewed by the QP who should confirm compliance with national requirements for parallel trade and EU rules for parallel distribution.

Our analyses suggest that the risk of shortages in the EU27/EEA may particularly affect vaccines, human plasma and blood-derived medicinal products, advanced therapy medicinal products and medicines including essential medicines manufactured or imported through the UK.

Figure 5: Regulatory clearance and quality controls under Scenario 2



Notes: Green lines reflect quality control and regulatory procedures that are mutually recognised (centralised) and not subject to duplications. In Scenario 2 this involves GMP/GDP certification and periodical inspections. Green lines also reflect all quality controls and regulatory procedures (not mutually recognised) performed internally within the UK (EU27/EEA) for finished medicines manufactured and distributed within the UK (EU27/EEA). Red lines reflect quality control and regulatory procedures that must be duplicated when companies export finished medicines from the UK/EU27/EEA to EU27/EEA/UK. This involves QP certification, batch testing and batch release which should be done by duplicate within the importing country either in the UK or in the EU27/EEA. For a more detailed explanation of this diagram see the Technical Annex.
*Countries with which the EU has currently active MRAs are Australia, New Zealand, Canada, Japan, Israel, Switzerland and the US.

3.1.3.Public health consequences associated with Scenario 3

The public health cooperation is the same here as for Scenario 2, thus any additional public health impacts in Scenario 3 are a result of changes to the trade agreements between the UK and the EU, which is assumed to be WTO MFN agreements[8], plus the zero-for-zero agreement with established countries[9]. Figure 6 shows the trade relationship between the UK and the EU27/EEA under Scenario 3. The figure shows that many stakeholder groups will be affected under Scenario 3.

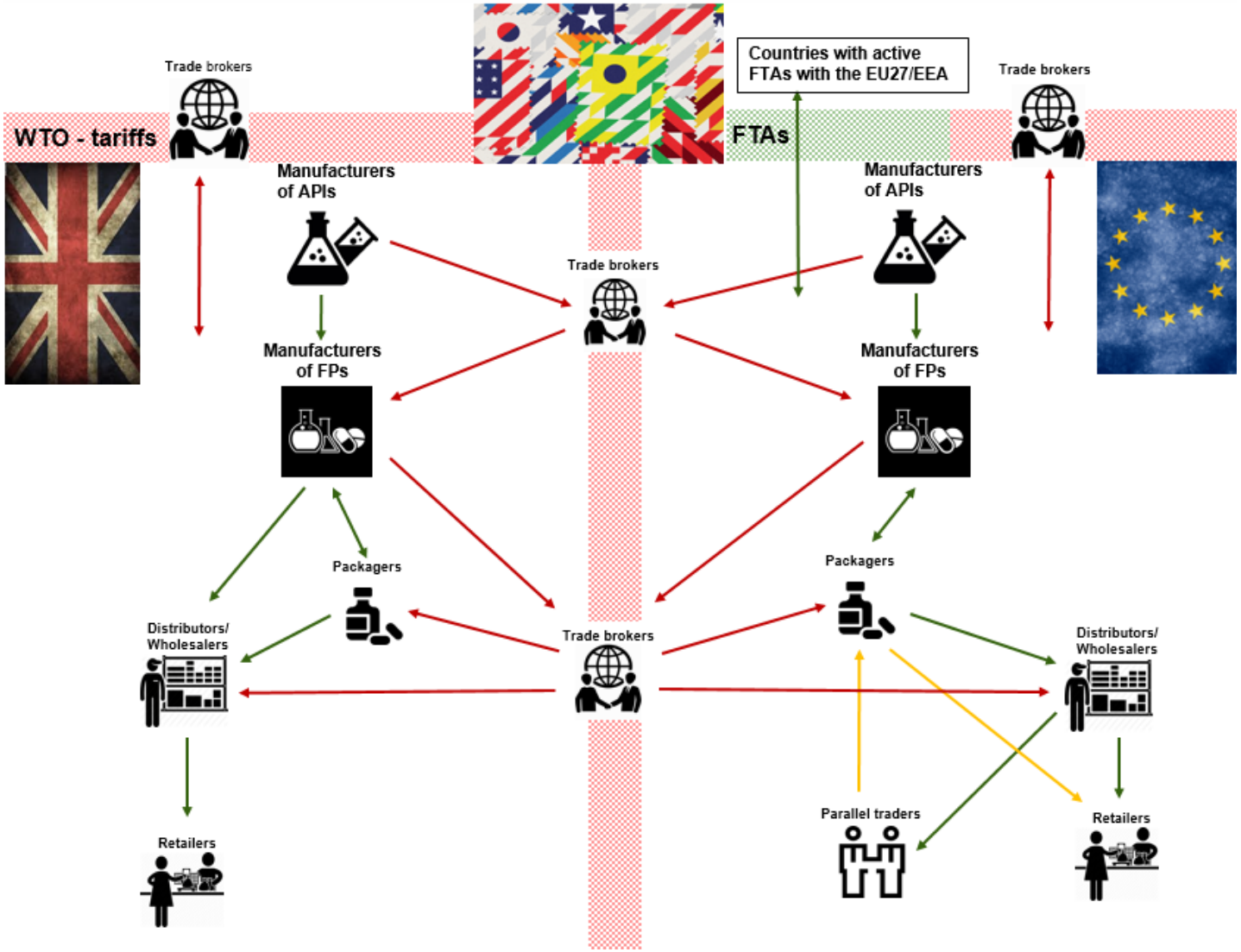
In particular the following impacts for stakeholders –from the perspective of a UK based manufacturer of finished products – are in addition to the supply chain impacts of Scenario 2 (related to changes in regulation):

- Manufacturers of Active Pharmaceutical Ingredients (APIs): EU27/EEA based manufacturers exporting APIs and intermediate products to the UK may be subject to tariffs and custom duties. This may put them at a competitive disadvantage compared to UK-based manufacturers of APIs. Additionally, the UK could impose non-tariff measures to APIs and intermediate inputs at customs that would involve delays in supply and additional costs at the custom clearance stage.
- Manufacturers of finished pharmaceuticals: tariff measures over the APIs and intermediate inputs will increase the cost of manufacturing final products, in addition non-tariff measures over the same intermediates could lead to delays and shortages in their supply. Furthermore non-tariff measures applied over final products exported to the EU27/EEA, could lead to delays and shortages which means that companies would face increased costs of storage, administrative paperwork and logistics of exporting.
- Distributors/Wholesalers: parallel trade would cease having a significant negative effect on UK-based Distributors/Wholesalers. EU27/EEA-based Distributors/Wholesalers will face both non-tariff measures and tariff measures and as a consequence the potential shortages, delays, administrative costs and custom duties they involve.
- Parallel traders: would lose the market as parallel trade would cease.

[8] MFN is a principle that ensures that countries do not discriminate between their trading partners by granting different – more or less beneficial – customs duty rates. Under MFN the most beneficial custom duty rate granted to a trade partner is automatically granted to all trade partners.

[9] Zero-for-zero agreements are multi-lateral FTAs applied only to specific goods by signing countries. In particular, for finished medicines there is an established zero-for-zero agreement (The Pharmaceutical Tariff Elimination Agreement; 1995) agreed by Australia, Canada, Czech Republic, European Communities, Japan, Norway, Slovak republic, Sweden, Switzerland, and United States. Tariffs under WTO MFN with non-signing countries can vary between 1-15%.

Figure 6: Trade under WTO MFN tariffs rules



Note: Green lines reflect trade flows (either domestic or international but covered by FTAs) which are not subject to tariffs or non-tariff measures. Red lines reflect the international trade flows subject to WTO tariffs and non-tariff measures. Yellow lines reflect the parallel trade or the re-importation of medicines between EU27/EEA countries. For a more detailed explanation of this diagram see Technical Annex.

Trading under WTO MFN agreements in this scenario means that imports and exports between the UK and the EU27/EEA will be subject to tariff and non-tariff measures. These measures can increase costs, administrative burden, and cause delays at customs. Major changes to the supply chain of medicines manufactured in the UK and in the EU27/EEA are therefore expected as a consequence of tariff and non-tariff measures[10].

If companies are not able to increase medicines prices, then manufacturing and exporting medicines will become less profitable. Manufacturers might consider not supplying medicines to the UK or to some EU27/EEA member states. Alternatively, if companies are able to increase prices, then importing countries could face affordability constraints and might decide to neither fund nor deliver to patients particular medicines. Changes modelled in Scenario 3 could therefore contribute to an increased frequency of medicines shortages. To provide a gauge of the magnitude of this problem, our analyses (see the Technical Annex for details) revealed that:

- The UK exports an average €65 billion worth of chemical and related products annually, of which 53% go to the EU27/EEA;
- In 2016, the UK exported €15,816 million of pharmaceutical products and imported €7,768 million;
- The UK imports around 54% of its pharmaceuticals from Germany, the Netherlands and Belgium;
- The UK exports 48% of its medicines to three EU countries: Germany, the Netherlands and France;
- The UK has the highest number of sites certified to import pharmaceuticals from third countries (357), ahead of Germany (262);
- The UK is specialised in the manufacturing, importation and batch certification of advanced therapy medicinal products (gene and cell therapies);
- 37% of the active substances processed in the UK are included in the World Health Organization's list of essential medicines.

These figures show that exports and imports of pharmaceuticals between the EU27/EEA and the UK are substantial[11]. Customs delays and/or tariff measures that complicate the movement of this quantity of products between the UK and the EU27/EEA could have substantial implications for public health in both jurisdictions, particularly if they exacerbate medicines shortages.

Parallel trade, which stems from the free movement of goods in the single market, is assumed to cease in this scenario, which could also contribute to medicines shortages in various countries of the EU27/EEA and/or the UK[12].

Finally, it not beyond reason that likely increases in the price of medicines (due to the additional burden on companies) could have secondary indirect public health repercussions on the EU27/EEA and UK healthcare systems, although it is difficult to estimate the magnitude of such an effect.

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[10] Baker McKenzie (2017) estimate that the total additional cost for the UK Health Care sector of tariff and non-tariff barriers would amount to £0.3bn, of which 57% is due to non-tariff barriers.
[11] Baker McKenzie (2017) estimates the total decrease of exports value for the Health Care sector due to the Brexit to be £2 billion (WTO MFN agreement scenario).
[12] Medicine shortages resulting from a reduction in parallel trade are more likely in countries with high prices, as they no longer benefit from the parallel trade from countries with lower prices. There could also be an increase in prices, although this effect is likely to be marginal given price regulation rules in most EU27/EEA countries.

3.1.4.Public health consequences associated with Scenario 4

Scenario 4 is likely to lead to the most significant impact on public health due to the complete absence of public health, customs and trade cooperation after Brexit. Figure 7 reveals the complexity of quality controls and regulatory procedures under Scenario 4.

It is clear that, in addition to the effects outlined for Scenarios 1-3 (including those related to changes in the trade agreements), the absence of an MRA complicates the GMP certification of manufacturing, importation and distribution sites. Our analysis showed that the UK hosts the second highest number of GMP sites (684) and manufacturing sites (444), second to Germany (969 and 695 sites, respectively). This means that the MHRA and EU27/EEA-based regulatory bodies would face a substantial increase in inspection workload under Scenario 4. In terms of the products affected, we found that GMP sites conducting importation of immunological (i.e. vaccines) and blood products (i.e. human blood derived medicinal products) are disproportionately located in the UK compared with the rest of the EU (see Technical Annex).

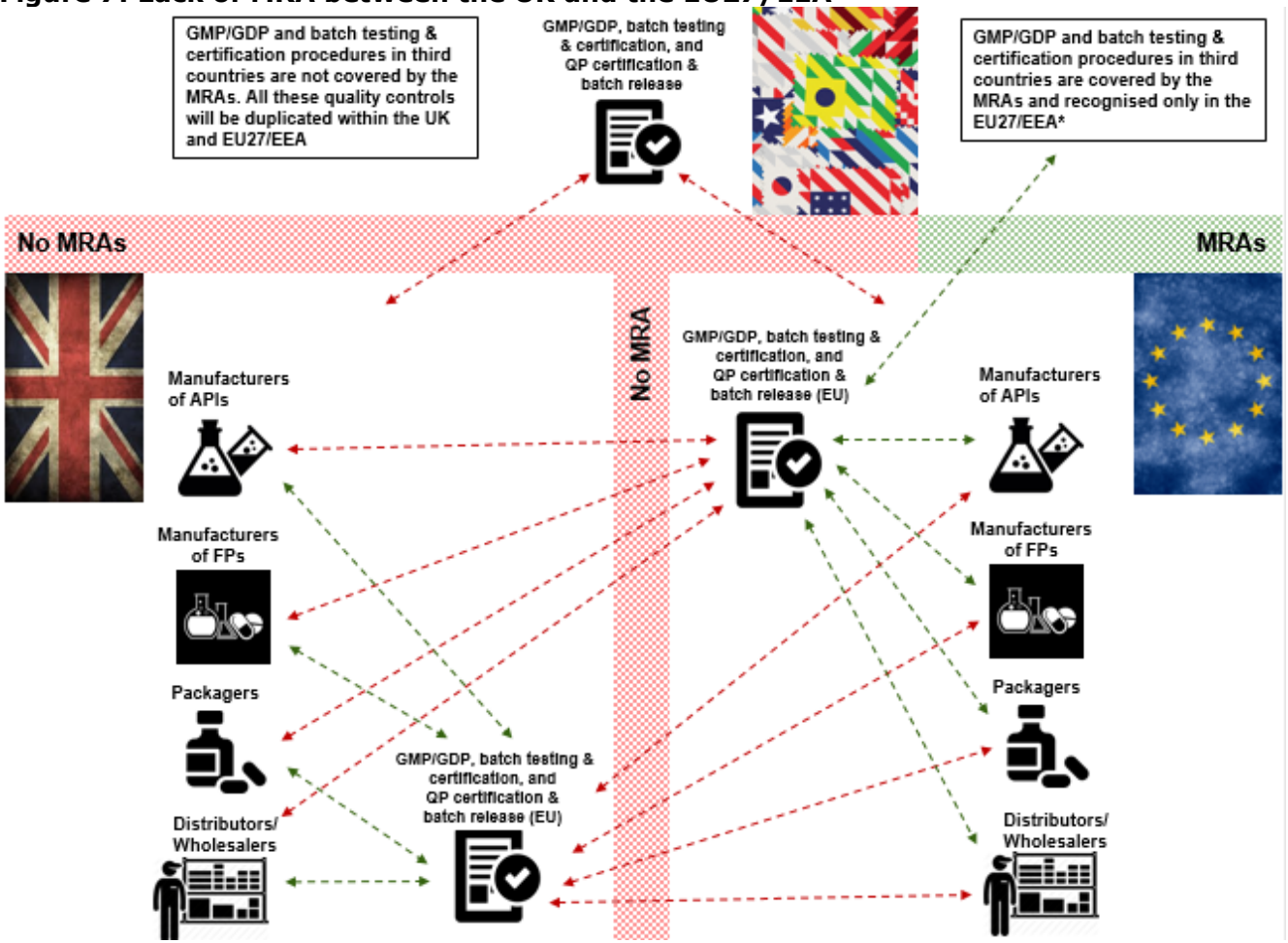
Expected impacts for each stakeholder in the supply chain of Scenario 4 (in addition to the impacts of Scenarios 1-3) are summarised below (UK-based stakeholders' perspective).

- Manufacturer of APIs: any EU27/EEA-based manufacturer of APIs shall accompany active substances with a written confirmation from the EU27/EEA National Competent Authorities (NCAs) specifying that the plant manufacturing the exported APIs is subject to a GMP control equivalent to those in the UK.[13] Additionally the QP of the UK-based manufacturer of finished pharmaceuticals must certify the validity of such a written confirmation. This would be a duplicated cost that would affect manufacturers of APIs in the EU27/EEA but could also be transferred in part to the manufacturer of finished pharmaceuticals in the UK.
- Manufacturer of finished pharmaceuticals: based in the UK, they would need to be GMP certified and periodically inspected by both MHRA and EMA (through one member state NCA) in order to supply medicines internally within the UK and export medicines to the EU27/EEA.
- Packagers: UK-based packagers would now be GMP certified by the MHRA in the UK and by the EMA (through an NCA) in the EU27/EEA. This would involve a duplication of costs.
- Distributors/wholesalers: UK-based distributors/wholesalers, and EU27/EEA-based, must be good distribution practice (GDP) certified by both the MHRA and the EMA (through a NCA) if they want supply medicines in both EU27/EEA and the UK. Additionally the QP must certify that medicines have been stored and distributed in compliance with the GMP standard of both regulatory areas. This involves a cost duplication. Additionally, in absence of MRA and FTA, may be unlikely that a UK-based distributor/wholesaler is able to export pharmaceuticals directly to a EU27/EEA retailer and vice versa.

A summary of all supply chain impacts by scenario is provided in Table 3.

[13] See EC regulation of importation of active substances (directive 2011/62/EU): https://ec.europa.eu/health/human-use/quality_en#gmp

Figure 7: Lack of MRA between the UK and the EU27/EEA



Note: Green lines reflect all quality controls and regulatory procedures performed intra-country to allow the supply of medicines within the domestic market. Red lines reflect quality controls and regulatory procedures performed between countries (UK and EU27/EEA) for the supply (export/import) of medicines. For instance, an EU27/EEA-based manufacturer of finished pharmaceuticals would need to be GMP certified by the EMA and perform the batch testing and release within the EU27/EEA to supply medicines in the single European market (green line) but it would need to duplicate all these controls within the UK to supply (export) medicines to the UK (red line). UK API manufacturers would only have to be GMP certified/inspected by EMA or an EU member state if the UK was not 'white listed' as a country of origin for APIs. For a more detailed explanation of this diagram see the Technical Annex.

*Countries with which the EU has currently active MRAs are Australia, New Zealand, Canada, Japan, Israel, Switzerland and the US.

Table 3: Summary of the impacts of Brexit on the manufacturing, distribution and supply of medicines as per scenario

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
	Cumulative impact →			
Manufacturer of APIs	No impact	No impact	Tariff measures and non-tariff measures applied to exported APIs and intermediate inputs	Duplication of written confirmation of compliance with GMP from the NCA QP of manufacturer of finished products must certify the validity of the written confirmation
Manufacturer of finished pharmaceuticals	No impact	Transfer of QP and batch release facilities to the EU27/EEA or the UK	Tariff measures and non-tariff measures applied to imported APIs and intermediate inputs Non-tariff measures s applied to exported finished medicines	Duplication of GMP certifications Duplication of inspections of GMP compliance Batch testing and certification
Packagers	No impact	QP of the EU27/EEA or the UK must certify (duplicated) any repackaging for the parallel trade	No additional impact: *Scenario 2* maintained	Duplication of GMP certifications Duplication of inspections of GMP compliance
Distributors / Wholesalers	No impact	Minimal impact	Parallel importations to the UK will cease (business lost for D/W) Tariff measures and non-tariff measures to the importations from the UK to EU27/EEA and vice versa	Duplication of GDP certifications Duplication of inspections of GDP compliance
Parallel traders	No impact	Duplication of reviewing and approval of repackaging activities for parallel trade by QP	Parallel trade with the UK will cease (market lost to EU27/EEA)	No additional impact: *Scenario 3* maintained
	Diminishing level of mutual regulatory acceptance and free trade agreements →			
Quality control and regulatory	Negotiation of MRA between the UK and the EU27/EEA (*comprehensive*) and continued UK participation in EU27/EEA third country MRAs	Negotiation of MRA between the UK and the EU27/EEA and continued UK participation in EU27/EEA third country MRAs	Negotiation of MRA between the UK and the EU27/EEA and continued UK participation in EU27/EEA third country MRAs	No requirement needed to fulfill
International Trade	Negotiation of an FTA and 'grandfathering' of EU27/EEA FTAs	Negotiation of an FTA and 'grandfathering' of EU27/EEA FTAs	No requirement needed to fulfill	No requirement needed to fulfill

Abbreviations: API: Active Pharmaceutical Ingredient; EU27/EEA: remaining countries of the EU and the European Economic Area; FTA: Free Trade Agreement; GDP: Good Distribution Practice; GMP: Good Manufacturing Practice; MRA: Mutual Recognition Agreement; NCA: National Competent Authority; QP: EU qualified person; UK: United Kingdom. Notes: See Table 1 and the Technical Annex for more detail on the scenarios.

3.2. Economic implications for pharmaceutical companies

In this section we present two hypothetical examples of companies, UK-based and US-based, to provide a 'ballpark' estimate of the cost of Brexit to companies. Costs have been taken from estimates collected from various companies via case studies (see Technical Annex for full details), and where necessary these have been scaled up by size to reflect an expected absolute estimate. We were not able to obtain estimates for every possible source of cost increase, and thus this is a conservative estimate of the cost of Brexit to companies.

3.2.1. Example 1: US-based large size company exporting/importing to the UK/EU through EU or UK

This example is based on Case Study 1 (see Technical Annex). Although the company is accessing the EU through the EU27/EEA and UK, its activity (and market) is mainly in the EU27/EEA. We assume all the implementation and maintenance costs of Case Study 1. Cost of trade under WTO MFN agreements have been also estimated (see Technical Annex for details).

The estimated cost of Brexit in year 1 for a large US-based company is assumed to be negligible if the negotiations lead to Scenario 1; £64.63 million under Scenario 2; £72.43 million under Scenario 3; £101.03 million under Scenario 4. See Table 4 for details.

To provide some context for these figures, we estimate that the £101.03 million cost in year 1 under Scenario 4 would be around 1.5% of EU revenue, and around 8% of UK revenue for this company.

3.2.2. Example 2: UK-based global pharmaceutical company exporting/importing to the EU27/EEA/rest of world through UK's current member state status

This example has been created based on Case Study 2 (see Technical Annex). Where cost estimates are sourced from Case Study 1 and are not volume related or variable we assume the same magnitudes. All maintenance costs estimates reported in Case Study 1 which are dependent on the volume of business or variable, have been scaled down proportionally to adjust for relative total turnover between case studies 1 and 2.

The estimated cost of Brexit in year 1 for a UK-based company is assumed to be negligible if the negotiations lead to Scenario 1; £42.2 million under Scenario 2; £72.6 million under Scenario 3; £86 million under Scenario 4. See Table 5 for details.

To provide some context for these figures, we estimate that the £86 million cost in year 1 under Scenario 4 would be around 2.3% of EU revenue, and around 6.07% of UK revenue for this company.

Table 4: Estimated cost of Brexit for a US-based large company

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Implementation costs	No impact	Establishing an EU27/EEA distribution operation for IMPs to supply clinical trials: £19.3 million Duplication of batch release sites and QP certification in UK/EU27/EEA: £6 million Transfer MAs to EU27/EEA/UK holder: £19 million (assuming 600 products affected) Maintain MAs in the UK: £2 million Change all the artwork (e.g. labelling, packaging) associated to MAs updates: £8.6 million	As for Scenario 2.	As for Scenarios 2 and 3, plus: Transfer batch testing facilities and methods to the UK (finished pharmaceuticals): £7 million Transfer batch testing facilities and methods into the EU27/EEA (finished medicines): £0.6 million GMP/GDP registering and certificating for UK CMOs: £0.4 million
Total implementation cost [1]	£0	£54.9 million	£54.9 million	£62.9 million
Maintenance costs	No impact	Sample management of imported products into the UK from the EU27/EEA: £1 million annually Personnel for the batch release of imported products into the UK: £3 million annually QP batch certification of products imported into the	As for Scenario 2, plus: Additional duty on current transactions including APIs imported to the UK: £7 million annually Broker fees: £0.8. annually	As for Scenario 3, plus: Testing finished products imported into the UK from the EU27/EEA: £17 million annually Testing finished products imported into the EU27/EEA from the UK: £3 million annually

		UK from the EU27/EEA: £1.9 million annually QP batch certification of products imported into the UK from the UK: £0.4 million annually Sample management and personnel (including QPs) for the batch release of exported products to the EU27/EEA from the UK: £3 million annually OMCL/NIBSC testing for vaccines/biologicals imported to the UK from the EU27/EEA: £0.4 million annually Additional cost for additional national MAs in the UK: £32,000 annually		Inspections for GMP/GDP: £0.6 million annually
Total maintenance costs [2]	£0	£9.73 million	£17.53 million	£38.13 million
Total cost in year one after Brexit: [1]+[2]	£0	£64.63 million	£72.43 million	£101.03 million

Note*:* Estimates presented in the table are based on the data collected from case studies 1 and 2. Data do not cover all potential sources of cost increases (see Technical Annex) and therefore are underestimating the total cost. As companies continue to refine their plans and estimates, the numbers from case studies will change. Abbreviations: CMO Contract Manufacturing Organisation; EU27/EEA: Remaining countries of the EU and the European Economic Area; GDP: Good Distribution Practice; GMP: Good Manufacturing Practice; IMP: investigational medicinal product; MA: Marketing Authorisation; UK: United Kingdom.
Notes: See Table 1 and the Technical Annex for more detail on the scenarios.

Table 5: Estimated cost of Brexit for a UK-based large company

	Scenario 1	**Scenario 2**	**Scenario 3**	**Scenario 4**
Implementation costs	No impact	Establishing an EU27/EEA distribution operation for IMPs to supply clinical trials: £19.3 million Duplication of batch release sites and QP certification in UK/EU27/EEA: £6 million Transfer MAs to EU27/EEA holder: £11.7 million Maintain the MAs into the EU27/EEA: £0.7 million Change all the artwork (e.g. labelling, packaging) associated to MAs updates: £4.5 million	As for Scenario 2.	As for Scenario 2 and 3, plus: Transfer batch testing facilities and methods into the EU27/EEA (finished products): £7 million GMP/GDP registering and certificating for UK CMOs: £0.4 million
Total implementation cost [1]	£0	£42.2 million	£42.2 million	£49.6 million
Maintenance costs	No impact	Sample management of imported products into the EU27/EEA from the UK: £220,000 annually Personnel resources for the batch release (including QPs) of imported products into the	As for Scenario 2, plus: Additional duty on current transactions: £23.5 million annually Additional duty on imports of APIs to the UK: £3.8 million annually	As for Scenario 3, plus: Testing finished products imported into the EU27/EEA from the UK: £5.9 million annually Inspections for GMP/GDP: £133,000 annually

		EU27/EEA: £660,000 annually QP batch certification of products imported into EU27/EEA the from the UK: £1.9 million annually OMCL/NIBSC testing for vaccines/biologicals imported to the EU27/EEA from the UK: £88,000 annually Additional cost for additional National MAs in the EU27/EEA: £32,000 annually	Broker fees: £193,000 annually	
Total maintenance costs [2]	£0	£2.9 million	£30.4 million	£36.4 million
Total cost in year one after Brexit: [1]+[2]	£0	£45.1 million	£72.6 million	£86 million

Note: Estimates presented in the table are based on the data collected from case studies 1 and 2. Data do not cover all potential sources of cost increases (see Technical Annex) and therefore total costs reported in this table are underestimating the true cost. Abbreviations: CMO Contract Manufacturing Organisation; EU27/EEA: Remaining countries of the EU and the European Economic Area; GDP: Good Distribution Practice; GMP: Good Manufacturing Practice; IMP: investigational medicinal product; MA: Marketing Authorisation; UK: United Kingdom.
Notes: See Table 1 and the Technical Annex for more detail on the scenarios.

4. CONCLUDING REMARKS

Our study demonstrates that the public health implications of Brexit will become more severe as public health cooperation and trade relationships lessen between the EU27/EEA and the UK (i.e. as we progress through the scenarios from Scenario 1 to Scenario 4). Importantly, the public health impacts may not just occur in the UK, but many may also be significant in the EU27/EEA.

The withdrawal of the UK from the EU will induce legal and regulatory changes both for marketing authorisation holders in the UK and in the EU27/EEA. In particular, companies will have to adapt their procedures or relocate some of their processes to comply with the new legal UK and EU27/EEA requirements for the authorisation and supervision of medicines for human use (for example recruitment of new QPs, relocation of the testing and batch release facilities, modification of the management of the supply chain of the medicines, management of parallel regulatory submissions). A transition period that gives sufficient time for companies to adapt to these important changes is important to avoid aggravating the public health impact of the withdrawal of the UK from the EU.

If comprehensive agreements (FTA and MRA) cannot be negotiated, the public health impacts will be felt in terms of reduced availability of medicines in the UK; delays of two to three months or more for marketing authorisation applications to be submitted in the UK; delays of up to five months in signal detection and management for pharmacovigilance; delays in the management of crises and public health threats in the UK and the EU27/EEA, and shortages of medicines in both jurisdictions (Scenarios 2-3).

If FTAs are not finalised by the end of the negotiation period (Scenario 3 and 4), companies will face tariff measures and non-tariff measures (including delays) which might lead to medicines shortages and thus have public health impacts in the UK and the EU27/EEA.

The estimated cost of Brexit in year 1 for a UK-based company is assumed to be negligible if the negotiations lead to Scenario 1; £39.1 million under Scenario 2; £66.6 million under Scenario 3; £80 million under Scenario 4. These costs could distort incentives for manufactures by reducing the attractiveness of manufacturing and investing in the UK. In addition, our analysis has assumed that these costs will accrue from March 2019. In reality, in the absence of a clear signal from Government about the exact nature of any transition period post March 2019, companies may be forced to plan for the 'worst case' (i.e. Scenario 4) and some of the costs that we have identified may be incurred in advance of this deadline.

Finally, it is worth noting that some of the consequences that we have outlined could be mitigated, in particular by the adoption of transitional arrangements which would give sufficient time to pharmaceutical companies to comply with the new legal requirements. In order to mitigate the absence or delays in submission of marketing authorisation applications for new medicinal products in the UK, it may be useful to explore the causes of these delays and absences, and seek to develop appropriate incentives to tackle them.

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Note: Further detail of data sources for each analysis is provided in the Technical Annex.