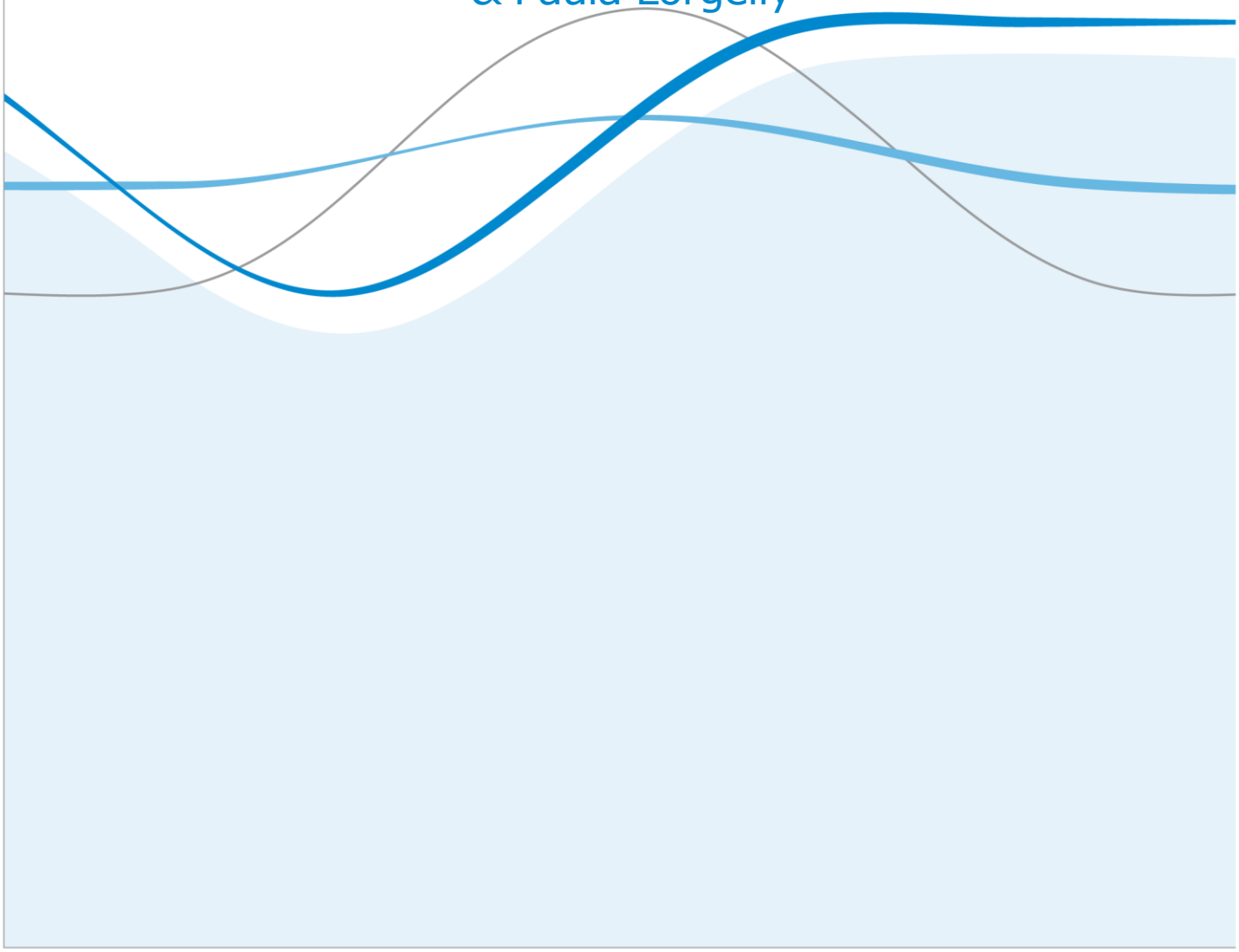
Office of Health Economics Consulting

Technical Annex

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



Technical Annex: Consequences of the Exit of the United Kingdom from the European Union and from the Single Market

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Office of Health Economics

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About This Report

This is the Technical Annex to a report 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.

The main report is entitled: Executive Report: Consequences of the Exit of the United Kingdom from the European Union and from the Single Market, and is available from the Office of Health Economics Website (www.ohe.org).

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We also acknowledge the contribution of Amy Livingstone for the data retrieval from the EudraGMDP database.

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ABBREVIATIONS

ABPI	Association of the British Pharmaceutical Industry
API	Active Pharmaceutical Ingredient
BIA	UK BioIndustry Association
Brexit	United Kingdom's withdrawal from the European Union
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
CIRS	Centre for Innovation in Regulatory Science
CMO	Contract Manufacturing Organisation
CMDh	Co-ordination group for mutual recognition and decentralised procedures for human medicinal products
DHPC	Direct Healthcare Professional Communication
DSUR	Development Safety Update Report
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU27/EEA	European Union with the remaining 27 member states following the withdrawal of the UK from the EU and the European Economic Area
EudraGMDP	EMA Database on manufacturing, import and wholesale-distribution authorisations
EudraVigilance	EU data processing network of individual case safety reports of adverse drug reactions
FDA	Food and Drug Administration, United States
FP	Finished pharmaceutical
FTA	Free Trade Agreement
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HTA	Health Technology Assessment
IT	Information Technology
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder

MCA	Medicines Control Agency
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
PSUR	Periodic Safety Update Report
PTEA	Pharmaceutical Tariff Elimination Agreement
QP	EU Qualified person (batch release)
QPPV	EU Qualified Person Responsible for Pharmacovigilance
RMP	Risk-management plan
SME	Micro, Small and Medium-sized Enterprises
SITC	Standard International Trade Classification
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Therapeutic Goods Administration, Australia
UK	United Kingdom
WHO	World Health Organization
WTO	World Trade Organization

ANNEX 1: AREAS FOR CONSIDERATION BY THE DEPARTMENT OF HEALTH IN BREXIT NEGOTIATIONS

Table A1: Areas for consideration by the Department of Health in Brexit negotiations

Topic Area	**Key considerations**	**Further detail**
Medicines, medical devices and equipment, human blood, cells and organs, clinical trials and health research	Continued availability of safe and effective medicines, devices and equipment and substances of human origin	• Marketing authorisation of medicines and future relationship with relocated EMA • Packaging, labelling and advertising • Arrangements for orphan medicines, medicines for paediatric use, status of homeopathic medicines, food/medicine interface, cosmetics/medicine interface • Recognition of certification system for medical devices and equipment, status of notified bodies which certify safety in remaining EU member states • Pharmacovigilance reporting mechanisms • Liability for defective medicines, devices and equipment • Securing safe supply chains, counteracting falsified and counterfeit medicines • Securing safe import of human tissue, safety alert mechanisms, non-commodification rules • Securing inward investment in new health technology development including access to funding, intellectual property protection, adherence to EU clinical trials and good laboratory practice law, EU data protection law • Implications for UK economy (including income of MHRA and other UK-based contractors and supplier) of relocation of EMA
	Continued participation of UK-based (public and private) organisations in Europe-wide clinical trials and other health research	• Ability of researchers in remaining EU member states to work in the UK

Source: Wollaston (2016).

ANNEX 2: REGULATORY CHANGES AND IMPLEMENTATION ISSUES

Methods

We conducted a bibliographical search of the documents (including official reports and official inquiries conducted by the UK Parliament), documents and pieces of legislation relevant to the withdrawal of the UK from the EU. The scope of our search included information on the trade agreements between the EU and third countries, and the pieces of legislation, guidance documents relevant to the development, authorisation and supervision of medicinal products in the EU. We also collected a selected amount of relevant articles from the general and medical press.

In a second stage, we conducted a concise assessment of the EU and UK legislation to highlight the main implementation issues associated with the withdrawal of the UK with respect to the implications for the supply chain of medicinal products in the EU (from the manufacturing of the Active Pharmaceutical Ingredient (API) to wholesale and parallel distribution).

Results

The pieces of legislation relevant to the development, authorisation and supervision of medicinal products for human use in the EU are included in Table A2.

Table A2: EU legislation relevant to the development, authorisation and supervision of medicinal products for human use in the EU

Law / Regulation	Area of impact
Directive 2001/83/EC, as amended Community code relating to medicinal products for human use	**Principal Legislation** for the regulation of medicinal products – general purposes, including marketing authorisation, manufacturing and importation, labelling, distribution, advertising, pharmacovigilance, falsified medicines and regulatory data protection (quasi intellectual property right)
Regulation (EC) 726/2004, as amended Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency	**Principal Legislation** for the regulation of medicinal products – EU centralised authorisation procedure and EMA functioning, including regulatory data protection (quasi intellectual property right)
Commission Regulation (EC) 507/2006 on conditional marketing authorisation for medicinal products for human use	Conditional Marketing Authorisation (centralised procedure)
Commission Regulation 1234/2008 on variations to marketing authorisations, as amended	Variations to Marketing Authorisations granted both centrally and nationally
Commission Regulation (EC) 2141/96 on transfer of marketing authorisations, as amended	Transfers of Marketing Authorisations (centralised procedure)
Regulation (EC) 1901/2006 on medicinal products for paediatric use and amending Regulation 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation 726/2004	Paediatric use – paediatric investigation plans, obligations, procedures and exclusivity extensions (SPC, orphan, regulatory data protection/PUMA)
Regulation (EC) 141/2000 on orphan medicinal products	Orphan medicines – centralised designation process, approval procedure, incentives and market exclusivity

Regulation (EC) 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation 726/2004	Cell, gene and tissue based products –classification, centralised marketing authorisation procedure and financial incentives
Regulation (EU) 536/2014 on Clinical Trials - repealing and replacing existing requirements established under Directive 2001/20/EC	Approval and conduct of clinical trials – future legislation - adopted by the European Parliament and Council, but not yet in force (expected by October 2018)
Directive 2001/20/EC on **Clinical Trials** **Directive 2005/28/EC** on **Good Clinical Practice** **Directive 2003/94/EC on Good Manufacturing Practice**	Approval and conduct of clinical trials – current Directives, transposed in UK law and in force, including authorisation of the manufacturing or importation of investigational products
Directive 2011/62/EU on Falsified Medicines and the Delegated Regulation	Implementation of safety features , due by February 2019
Directive 90/385/EEC on Active Implantable Medical Devices, **Directive 93/42/EEC on Medical Devices**, and **Directive 98/79/EC on In Vitro Diagnostic Medical Devices**	Medical devices legislation of relevance for companion diagnostics and combination products – current Directives, transposed in UK law and in force; expected to be replaced by 2 new EU regulations which are as yet not formally adopted and will take 3-5 years thereafter to be applicable
Regulation (EC) 469/2009 on Supplementary Protection Certificate for Medicinal Products	Key intellectual property right for medicines
Regulation supporting resourcing of regulatory agencies • Council Regulation (EC) 297/95 on fees payable to the European Agency for the Evaluation of Medicinal Products Fees payable to EMA for evaluation of medicinal products • Regulation (EU) 658/2014 on fees payable to EMA for conduct of pharmacovigilance activities	Resourcing of Agencies
Regulation regarding assistance from the EMA to SMEs and SME fees • **EC 2049/2005**	
Directive 2004/9/EC and 2004/10/EC – Good Laboratory Practice	
Directive 2009/35/EC on the colouring matters which may be added to medicinal products	
Directive 2010/63/EU on the protection of animals used for scientific purposes	Animal, experimental pharmacology and toxicology studies
Processes of importing live animals and animal products to UK via EU, and export from UK to EU. • Commission Decision 2007/275/EC • Regulation 1/2005 on the protection of animals during transport and related operations and amending Directives 64/432/EEC and 93/119/EC and Regulation 1255/97	Animal, experimental pharmacology and toxicology studies
Regulation on use, transport, technical requirements for use of human and animal tissues and cells. • Directive 92/65/EEC laying down animal health requirements governing trade in and imports into the Community of animals, semen, ova and embryos not subject to animal health requirements laid down in specific Community rules referred to in Annex A (I) to Directive 90/425/EEC (Balai Directive) • Directive 90/425/EEC concerning veterinary and zootechnical checks applicable in intra-Community trade in certain live animals and products with a view to the completion of the internal market	Research on human tissues, regulation of starting materials for ATMPs

• Directive (EU) 2015/566 implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells Directive 2012/39/EU amending Directive 2006/17/EC as regards certain technical requirements for the testing of human tissues and cells • Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells as amended below: • Directive (EU) 2015/565 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells	
Directive (EU) 2015/565 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells; **Directive (EU) 2015/566 implementing Directive 2004/23/EC** as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells	Standardisation; Manufacturing and research
Regulation 511/2014 on compliance measures for users from **the Nagoya Protocol on Access to Genetic Resources** and the Fair and Equitable Sharing of Benefits Arising from their Utilization in the Union	Research, ATMPs
Directive 2002/98/EC – human blood and blood components	
Regulation (EC) No 470/2009 – Residue limits	
EU Data Protection Legislation: **Directive 95/46/EC** on the protection of individuals with regard to the processing of personal data and on the free movement of such data: currently transposed in UK law, in force; **Regulation (EU) 2016/679** on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, repealing Directive 95/46/EC : **directly applicable from 25 May 2018;** **Directive (EU) 2016/680** on the protection of natural persons with regard to the processing of personal data by competent authorities for the purposes of the prevention, investigation, detection or prosecution of criminal offences or the execution of criminal penalties, and on the free movement of such data, and repealing Council Framework Decision 2008/977/JHA: **to be transposed into national law by 6 May 2018**	Not specific to life sciences, but important for clinical research, adaptive pathways and RWE

The exit of the UK from the European Union will lead to implementation issues associated with regulatory changes in the development, authorisation and supervision of medicinal products in the EU27/EEA and in the UK. These changes are linked to the following issues:

1. Unless the EU Regulations are transposed in the UK in the repeal bill, the provisions of EU legislation covered by Regulations will not apply to the UK after 30th March 2019. The activities and procedures described in Regulations include:

- Regulation (EC) No 726/2004 which describes the procedures for the authorisation and supervision of medicinal products for human (and veterinary) use in the EU (according to the centralised procedure).
- Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (and repealing Directive 2001/20/EC).
- Regulation (EC) No 141/2000 on orphan medicinal products and the Commission Regulation (EC) No 847/2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product.
- Regulations on paediatric medicines including Regulation (EC) No 1901/2006 and Regulation (EC) No 1902/2006.
- Regulation (EC) no 1394/2007 on advanced therapy medicinal products.
- Commission Regulation (EC) No 2049/2005 laying down the rules for Micro, Small and Medium-sized Enterprises (SMEs) (European Commission, 2005).

In addition, the European Medicines Agency (EMA) coordinates the activities of the co-ordination group for mutual recognition and decentralised procedures for human medicinal products (CMDh).

The European Medicines Agency (EMA) has put in place some mechanisms to support global efforts to respond to existing and emerging public health threats such as antimicrobial resistance, the risk of falsified medicines, biological and chemical threats and emergencies such as an outbreak or a pandemic (e.g. pandemic influenza, Ebola virus). In such circumstances, the EMA works closely with European and international partners, including the European Commission, the World Health Organization and European Union agencies, including the European Centre for Disease Prevention and Control, to address existing and emerging threats and during public health emergencies.

The EMA is also cooperating with international anti-counterfeiting trade agreements and other criminal-law instruments, such as the Council of Europe's Medicrime convention and the Organisation for Economic Co-operation and Development (OECD) project on counterfeiting and piracy.

2. Some procedures and activities currently laid down in the EU legislation, for example in Directive 2001/83/EC, as amended are specific to the EU, can only be conducted within the EU or depend on exchange of information within the EU or between EU member states, this includes for example:
   - The good manufacturing practice (GMP) inspections and GMP certificates need to be conducted and issued by EU national regulatory authorities unless the inspection is conducted by a third country with which the EU has negotiated a mutual recognition agreement (MRA).
   - The batch release of medicines and the official batch release of biological, immunological medicinal products and blood derivatives need to be undertaken in the EU and by EU competent authorities. The EU qualified person (QP), responsible for the quality controls and batch release needs to be located in the EU[1] (i.e. EU27/EEA after the exit of the UK from the EU). Switzerland is currently the only country for which an MRA recognises the batch releases and official batch releases conducted in that country.

[1] This requirement also applies to the QP responsible for the control and release of investigational medicinal products used in interventional clinical trials.

- The parallel Health Technology Assessment (HTA)-regulatory advice given to companies currently involves the EU HTA authorities and the Committee for Human Medicinal Products (CHMP).
- Some parts of the Common Technical Document are region specific (e.g. administrative information in module 1, summary of products characteristics, etc.).
- The clinical development of medicinal products should comply with EU scientific guidelines (quality, non-clinical, clinical efficacy and clinical safety, multidisciplinary).
- The marketing authorisations of the medicinal products authorised according to the centralised or decentralised procedures are only valid in the EU and therefore will have to be transposed in the UK law (likewise, the rapporteur and reference member states responsibilities of the UK for the centralised, decentralised and mutual recognition procedures will have to be reallocated).
- The EU QPPV needs to be located within the EU.
- The access and reporting rules of individual case safety reports or suspected unexpected serious adverse drug reactions in clinical trials (SUSARs) to EudraVigilance depend on the membership to the EU and location within the EEA or in third countries.
- The access to the EU regulatory databases (EudraGMDP, European Clinical Trials Database, EudraVigilance, Periodic Safety Update Report (PSUR) repository, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register, EPITT, etc.) is currently only granted to the EEA member states and may be denied to the Medicines & Healthcare products Regulatory Agency (MHRA) after 30 March 2019.

Unless specific confidentiality arrangements for the exchange of information are negotiated between the EMA and the MHRA, the reporting requirements and exchange of clinical safety and pharmacovigilance information (communication of emerging safety information, communication of signals detected by regulatory authorities, products defects) is likely to be channelled via the marketing authorisation holders (MAH).

ANNEX 3: SCENARIOS

A3.1. Scenario 1

Full cooperation on public health; negotiation of a free trade agreement (tariffs and customs) between the UK and the EU27/EEA; transitional adoption of the existing EU free trade agreements (FTAs).

Note: This scenario could accommodate an agreement by which the UK negotiate a new customs arrangement as considered by the Department for Exiting the European Union and recommended by the House of Lords (European Union Committee, 2016).

A3.1.1. Public health cooperation

In this scenario the UK operates within the EU27/EEA public health regulatory network.

This scenario involves direct involvement of the MHRA in the centralised, mutual recognition and decentralised procedures via work sharing procedures. This cooperation would also be covered by the negotiation of mutual recognition agreements (inspections) for the quality and manufacturing procedures.

Clinical development of medicines

Under this scenario, the UK would remain aligned with the EU on clinical trial regulations and processes of authorisation, supervision and reporting (including urgent safety measures). The Development Safety Update Reports (DSURs) would be submitted and assessed on a work sharing principle. The MHRA would have access to the Common European Submission Portal (see IT public health network).

In addition, the MHRA would be involved in the pre-authorisation activities including: the Paediatric Investigation Plans, Orphan Drug Designations, priority medicines designations, CHMP / Scientific Advice Working Party and EMA-Health Technology Assessment (HTA) parallel scientific advice.

The good clinical practice (GCP) inspections conducted by the MHRA would be recognised by the EU27/EEA (and vice-versa).

Manufacturing and supply chain

GMP and good distribution practice (GDP) requirements would be covered via mutual recognition agreements (MRAs) (see Doc. Ref.: EMEA/MRA/22/03 Final); the testing and release of batches conducted in the UK and in the EU27/EEA would be mutually recognised via this mutual recognition agreement. Therefore, the MHRA would therefore continue to carry out inspections (GMP and GCP) recognised by the EU27/EEA and the National Institute for Biological Standards and Control (NIBSC) would perform quality controls for the official releases of batches (biological medicinal products) on behalf of the EU27/EEA (and vice versa).

Under this scenario the territorial application of the MRAs would apply (tests and controls must be conducted depending whether the active substance and the finished product were manufactured in the EU or in a third country covered by an MRA) (see Doc. Ref.: EMEA/MRA/22/03 Final). The batch release and testing procedures could be performed in the UK, as a third country (the MRA would waive any requirements for batch testing of products on entry into their territories). The QP would have to be located in the EU27/EEA but could rely on testing procedures conducted in third countries covered by a

MRA including the UK. However, if the product was partially manufactured in a third country, the MRA would not apply.

Falsified medicines: the UK would have to comply with the provisions of the falsified medicines delegated regulation.

Authorisation and supervision of new medicinal products via the centralised procedure

This scenario would assume the following:

- The MHRA would be fully involved in the EMA evaluation and supervision activities including full membership of the CHMP and its working groups (including the Scientific Advice Working Party), Committee for Orphan Medicinal Products, Paediatric Committee (PDCO), Committee for Advanced Therapies (CAT) (as an active member or as an observer).
- The MHRA would take part in EMA maintenance (all post-authorisation procedures including variations, annual reassessments and renewals) and supervision activities of the Pharmacovigilance Risk Assessment Committee (PRAC) (signal management, risk management plan (RMP) and risk management activities and referral procedures) leading to harmonised decisions (e.g. RMP common to the EU27/EEA and to the UK).
- This scenario assumes that 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. access to the Pharmacovigilance database in a single point, EU Qualified Person Responsible for Pharmacovigilance (QPPV), pharmacovigilance master file, etc.).

Authorisation and supervision of centrally authorised products which received a marketing authorisation in the EU before 30 March 2019

This scenario would not require any transfer of marketing authorisations granted before 30 March 2019.

Authorisation of new medicinal products via the national procedures

In addition, under this scenario the UK/MHRA would be fully involved in the decentralised and mutual recognition procedures in full cooperation with the CMDh (e.g. work sharing agreement).

For the existing products, the UK would keep their responsibilities as Reference Member State for mutual recognition/decentralised procedures.

Access to the EU IT public health network

- Under this scenario the MHRA would be fully connected the EU telematics network (CESP, European Clinical Trials Database, EudraGMDP (database on manufacturing, import and wholesale-distribution authorisations), EudraVigilance Medicinal Product Dictionary, PSUR repository, Electronic Standards for the Transfer of Regulatory Information gateway).
- The MHRA would retain its access to EudraVigilance (i.e. this scenario consequently assumes that no changes to the sponsors of clinical trials, MAH and MHRA reporting obligations of SUSARs/ individual case safety reports would be introduced; the MHRA would be able to perform its signal detection activities on EudraVigilance and would exchange information on signals in line with the current procedures.

A3.1.2. Trade

This scenario assumes a free trade agreement (tariffs and customs) between the EU27/EEA and the UK and transitional adoption of the existing EU FTAs.

Under this scenario, the import and export of goods and services from the UK to the EU27/EEA would be covered by an FTA at the end of the negotiations (e.g. new customs arrangements or FTA similar to the CETA, which is the FTA negotiated between the EU and Canada). Therefore, the UK may keep the advantages of the single market (note: the negotiation of new customs arrangements would fall under this scenario).

The transitional adoption of the existing EU FTAs would mean that the UK would not lose the benefits of the FTA agreed or under ratification between the EU and other third countries:

- EU customs and union including Andorra, Monaco, San Marino and Turkey;
- European Economic Area (EEA);
- Preferential FTAs in place, Economic Partnership Agreements and Deep and Comprehensive Free Trade Areas with countries like South Africa, South Korea, and Algeria;
- Agreements awaiting ratification with countries like Canada and some African countries.

In particular, the FTA between the UK and the EU27/EEA would:

- have no customs duties;
- make it easier for EU firms to bid for UK public contracts and vice-versa;
- allow for the mutual recognition of inspections and certification procedures (e.g. MRAs).

The trade agreement would also cover the small and medium size enterprises (SMEs) designation and support through the life-cycle of development of new medicines.

A3.2. Scenario 2

Public health cooperation between the UK (MHRA) and the EU27/EEA via the referencing of EMA scientific opinions and mutual recognition agreements (inspections); negotiation of an FTA (tariffs and customs) between the UK and the EU27/EEA; transitional adoption of the existing EU FTAs.

This scenario would mimic the current level of public health cooperation between the EU/EMA and countries like Australia and New Zealand.

A3.2.1. Public health cooperation

The MHRA would reference the scientific opinions of the EU regulatory authorities in the field of authorisation and supervision of medicines. Manufacturing procedures would be covered by an MRA.

This scenario is based on a principle of the MHRA using the scientific opinions (or designations) given by the CHMP (or any other EMA's scientific committee) as a reference to issue their authorisations (including marketing authorisations) in the UK. Other activities (GMP, GCP and Pharmacovigilance inspections) would be covered by MRAs. The UK/MHRA would not retain its access to the EU IT Public health network and databases.

Clinical development of medicines

Under this scenario, the UK would remain aligned with the EU on clinical trial regulations and processes of authorisation, supervision and reporting.

Manufacturing and supply chain

The inspections (GMP and GCP) conducted by the MHRA and certificates for the releases of batches conducted in the UK and the EU27/EEA would not be mutually recognised. Under this scenario which only covers a "standard" MRA, the NIBSC would not perform quality controls for the official releases of batches (biological medicinal products) on behalf of the EU27/EEA. A QP would have to be located in the EU27/EEA and in the UK.

Authorisation and supervision of new medicinal products via the centralised procedure

Under this scenario, the MHRA would perform a targeted and accelerated assessment (compared to the current EU authorisation timelines) following the adoption of the CHMP opinion on the basis on a marketing authorisation application (Common Technical Document containing some regional information) and the CHMP opinion (and other procedural documents including for example assessment reports, list of questions, etc.) submitted by the Company. The MHRA would conduct this assessment during the European Commission's 67-days decision phase in order to minimise any delay in the granting of the authorisation between the EU and the UK. Consequently, this scenario could therefore lead to differences in the terms of the marketing authorisations (e.g. different indications or different product information, refusal of a marketing authorisation) or conditions of the marketing authorisations (RMP, legal status, post-authorisation commitments) between the UK and EU27/EEA, but differences would be expected to cover a limited number of medicinal products.

This would cover the EC, EMA decisions and opinions related to the activities of the following committees: CHMP, COMP, PDCO, PRAC and CMDh.

This scenario would reflect a closer level of cooperation than the one with third countries like Canada, Switzerland or Japan which have only negotiated cooperation agreements with the EMA (confidentiality arrangements) and mutual recognition agreements for the inspections.

Authorisation and supervision of centrally authorised products which received a marketing authorisation in the EU before 30 March 2019

This scenario would require the transfer of marketing authorisations granted before 30 March 2019 to a holder located in the EU27/EEA and in the UK.

Authorisation of new medicinal products via the national procedures

In addition, under this scenario, the scientific opinions by the CMDh would also be referenced by the UK which would conduct a targeted and accelerated assessment following the finalisation of the MRP/DCP.

Access to the EU IT public health network

Under this scenario the MHRA would not retain its access to the EU IT network incl. EudraVigilance (i.e. changes to the sponsors of clinical trials, MAH and MHRA reporting obligations of SUSARs/individual case safety reports would have to be introduced, the MHRA would not be able to perform its signal detection activities on EudraVigilance and

would have to implement new procedures of detection, exchange and management of signals with the MAHs and other competent authorities).

A3.2.2. Trade

The same trade agreement would apply as above (Scenario 1).

The transitional adoption of the existing EU FTAs would mean that the UK would not lose the benefits of the FTA agreed or under ratification between the EU and other third countries:

- EU customs and union including Andorra, Monaco, San Marino and Turkey,
- EEA,
- Preferential FTAs in place, Economic Partnership Agreements and Deep and Comprehensive Free Trade Areas with countries like South Africa, South Korea, and Algeria;
- Agreements awaiting ratification with countries like Canada and some African countries.

The trade agreement would also cover the small and medium size enterprises (SMEs) designation and support through the life-cycle of development of new medicines.

A3.3. Scenario 3

Public health cooperation between the UK (MHRA) and the EU27/EEA via the referencing of EMA scientific opinions and mutual recognition agreements (inspections); trade cooperation regulated by the World Trade Organization (WTO) most favoured nation (MFN) agreements (tariffs and non-tariff measures), no transitional adoption of the existing EU FTAs.

Public health cooperation is the same as in Scenario 2. The UK would face the same tariffs and barriers that other countries without an EU trade deal or bilateral agreements do, which means following WTO MFN agreements[2] and zero-for-zero agreements for finished pharmaceuticals[3]. Mutual recognition agreements were put in place on 1 January 1999 under this cooperation including GMP Inspection and Batch Certification to the MRA in relation to conformity assessment, certificates and markings.

A3.3.1. Public health cooperation

Same as Scenario 2.

A3.3.2. Trade

Conducted under the WTO agreements (MFN agreement for tariff and other non-tariff barriers, no customs agreement).

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[2] 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.

[3] 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%.

If no alternative trade arrangement is in place two years after Article 50 is triggered, UK-EU trade would by default take place under WTO MFN rules. As the UK is unlikely to be able to retain access to the EU's FTAs with third countries after Brexit, WTO MFN rules will also form the basis of the UK's trade with the rest of the world. But trading under WTO rules – often described as a fallback option – is not straightforward. The UK would have to establish its own schedules of concessions, and negotiate with the EU its share of tariff rate quotas and subsidies. While the technical details appear relatively straightforward, politics may intrude: negotiations with the EU and other WTO members could complicate this process, further adding to the uncertainty.

Under this scenario, in absence of a FTA, the import and export of goods and services would be regulated by the existing WTO MFN agreements (like it is currently with the import and export of goods and services with the US). Note: the UK would not be allowed to be involved in EU27/EEA public procurement procedures even as sub-contractors.

The UK would lose the advantages of the single market but also lose the benefits of the FTA agreed or under ratification between the EU and other third countries:

- EU customs and union including Andorra, Monaco, San Marino and Turkey;
- EEA;
- Preferential FTAs in place, Economic Partnership Agreements and Deep and Comprehensive Free Trade Areas with countries like South Africa, South Korea, and Algeria;
- Agreements awaiting ratification with countries like Canada and some African countries.

Under this scenario, it is understood that the UK would have to negotiate WTO schedules to trade with the third countries.

A3.4. Scenario 4

No public health cooperation between the UK (MHRA) and the EU27/EEA including no mutual recognition agreements (inspections); trade cooperation regulated by the WTO MFN agreements (tariffs and non-tariff barriers), no transitional adoption of the existing EU FTAs.

This scenario would cover the current cooperation between the EU and a third country with which the EU does not have any mutual recognition agreement covering the manufacturing activities. The UK would face the same tariffs and barriers that other countries without an EU trade deal or bilateral agreements do.

A3.4.1. Public health

Under this scenario, the MHRA as UK regulator could issue marketing authorisations via an independent standalone procedure (the submission of the marketing authorisation application would not depend on the EMA evaluation procedure).

Clinical development of medicines

Under this scenario, the UK would remain aligned with the EU on clinical trial regulations and processes of authorisation, supervision and reporting.

Manufacturing and supply chain

The inspections (GMP and GCP) conducted by the MHRA and certificates for the releases of batches conducted in the UK and the EU27/EEA would not be mutually recognised. The EU manufacturing, control and distribution procedures would have to be applied at all stages of the supply chain (manufacturing of the API, finished product, batch release, packaging and distribution). In particular, the batch release facilities would have to be (re)located in the UK and EU27/EEA.

Authorisation and supervision of new medicinal products via the centralised procedure

Under this scenario the MHRA would perform the post-authorisation maintenance, pharmacovigilance activities independently of the EU procedures.

Access to the EU IT public health network

Under this scenario the MHRA would not retain its access to EudraVigilance (i.e. changes to the sponsors of clinical trials, MAH and MHRA reporting obligations of SUSARs/ individual case safety reports would be introduced), the MHRA would therefore not be able to support its signal detection and management activities with EudraVigilance and would have to implement new procedures for the exchange information on signals.

Authorisation of new medicinal products via the national procedures

Under this scenario, the MHRA could issue marketing authorisations via an independent standalone procedure (the submission of the marketing authorisation application would not depend on the CMDh evaluation procedure).

Authorisation and supervision of centrally authorised products which received a marketing authorisation in the EU before 30 March 2019

This scenario would impose the transfer of marketing authorisations granted before 30 March 2019 to a holder located in the UK and the EU27/EEA.

A3.4.2. Trade

Under this scenario, in absence of FTA, the import and export of goods and services would be regulated by the existing WTO MFN agreements (like it is currently with the import and export of goods and services with the US). Note: the UK would not be allowed to be involved in EU27/EEA public procurement procedures even as sub-contractors.

The UK would lose the advantages of the single market but also lose the benefits of the FTA agreed or under ratification between the EU and other third countries (see above).

ANNEX 4: PUBLIC HEALTH ANALYSES

A4.1. Methods

A4.1.1. Number of centrally authorised medicinal products

The purpose of this analysis was to estimate how many products would need to be transferred (or duplicated) to market authorisation holders in the UK and/or the EU27/EEA, and similarly, how many batch release facilities may need to be established in the UK and/or the EU27/EEA, should regulatory changes require this.

To do this, we obtained from the EMA the list of centrally authorised medicinal products for human use currently authorised in the EU with the country of residence of the MAH and the name and country of location of the batch release site facilities for these products.[4] Using these data we computed the number of centrally authorised medicinal products for whom the MAH and the batch release facilities were located in the UK and in the other EU member states (outside the UK).

We also retrieved the Annex 10 of the 2016 annual report of the European Medicines Agency (Doc. Ref.: EMA/4995/2017 dated 8 May 2017).[5] From this document we extracted and analysed the timelines of the Committee for Medicinal Products for Human Use (CHMP) opinions on initial evaluations and extensions of therapeutic indications which received a positive CHMP opinion, we retrieved the minimum and maximum and computed the median evaluation times. This will enable us to provide an estimate of when the MHRA should consider implementing a parallel evaluation to cover the procedures which will overlap the date the UK leaves the EU (30 March 2019).

A4.1.2. Delays in the submission of marketing authorisation applications

The purpose of this analysis was to explore the existence and extent of possible delays in the availability of medicines should the UK no longer be involved in EU public health initiatives.

To do this, we compared the elapsed time between the date of submission of marketing authorisation applications for medicinal products containing a new active substance in the EU, with the date of the same submission in third countries (a proxy for the UK after Brexit). We chose three countries that could be considered comparable to the UK market following the withdrawal of the UK from the EU: Australia, Canada and Switzerland. The comparison was conducted using the date of submission rather than the date of authorisation because different regulators have different timeframes granting marketing authorisations, and we did not want to capture this effect.

The dates of submission for all marketing authorisation applications for medicinal products containing a new active substance authorised according to the centralised procedure were obtained from the Centre for Innovation in Regulatory Science (CIRS) for the years 2013-2015. Generics, similar biological medicinal products (known as biosimilars), informed consent, and hybrid applications were excluded from the analysis.

We analysed the deviation between the timing of EU marketing authorisations and those of selected third countries. We also estimated the proportion of products for which an

[4] EMA request reference ASK-30489 dated 17 May 2017 and received on 17 July 2017.
[5] This document is available on the EMA website at the following URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000208.jsp&mid=WC0b01ac058002933a [accessed on 2 August 2017]

application was only submitted in one or two of these countries or not submitted at all (by the end of 2016), following the submission to the EMA.

A4.1.3. Supervision and pharmacovigilance activities

The purpose of our analyses was to assess the impact of the withdrawal activities on the supervision and pharmacovigilance activities. For that reason, we have focused our analysis on important pharmacovigilance activities undertaken by Regulators in the EU and on activities which rely on resources from academia. These activities are: the detection of new signals, the incident and crises management activities, and the conduct of pharmacoepidemiology studies.

EU signal detection and management activities

This part of the analysis focused on the pharmacovigilance activities that are likely to have the most significant and immediate impacts in terms of public health: quality defects, detection of new emerging risks associated with the use of medicinal products and triggering major regulatory procedures (referral and risk/benefit evaluation procedures). The purpose was to establish the extent of the contribution of the UK's MHRA to signal detection activities in the EU, in order to infer the magnitude of expertise and experience that could be lost to the UK and the EU27/EEA should the UK no longer be involved in these activities.

Data were obtained via a request for information to the EMA on the signals identified and discussed at the Pharmacovigilance and Risk Assessment Committee (PRAC) since the implementation of the EU legislation on pharmacovigilance in July 2012.[6] We estimated the contribution of the MHRA to the signal detection activities in the EU by comparing the number and public health impact of signals detected and evaluated by the MHRA to the number and impact of the signals detected and evaluated by the other competent authorities.

The EMA signal management procedure is described in the module IX (signal management) of the Heads of Medicines Agencies/EMA guideline on good pharmacovigilance practices (HMA and EMA, 2012). The procedure described in this document specifies that following the detection and validation of a signal by the Rapporteur, the PRAC performs a signal assessment and adopts a recommendation for action. The recommendation for action is proportionate to the demonstrated or potential risk to public health and can include a wide range of different measures described in the guideline. These can include immediate measures like suspending the marketing authorisation of the medicinal product for signals indicating an immediate major risk to public health, or recommendations for monitoring of the signal in routine pharmacovigilance procedures. In addition, the PRAC may recommend conducting a Post-Authorisation Safety Study (PASS) for signals needing further characterisation (HMA and EMA, 2016) or the circulation of a direct healthcare professional communication (DHPC) (HMA and EMA, 2013). A DHPC is defined as a communication intervention by which important safety information is delivered directly to individual healthcare professionals by the MAH or the competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. Therefore, DHPCs are regarded as reflecting the detection of signals with a more serious impact on public health than the signals handled via routine procedures or variations.

[6] EMA request reference ASK-30865 dated 31 May 2017 and received on 12 June 2017.

Finally, referral procedures can also be triggered following the detection of a signal. A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the EU. The medicine, or the class or medicines, is 'referred' to the EMA so that it can make a recommendation for a harmonised position across the EU. Referrals can be started by the EC, by a member state, or by the company that markets the medicine. Referrals are usually triggered following the detection of signals indicating a potentially serious impact on public health.

We have assessed the public health impact of the signals validated, prioritised and assessed by the PRAC by using the regulatory decisions proposed by the PRAC in response to the signal as a proxy for the level public health risk. The ranking that we have adopted reflects the importance of the regulatory procedure and therefore the level of risk, as follows (beginning with that which has the greatest impact):

- Suspension or withdrawal of marketing authorisations;
- Referral procedure;
- DHPC;
- PASS;
- Update of the product information or;
- Update of the RMP;
- Further characterisation via routine pharmacovigilance activities (e.g. PSURs).

The signals which were under evaluation by the PRAC at the time of the study were categorised as "ongoing" in our analysis.

We estimated the role of the UK in active surveillance activities (EMEA, 2005) by looking at the conduct of PASS (HMA and EMA, 2016) since November 2010. This analysis was based on data retrieved from the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) database:

- A comparison of the number of ENCePP centres in the UK with the number in other member states[7];
- The list of PASS imposed as a condition of the marketing authorisation of products authorised in the EU and included in their RMPs;
- A comparison of the number centres (primary investigators) conducting PASS in the UK to the number of centres situated in other EU member states.

Interviews with pharmacovigilance experts

We also conducted telephone interviews with three EU QPPVs. The interviews discussed the following issues potentially impacted by the withdrawal of the UK from the EU:

- Major expected public health impacts associated with medicines for human use in the UK and EU27/EEA;
- Implications for pharmaceutical companies of possible future requirements concerning the need for both an EU27/EEA and an UK QPPV, the implications of the relocation of the current EU QPPVs (recruitment issues and implications in terms of public health);

[7] http://www.encepp.eu/encepp/resourcesDatabase.jsp [Accessed July 2017]

- Implications (public health and signal detection, internal procedures, modification of current pharmacovigilance databases) and costs of the changes to the reporting requirements of individual case safety reports (ICSRs) and suspected serious unexpected reports of adverse drug reactions (SUSARs) to EudraVigilance (HMA and EMA, 2017) and the implications and costs of possible new reporting requirements to the MHRA;
- Implications and costs of any divergence in requirements for PSUR/DSUR/RMP submissions;
- Implications on signal detection and management activities (including signal communication and exchange of information with the EU27/EEA and with the UK);
- Implications on the conduct of PASS and observational databases (both in the EU27/EEA and in the UK);
- Resources implications for the pharmacovigilance activities (e.g. pharmacovigilance inspections).

A4.1.4. Incident and crisis management

We retrieved and reviewed the Heads of Medicines Agencies and EMA procedure and guideline which describe the organisation of the EU regulatory network for the management of incidents or crises associated with the use of medicines for human use (EMA, 2017). Using this document we analysed the potential consequences of Brexit (and the nature of the Brexit) on the management of incident and crises. The EMA does not maintain any public registry of the incidents and crises managed by the EU regulatory network. Therefore, we have used the number of referral procedures made to the PRAC and the number of recalls due to a defect which presents a life-threatening or serious risk to health (class 1 recalls) to estimate the frequency of occurrence of such incidents or crises. We have supplemented this information with a review of the number of referral procedures made to PRAC and finalised between 2014 and 2016. We also analysed the number of quality defects and recalls associated with defects considered to pose a life-threatening or serious risk to health performed by the EMA between 2014 and 2016, as reported in the last three EMA annual reports covering 2014-2016 (EMA, 2014, EMA, 2015, EMA, 2016).

A4.1.5. Public health threats

The EMA includes the following issues under the activities aimed at responding to existing and emerging public health threats: antimicrobial resistance, the risk of falsified medicines (i.e. fake medicines that are designed to mimic real medicines), biological and chemical threats and emergencies such as an outbreak or a pandemic. Given that the UK has transposed into its internal law the EU legislation concerning the measures aimed at fighting against falsified medicines, we have focused our analysis on the implications of Brexit on the on the role of the EU regulatory network on the development and approval of medicines for use in the EU during influenza pandemics as an example. We retrieved and reviewed the EMA procedures and guidelines which describe the role and activities of the EMA in relation to pandemic influenza (EMA, 2006; EMA. ECDC and HMA, 2009; EMA, 2011). Given these procedures and guidelines, we evaluated the EMA's role under the different Brexit scenarios.

A4.1.6. Shortages of medicines in the EU27/EEA and in the UK

The withdrawal of the UK from the EU may result in a loss of recognition of GMP certificates, additional customs barriers and the disappearance of the parallel trade which could disrupt the supply chain of medicines and lead to medicines shortages. Therefore, we have analysed the information contained in the EudraGMDP database. We have also tried to understand which products could be impacted by these shortages, therefore we have linked the records of EudraGMDP with the World Health Organization's (WHO) model list of essential medicines[8]. In order to assess how Brexit could impact shortages of medicines in the EU27/EEA and the UK we conducted a brief literature search of the potential causes of these shortages. Based on our review, we focused on three key areas:

1. Imports and exports: We summarised the total value of pharmaceutical products imported into and exported between the UK and the EU27/EEA to provide a gauge of the potential for trade / customs issues leading to medicines shortages to impact the UK and/or EU27/EEA as a result of Brexit;
2. Number of GMP sites: A certificate of Good Manufacturing Practice (GMP) is issued to a manufacturer by the national competent authority that carried out an inspection if the outcome of the inspection confirms that the manufacturer complies with the principles of GMP, as provided by EU legislation. The GMP certificates are recorded in an EU database EudraGMDP defined in Directive 2004/27/EC on human medicinal products;
3. Manufacturing, distribution and importation of medicines included in the World Health Organisation (WHO) model list of essential medicines.

We estimated the value of the imports and exports of medicines between the UK from the EU27/EEA. We retrieved the volumes and value of imports and exports of pharmaceuticals from the Eurostat database.[9] We obtained details for the goods corresponding to the Standard International Trade Classification (SITC) codes 541 and 542 from January 2014 until July 2017.[10] Using this data, we calculated the sum and proportion of the imports and exports respectively by country, based on the value in Euros (€).

We retrieved information from the EudraGMDP database on the GMP certificates issued by EU regulatory authorities concerning the following operations defined in the Good Manufacturing Practice Guidelines[11]:

a. Manufacturing and importation from third countries APIs)[12] and finished products. The manufacturing and importation can involve the active substance (or API)

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[8] The list represent the minimum medicine needs for a basic health-care system, and thus we use it as a proxy to indicate medicines for which shortages would be particularly concerning.
[9] The Eurostat database of import and exports of goods in the EU is available at the following URL: http://ec.europa.eu/eurostat/web/international-trade-in-goods/data/database and (accessed on 11 July 2017).
[10] It should be noted that the SITC classification does not allow any distinction between the medicinal products for human and veterinary use.
[11] The Good Manufacturing Practice guidelines are included in the Volume 4 of "The rules governing medicinal products in the European Union" and can be found at the following URL https://ec.europa.eu/health/documents/eudralex/vol-4_en (accessed on 22 August 2017).
[12] An API (or Drug Substance) is defined in ICH Q7 as "any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the

included in the medicinal product or the manufacturing of the finished product defined as a medicinal product which has undergone all stages of production, including packaging in its final container;

b. Batch operations defined as the operations (testing and release) performed on a defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous;
c. Distribution of medicinal products.[13] Active substances and medicinal products shall be distributed in accordance with good distribution practices. Member states enter the certificates of Good Distribution Practices (GDP) which they issue in EudraGMDP in accordance with Art. 111(6) of the Directive 2001/83/EC as amended.

We calculated the number of GMP sites per country and per GMP operation (manufacturing, batch certification and importation of products from third countries). We also calculated the number of sites per operation per type of medicinal products and per country (UK versus EU27/EEA) recorded in the EudraGMDP database (i.e. API, aseptically prepared, biotechnology, blood, cell and gene therapy, immunological, non-sterile and sterile, tissue engineering and terminally sterilised products). Based on these figures (operation for a given type of medicinal products versus all other operations, UK versus EU27/EEA) we have computed the proportion of UK sites involved in the given operation relative to other EU27/EEA countries. This information was used to assess the role of the UK in manufacturing and in certifying batches of medicinal products in the EU, whereby a greater proportion of UK sites relative to other EU countries is assumed to be indicative of the UK having a more pronounced role in these operations compared with the other EU countries.

The information on the types of products manufactured in the UK was obtained from the GMP manufacturing, importation and distribution certificates and was used to explore the specific products that could be most affected. We collected the names of the APIs mentioned in the GMP/GDP certificates. We also retrieved the WHO model list of essential medicines as of March 2017.[14]. We mapped the APIs included in the certificates with the name of the medicines included in the WHO essential medicines list, this allowed us to cross-link the WHO list with the list of APIs manufactured, imported or distributed in the UK. We then calculated the number and proportion of APIs manufactured, imported into the UK from third countries and distributed in the UK and then compared these to the number and proportion of APIs included in the WHO essential medicines list.

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production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body". This definition is equivalent to the active substance defined in Directive 2001/83/EC. The ICH Q7 guideline is available at the following URL: http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html (accessed on 14 September 2017).

[13] http://eudragmdp.ema.europa.eu/inspections/displayHome.do [Accessed July 2017]

[14] This list was obtained from the WHO website http://www.who.int/medicines/publications/essentialmedicines/en/ (accessed on 4 August 2017).

A4.1.7. Supply chain

We sought to identify changes to the supply chain that may be necessary as a result of Brexit, and the implications of these for public health in the UK and EU27/EEA. These changes may also have economic implications for pharmaceutical companies. Potential changes to the supply chain have been classified into two different categories: regulatory and trade changes, and investigated by scenario.

In order to conduct this analysis we reviewed documents provided by the Association of the British Pharmaceutical Industry (ABPI) and by ABPI member companies, detailing the current supply chain. In some cases these documents also provided information how the current set up could change as a result of Brexit.

The supply chain differs by manufacturer and also by product, and as such this analysis necessarily focused on an indicative supply chain. Indicative supply chain diagrams were developed for Scenario 1 and also for the 'worst case' scenario (Scenario 4). These indicative supply chain diagrams were presented and discussed in detail at the joint ABPI and BIA (UK BioIndustry Association) Brexit Deep Dive for Trade (Medicines) meeting in June 2017. The feedback was used to develop the analysis further and to amend the diagrams for the remaining scenarios.[15] The indicative diagrams are used within the analysis to identify the possible impacts of changes in regulation and changes in trade agreements on the supply chain.

To build upon this, we use an illustrative example of a UK-based medicines manufacturer (corresponding to Manufacturer II in the list below) to assess the impact of Brexit. We assume that this manufacturer imports APIs and intermediate inputs from the EU27/EEA, and exports finished products (medicines) to the EU27/EEA.

Using this example we assess 1) time delays, and 2) additional costs to companies (both one-off and ongoing costs) that are likely to arise as a result of Brexit. We also highlight the impact for the following stakeholder groups:

- **Manufacturer of APIs**: manufacturers of APIs who typically supply to manufacturers of finished products;
- **Manufacturer of FPs** manufacturers of finished pharmaceuticals (FP) and/or MAHs that outsource the production of the finished medicine to Contract Manufacturing Organisation (CMO);
- **Packagers**: secondary packagers or businesses that package finished medicines to meet country specific packaging standards (e.g. language, dosage, presentation);
- **Distributors/Wholesalers**: businesses responsible for the distribution and sales of finished medicines in large quantities to retailers (i.e. pharmacies, hospitals, home care providers);
- **Parallel traders**: businesses or agents (often distribution/wholesale firms) that buy finished medicines from countries where the prices are lower and may re-sell those medicines in countries where the prices are higher.

[15] Note that Scenarios 2 and 3 are variants on the combination of elements in Scenarios 1 and 4, and as such the supply chains for these scenarios do not have specific diagrams.

Other stakeholders (for example retailers and trade brokers[16]) are also included in some of our supply chain diagrams, but specific impacts on these parties have not been taken into account within the analysis.

Additionally, due to the complexity and variety of processes and protocols the supply of medicines involve we have provided a glossary of terms, acronyms and definitions to aid the understanding of diagrams and analyses. This glossary is shown in Table A3 below.

Table A3: Glossary of terms and definitions

Term, acronym	Definition
Batch release[a]	The process by which the QP of the MAH is responsible for certifying that each batch of medicinal product to be placed on the EU/EEA market was manufactured in accordance with the marketing authorisation and EU GMP requirements (Article 51(1) of Directive 2001/83/EC).
Batch testing[a]	The manufacturing process where upon importation each production batch can undergo rigorous testing to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation (in accordance with Article 51(1)(b) of Directive 2001/83 the marketing authorisation holder needs to specify a site of batch control in the EU/EEA). In addition, a Member State laboratory may, but is not required to, test a batch of an immunological medicinal product or a medicinal product derived from human blood or plasma before it is placed on the market. This operation is conducted by the network of Official Medicines Control Laboratories (OMCL) (Article 114 of Directive 2001/83/EC relating to medicinal products for human use, as amended by Directive 2004/27/EC, of the European Parliament and of the Council).
FTA[b]	An arrangement that establishes unimpeded exchange and flow of goods and services between trading partners, regardless of national borders of member countries.
GDP[c]	A code of standards ensuring that the quality of a medicine is maintained throughout the distribution network, so that authorised medicines are distributed to retail pharmacists and others selling medicines to the general public without any alteration of their properties. Abbreviated as GDP.
GDP certification[a]	The GDP Certificate (issued by the corresponding NCA of a member state) certifies that that manufacturers and importers located in EEA perform their distribution activities within the EU28/EEA in compliance with GDP. Such compliance and certification is necessary to obtain a Wholesale Distributor Authorisation.
GDP inspections[a]	Inspections carried out routinely (or if there is suspicion of non-compliance) to authorised wholesale distributors within the EU28/EEA in order to ensure they comply with GDP. Inspections are performed by the corresponding NCA.
GMP[c]	A code of standards concerning the manufacture, processing, packing, release and holding of a medicine. Active substance

[16] Brokers act as an intermediary, facilitating sales between buyers and sellers of goods.

Term, acronym	Definition
	manufacturers must comply with GMP. In addition, the manufacturer of the finished product is obliged to ensure that the active substances they use have been manufactured in compliance with GMP.
GMP certification[a]	The GMP Certificate (issued by the corresponding NCA of a member state) certifies that that manufacturers and importers located in EEA perform their manufacturing activities within the EU28/EEA in compliance with GMP. Such compliance and certification is necessary to obtain a Manufacturing Authorisation.
GMP periodical inspection[c]	In the EU, NCAs are responsible for inspecting manufacturing sites located within their own territories. Manufacturing sites outside the EU are inspected by the national competent authority of the Member State where the EU importer is located, unless an MRA is in place between the EU and the country concerned. If an MRA applies, the authorities mutually rely on each other's inspections.
NCA[c]	A medicines regulatory authority in a European Union Member State (e.g. the MHRA in the UK) (see Directive 2001/83/EC and Regulation 726/2004, as amended).
Non-tariff measures[d]	Barriers to importations such as quotas, import licensing systems, sanitary regulations, prohibitions, etc.
QP[e]	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). One QP is responsible for ensuring that each 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). Another QP is the responsible person for pharmacovigilance (EU 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). QP must be located within the EU28/EEA and plays a role in other specific requirements such as ensuring and certifying that active pharmaceutical ingredients (APIs) imported from third countries have been manufactured in compliance with GMP.
QP certification[e]	The certification of the finished product batch performed by a QP signifying that the batch is in compliance with GMP and the requirements of its MA. This represents the quality release of the batch. This could happen in a site other than where the release of the batch is performed. In such a case the certification must accompany the batch until the site of its release and the arrangement should be documented in a written agreement between the sites.
Tariff measures[d]	Custom duties and taxes charged to imports at custom to give a price advantage to locally-produced goods over similar imported goods.

Term, acronym	Definition
WTO tariffs[d]	Custom duties on merchandise imports that give a price advantage to locally-produced goods over similar goods which are imported and raise revenues for governments.

Sources: [a]adapted from Council of Europe (n.d.); [b]Global Negotiator (n.d.); bEMA Glossary (n.d.); [c]World Trade Organization Glossary (n.d.); [d]adapted from EMA (2012).
Abbreviations: EU/EEA: European Union and European Economic Area; GMP: Good manufacturing practice; MA: Marketing authorisation; MAH: Marketing authorisation holder; MHRA: Medicines & Healthcare products Regulatory Agency; NCA: National Competent Authority; QP: Qualified person.

Finally, any relevant information that was gathered from the interviews with company representatives (see Annex 5) was also fed into this supply chain analysis.

A4.2. Results

A4.2.1. Number of Centrally Authorised Medicinal Products

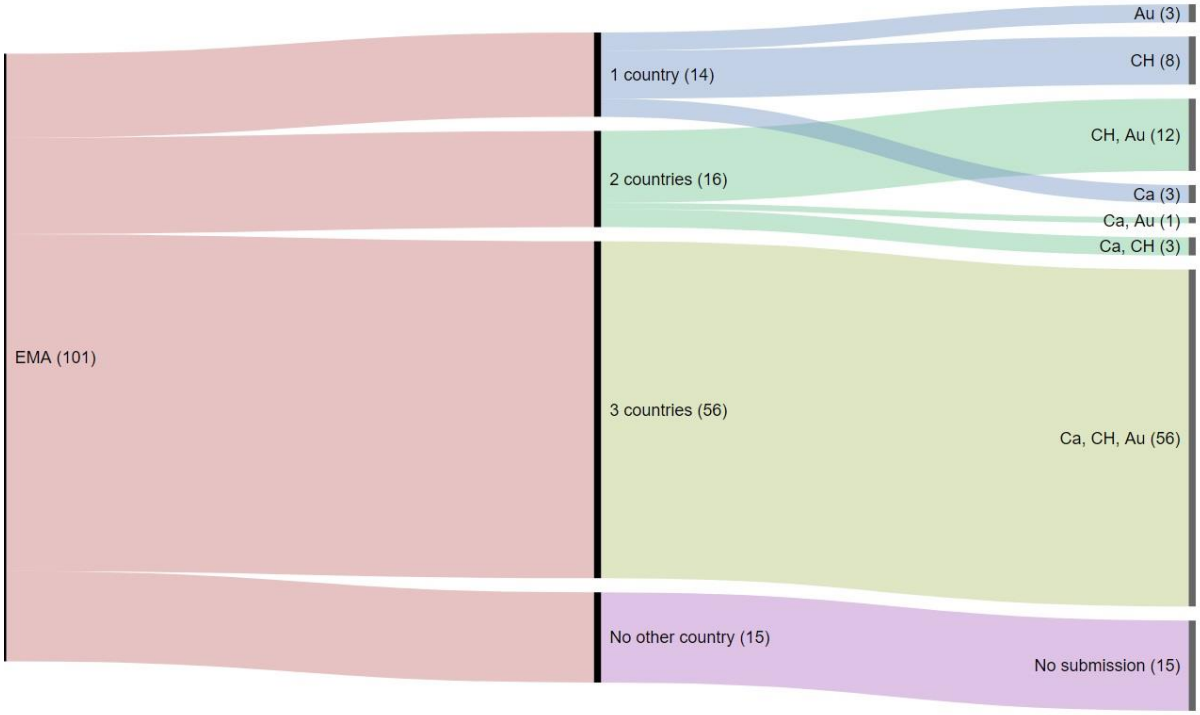
A transposition into UK law will have to be performed for 978 medicinal products which received a marketing authorisation via the centralised procedure between 1995 and July 2017. The MAH is currently located in the UK for over one third of these products (361; 37%). In 2016, the median time necessary to grant an initial marketing authorisation for the products containing a new active substance (Article 8(3) of Directive No 2001/83/EC) was approximately 14 months (minimum 8 months, maximum 31 months), the median time necessary to grant an extension of indication was approximately 9 months (minimum 4 months, maximum 19 months). In addition, the median time which separated the CHMP opinion and the publication in the Official Journal of the European Union for the initial authorisations was 102 days (minimum 71 days, maximum 148 days, approximately 5 months). This median time was much shorter for extensions of indications (36 days).

1,478 batch release facilities were authorised for these 978 products. The batch release sites are located only in the UK for 96 products (10%). 754 products (77%) have batch release sites located in the EU27/EEA but not in the UK. 128 products (13%) have batch release sites located both in the UK and in the EU27/EEA.

A4.2.2. Delays in the submission of marketing authorisation applications

Between 2013 and 2015, 101 medicinal products were authorised via the centralised procedure. Of these, a marketing authorisation was submitted to all three non-EU countries in our comparative analysis (Australia, Canada and Switzerland) in 56 cases (55%). No marketing authorisation application was submitted in any of the three countries in 15 instances (15% of the products). An application was submitted in only one or two of these countries in an additional 30 cases (by the end of 2016). Figure A1 shows the number of countries to which marketing authorisation applications for the 101 products authorised in the EU were submitted. The number of submissions to only one country are shown in blue, the number of submissions to two countries are in green, the number of submissions to three countries are in yellow and the number of products for which no applications were submitted to any other of the three countries are in pink.

Figure A1: **Number of marketing authorisation applications via the centralised procedure and subsequently submitted to Australia, Canada and Switzerland, 2013-2015**



Source: CIRS

The first submission was to the EMA in the vast majority of the cases:

- 63 medicinal products had applications submitted to both the EMA and to Health Canada; the submission was made first to the EU in 55 cases (87%).
- 72 products had applications submitted to both the EMA and the Therapeutic Goods Administration (TGA) in Australia; the first submission was to the EMA in 69 instances (96%).
- 79 products had applications submitted to both the EMA and the Swiss Medic; the first submission was to in the EU in 77 cases (97%).

The median submission gap was two months for Canada and Switzerland and three months for Australia. The analysis also revealed some extreme outliers, with delays stretching to more than three years in some cases (see Table A4).

We also observed a proportion of applications submitted more than a year after submission to the EMA. These occurred for approximately 15% of the applications in Australia (11/72 or 15%) and Switzerland (13/79 or 16%) and only 5% of the cases in Canada (3/62 or 5% of the marketing authorisation applications submitted to Health Canada after the EMA.

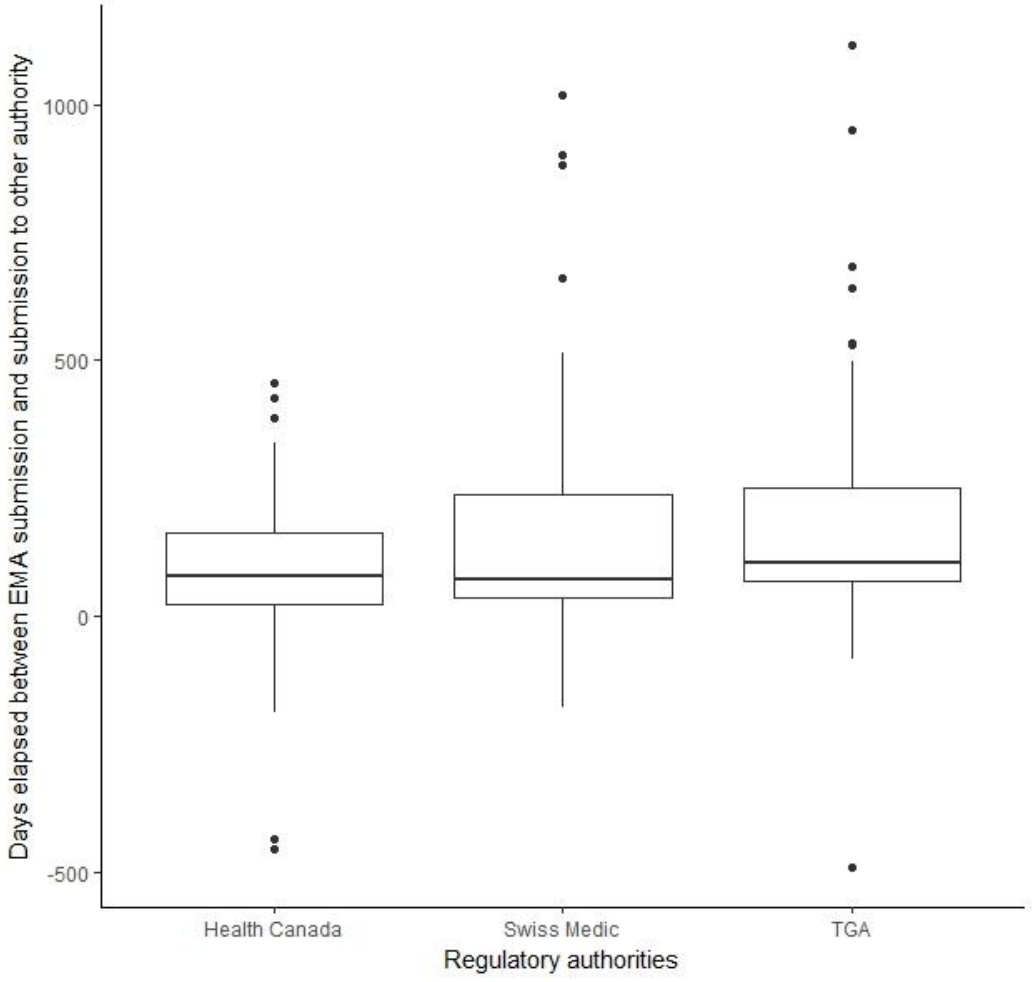
The boxplots of the distributions are shown in Figure A2. The diverging bars for Australia, Canada and Switzerland are shown in Figure A3, Figure A4 and Figure A5, respectively.

Table A4: **Time elapsed between submissions of marketing authorisation in each country compared to the EMA (days), 2013-2015**

Gaps expressed in days (months)	Australia	Canada	Switzerland
Minimum	-490 (1 year and 4 months)	-5,103 (14 years 2 months)	-178 (5 months and 28 days)
1st quartile	68 (2 months 8 days)	22 days	36 (1 month 6 days)
Median	103 (3 months and 13 days)	78 (2 months and 18 days)	73 (2 months 13 days)
3rd quartile	252 (8 months and 12 days)	163 (5 months and 13 days)	237 (7 months and 27 days)
Max	1,115 (3 years and 1 month)	455 (1 year and 3 months)	1,020 (2 years and 10 months)

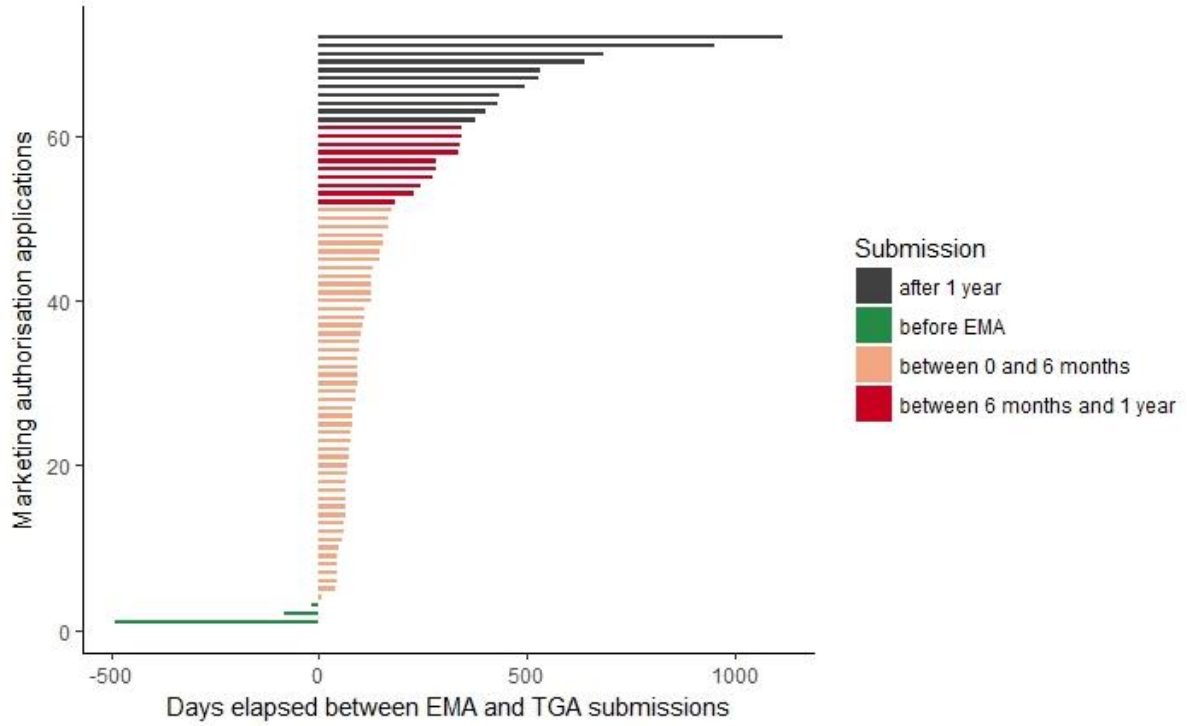
Source: CIRS

Figure A2: Boxplot of the distribution of the marketing authorisation submission gaps (days), 2013-2015



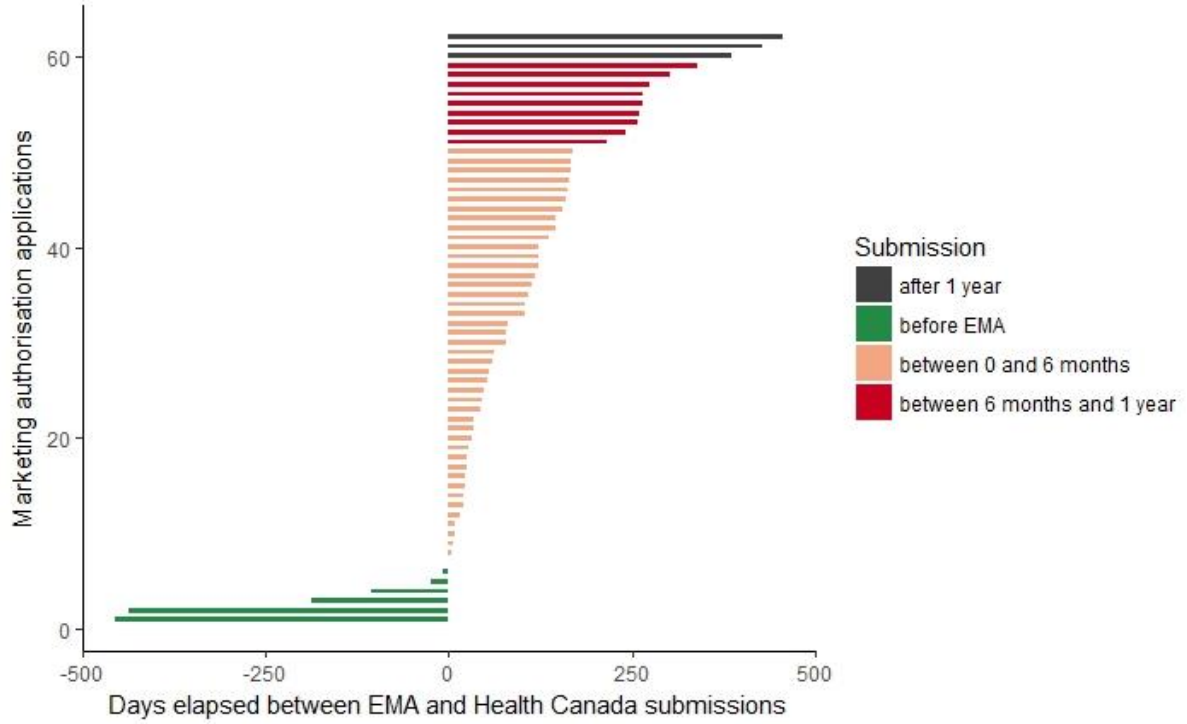
Source: CIRS. Note one outlier submitted to Health Canada 5103 days before the EMA is not shown.

Figure A3: Time elapsed between submission of marketing authorisation to the TGA and EMA (days), 2013-2015, n=72



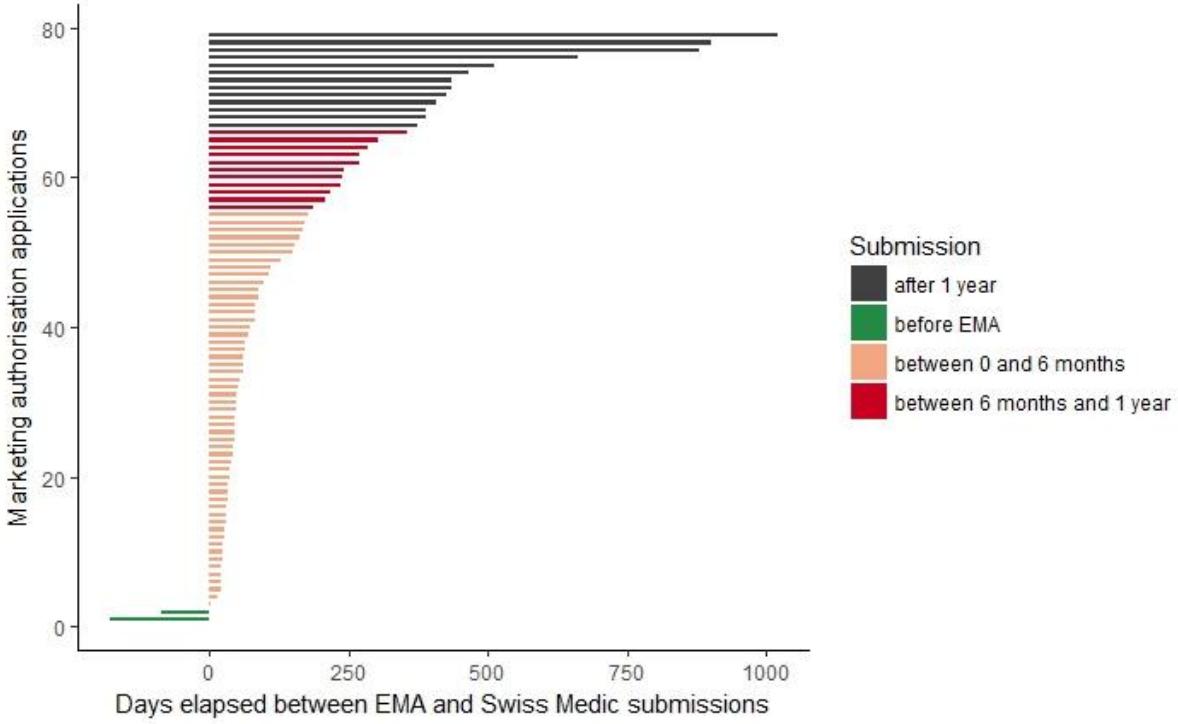
Source: CIRS. Note: orange, red and black bars show that the EMA received the submission before the TGA; green bars illustrate that the TGA received the submission before the EMA.

Figure A4: Time elapsed between submission of marketing authorisation to Health Canada and the EMA (days), 2013-2015, n=62



Source: CIRS. Note: one outlier submitted to Health Canada 5103 before the EMA is not shown; orange, red and black bars show that the EMA received the submission before Health Canada; green bars illustrate that Health Canada received the submission before the EMA.

Figure A5: Time elapsed between submission of marketing authorisation to Swiss Medic and the EMA (days), 2013-2015, n = 79



Source: CIRS. Note: orange, red and black bars show that the EMA received the submission before Swiss Medic; green bars illistrate that Swiss Medic received the submission before the EMA.

A4.2.3. Supervision and pharmacovigilance activities

EU signal detection and management activities

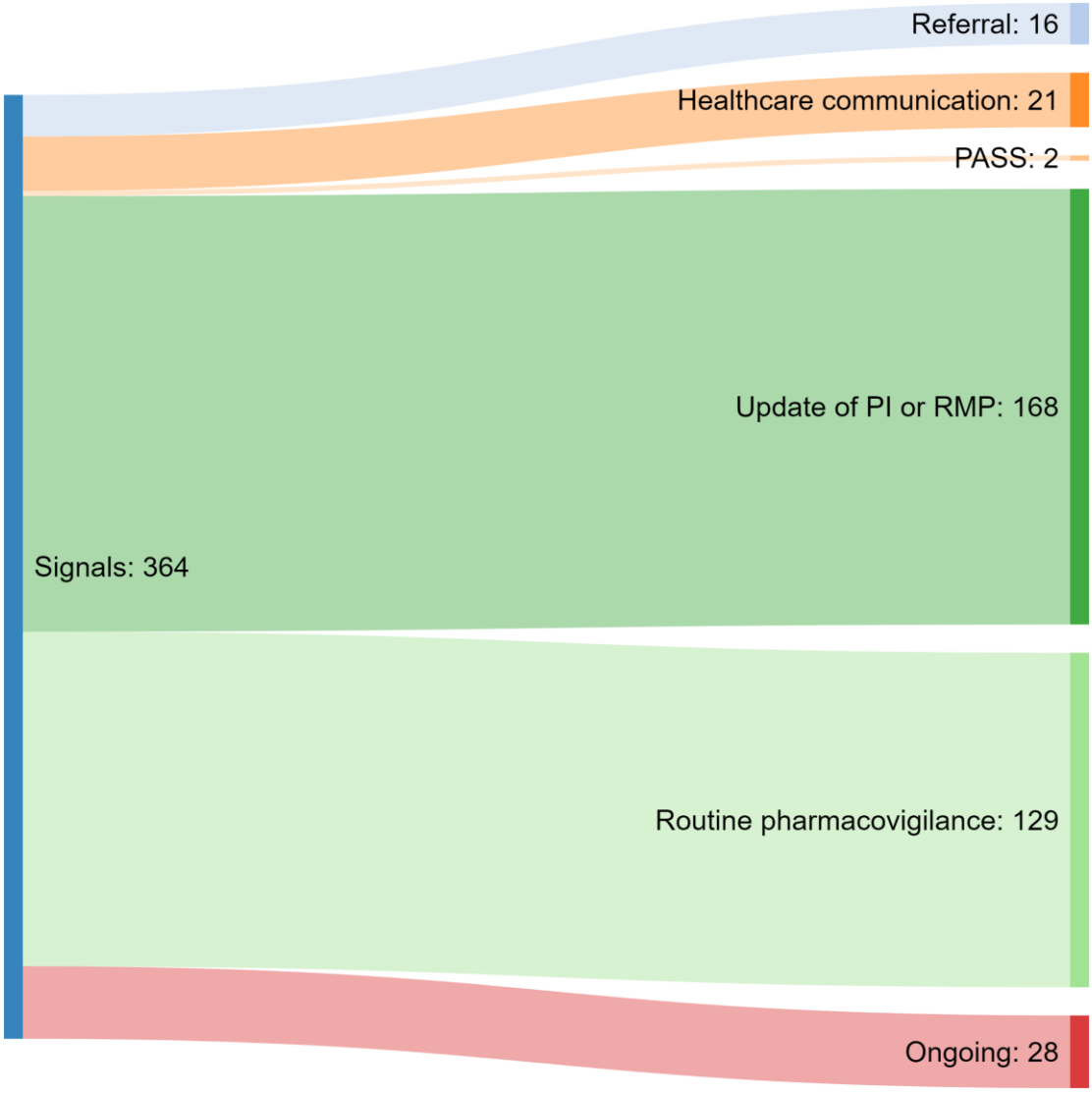
Since the implementation of new EU legislation on pharmacovigilance in July 2012, 364 signals have been detected, prioritised and assessed by the PRAC. Of these, 178 signals (49%) were identified or channelled[17] via the EMA. The remaining signals (186; 51%) were identified by the EU member states (Table A5). During this period, the MHRA detected 39 signals and was the leading member state in terms of number of signals detected and discussed by the PRAC (Table A5). The list of the signals identified by the MHRA, prioritised and discussed at the PRAC since July 2012 is given in Annex 4.

The outcomes of the signals show that most of the signals: (i) are ongoing, meaning that these signals are currently being assessed by the PRAC (28 or 7.7%); (ii) were handled via routine pharmacovigilance activities (129 signals or 35%); (iii) led to an update of the product information or risk management plans (46%); or (iv) resulted in the conduct of a PASS (2 signals or 0.006%). Importantly, 21 signals (or 5.8%) led to the circulation of a DHPC and 16 signals (or 4.4%) led to a referral procedure (this means that approximately four referral procedures were triggered each year following the detection or communication of a new signal). No signal detected and prioritised by the PRAC led to the suspension of marketing authorisations during the period covered by our study. The number and types of regulatory procedures recommended by the PRAC following the

[17] Some signals identified by regulatory authorities from third countries are communicated to the EMA and subsequently prioritised and discussed by the PRAC. Therefore, these signals are not originally identified by EU regulatory authorities.

detection of the 364 signals are shown in Figure A6 and Table A5. The number of regulatory procedures are ranked according to the importance of the regulatory procedure used to address the signal (in decreasing order). We can note from Table A6 that the signals identified or channelled by the EMA led to less DHPC and referral procedures than the signals identified by the EU member states. Table A7 provides details of each of the 16 referral procedures triggered following the prioritisation and assessment of the signals by the PRAC since July 2012.

Figure A6: Outcome of the signals discussed at the PRAC since July 2012



Source: European Medicines Agency.

Table A5: Number of signals prioritised (n=364) and assessed by the PRAC since July 2012 according to the EU regulatory authorities

EU Regulatory authorities	Number of signals detected by the EU Regulatory Authorities, validated and assessed by the PRAC	Number of signals assessed by the MS Regulatory Authorities
EMA (includes also the signals communicated by non-EU regulatory authorities)	178	n/a
United Kingdom	39	54
The Netherlands	29	54
France	19	30
Germany (Bundesinstitut für Arzneimittel und Medizinprodukte and Paul Ehrlich Institute)	21	48
Denmark	12	28
Italy	12	12
Spain	9	14
Sweden	9	65
Belgium	8	12
Portugal	8	22
Ireland	5	5
Finland	3	10
Poland	3	2
Austria	2	3
Estonia	2	2
Norway	2	6
Bulgaria	1	0
Cyprus	1	1
Latvia	1	1
Lithuania	0	1

Source: European Medicines Agency.

Two of the referral procedures were triggered following the original detection and communication of a signal by a regulatory authority from a third country (in both cases, the US Food and Drug Administration, FDA). These two signals were, firstly a signal of

fatal or life-threatening codeine toxicity in CYP2D6 ultra-rapid metabolisers (October 2012) and, secondly, a signal of diabetic ketoacidosis in patients treated with sodium-glucose cotransporter 2 (SGLT2) inhibitor (June 2015). The signals were prioritised and assessed by the PRAC one and two months after the FDA, respectively. For the codeine referral, the final recommendation was published on 20 February 2013 by the FDA, the PRAC recommendation published on 14 June 2013 with an endorsement by the Co-ordination group for mutual recognition and decentralised procedures for human medicinal products (CMDh) on 28 June 2013 (4 months after the FDA). The labelling of the SGLT2 inhibitors was updated on 4 December 2015 by the FDA and the final PRAC recommendation was published on 12 February 2016 (2 months after the FDA) and implemented by the European Commission on 18 May 2016 (5 months after the FDA).

Our analysis shows that the MHRA is the member state regulatory authority which has detected the highest number of signals. Although the Bundesinstitut für Arzneimittel und Medizinprodukte (German regulatory authority) and the Agenzia Italiana del Farmaco (Italian regulatory authority) detected more signals which led to the triggering of a referral procedure (three signals for the Bundesinstitut für Arzneimittel und Medizinprodukte and two for the Agenzia Italiana del Farmaco led to a referral), the MHRA detected signals of major public health importance: one signal detected by the MHRA led to the triggering of a referral procedure (Table A5), and the MHRA is the regulatory authority (with Agence Nationale de Sécurité du Médicament et des Produits de Santé , the French regulatory authority) which detected signals which led to the distribution of the highest number (four signals) of a healthcare communications (representing 20% of the DHPC requested by the PRAC).

Table A5 shows that the MHRA was the regulatory authority which assessed the second highest number of signals discussed at the PRAC, joint with the Medicines Evaluation Board, the regulatory authority from The Netherlands.

Active pharmacovigilance activities

The ENCePP resources database listed 161 different EU centres of pharmaco-epidemiology at the time of our query (5th July 2017). The UK is the country which contains the highest number of centres (35; 22%). These centres include pharmacoepidemiology resources that are used globally (including the Clinical Practice Research Datalink, London School of Hygiene and Tropical Medicine, the University of Bath, and the Drug Safety Research Unit). The complete list of the UK centres is given in Annex 7.

The analysis of the PASS requested in the RMPs of products authorised in the EU and recorded in the ENCePP PASS register (since November 2010) confirmed the strength of the UK in active pharmacovigilance activities. The UK has the highest number of centres responsible for the conduct of these studies (Figure A7).

We retrieved from the ENCePP PASS register information concerning 331 PASS included in the RMPs of products authorised in the EU. These PASS were conducted in 80 different countries worldwide. The vast majority of these studies are conducted in the EU (273), followed by North American countries (95) (see Figure A8). Most of these studies (193; 58%) are conducted in more than one country. The UK is 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 A9).

Table A6: Regulatory actions used by the PRAC to address the signals identified or channelled by the EMA, detected by the EU member states (excluding the UK) and by the UK since July 2012

Originator	Referral	DHPC	PASS	Update of PI or RMP	Routine pharmaco-vigilance (PSURs)	Ongoing	Total number of signals
EMA	4	6	1	86	70	11	174
EU member states (excluding UK)	11	11	1	62	45	17	136
UK	1	4	0	20	14	0	39

Source: European Medicines Agency data.

Table A7: List of referral procedures made to the PRAC following the detection and validation of a signal since July 2012[18]

Date of the PRAC	Active substance	Scope of the referral procedure	Originator
October 2012	Codeine	Fatal or life-threatening drug toxicity in CYP2D6 ultra-rapid metabolisers (signal originating from the FDA in August 2012)[19] Final recommendation published on 20 February 2013 by the FDA[20], PRAC recommendation published on 14 June 2013 with a CMDh endorsement on 28 June 2013[21].	EMA
October 2012	Olmesartan	Increased risk of fatal cardiovascular events in patients with type 2 diabetes at increased cardiovascular risk	Germany (BfArM)
October 2012	Short-acting beta agonists: hexoprenaline; fenoterol; ritodrine; salbutamol; terbutaline	Maternal cardiovascular events following use in tocolysis	United Kingdom
October 2012	Hydroxyethyl starch (blood plasma substitutes)	Increased risk of mortality versus Ringer's acetate in severe sepsis	Germany (BfArM)
February 2013	Thiocolchicoside	Risk of genotoxicity	Italy
February 2013	Domperidone	Cardiotoxicity	Belgium
April 2013	Valproate	Neurodevelopmental effects following in utero exposure	Denmark
April 2013	Agents acting on the renin-angiotensin system	Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials (signal from literature)	EMA
June 2013	Zolpidem	Next-morning impaired mental alertness, including impaired driving ability	Italy
March 2014	Testosterone	New publications suggesting the risk of cardiovascular events	Estonia

[18] Other referrals were made to the PRAC since July 2012 but the information which triggered the referral was not a signal.
[19] See FDA drug safety communication dated 15 August 2012. https://www.fda.gov/Drugs/DrugSafety/ucm313631.htm and Article 31 referral notification dated 3 October 2012 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine-containing_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f.
[20] FDA Drug Safety Communication https://www.fda.gov/Drugs/DrugSafety/ucm339112.htm
[21] PRAC recommendation http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine-containing_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f

June 2015	Canagliflozin; dapagliflozin; empagliflozin; metformin	Diabetic ketoacidosis (signal originating from the FDA in May 2015)[22] The labelling of these products was updated on 4 December 2015 by the FDA[23] and the final PRAC recommendation was published on 12 February 2016 and implemented by the European Commission on 18 May 2016[24].	EMA
February 2016	Sofosbuvir	Hepatitis B reactivation (signal from literature)[25]	EMA
April 2016	Direct-acting antivirals indicated for the treatment of hepatitis C: daclatasvir; dasabuvir; ombitasvir, paritaprevir, ritonavir; simeprevir; sofosbuvir; sofosbuvir, ledipasvir	Unexpected early hepatocellular carcinoma recurrence	Spain
April 2016	Canagliflozin; canagliflozin, metformin	Increased risk of lower limb amputations in CANVAS trial	Germany (BfArM)
July 2016	Human coagulation factor VIII, Recombinant factor VIII, human von Willebrand factor.	Inhibitor development in previously untreated patients (PUPs) with haemophilia A treated with plasma-derived vs recombinant coagulation factor VIII concentrates	Germany (PEI)
May 2014	Ivabradine	Cardiovascular risk	Netherlands

Source: European Medicines Agency.

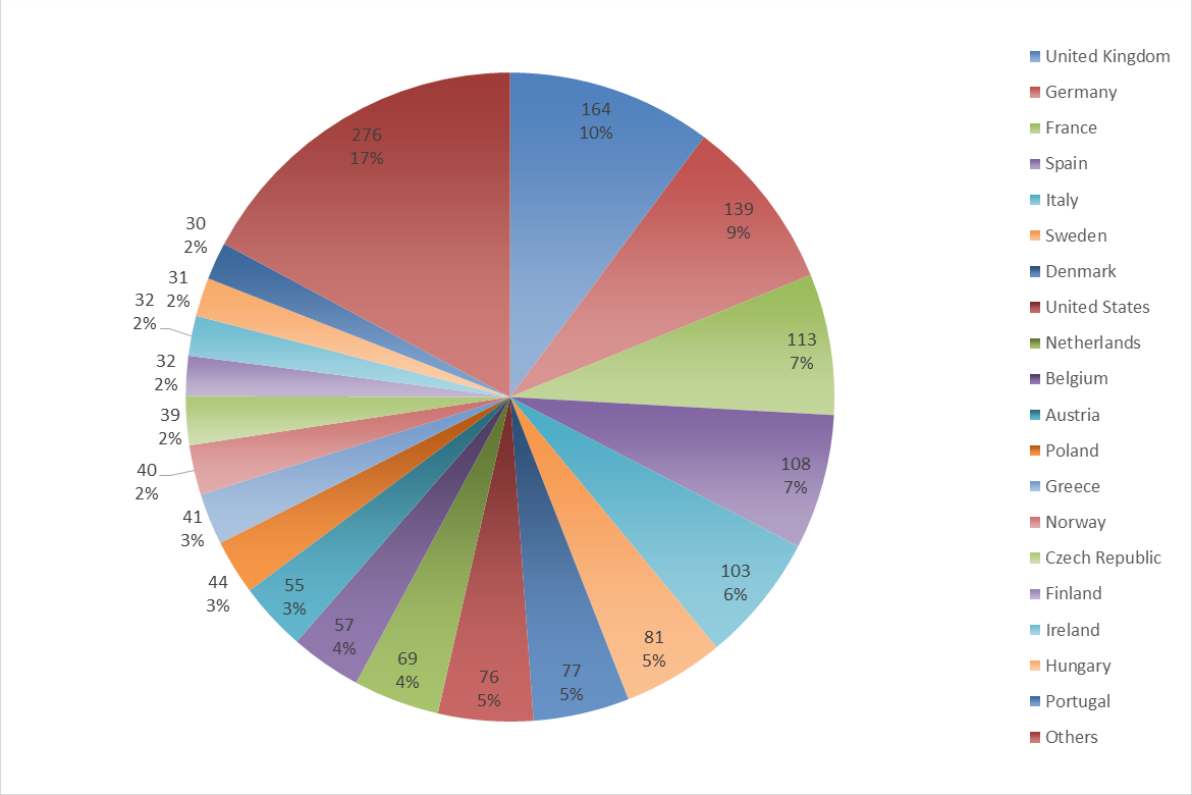
[22] See FDA drug safety communication dated 15 May 2015 https://www.fda.gov/Drugs/DrugSafety/ucm446845.htm and Article 20 referral notification dated 10 June 2015 http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/SGLT2_inhibitors/human_referral_prac_000052.jsp&mid=WC0b01ac05805c516f.

[23] FDA Drug Safety Communication https://www.fda.gov/Drugs/DrugSafety/ucm475463.htm

[24] SGLT2 inhibitors referral procedure http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/SGLT2_inhibitors/human_referral_prac_000052.jsp&mid=WC0b01ac05805c516f

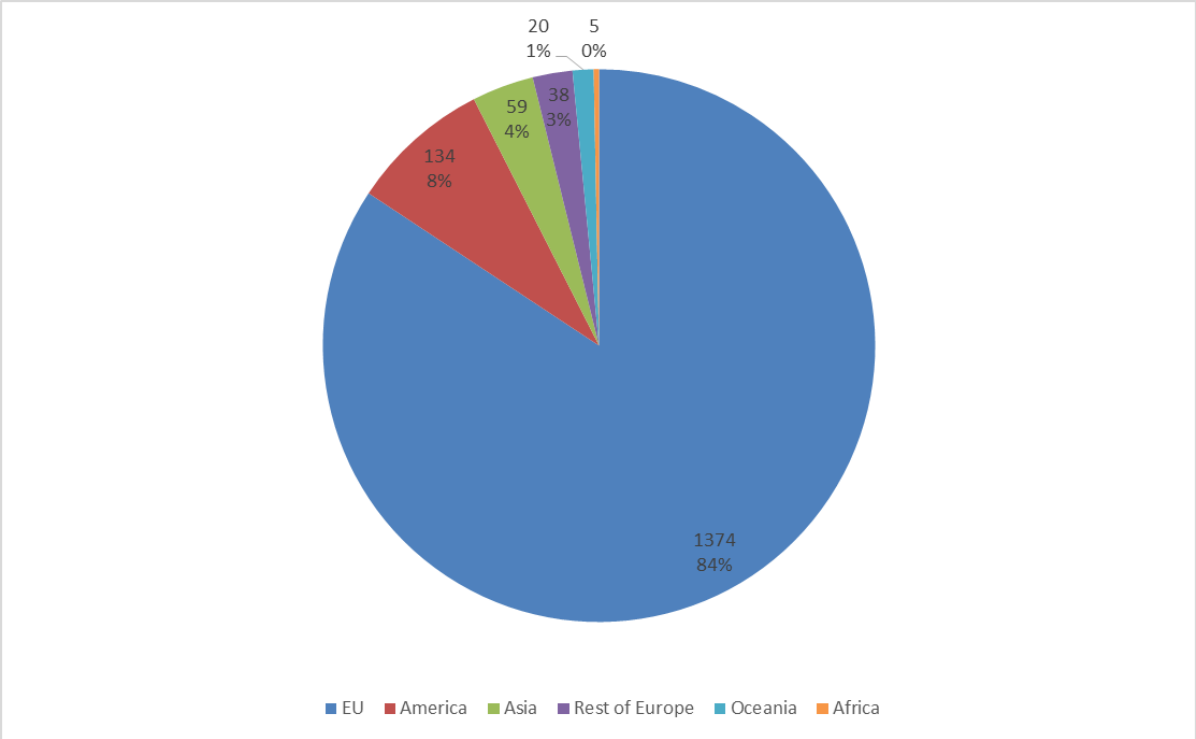
[25] See Article 20 referral notification http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Direct-acting_antivirals_indicated_for_treatment_of_hepatitis_C_(interferon-free)/human_referral_prac_000057.jsp&mid=WC0b01ac05805c516f

Figure A7: Location of the centres responsible for the conduct of the PASS requested in the RMPs of products authorised in the EU



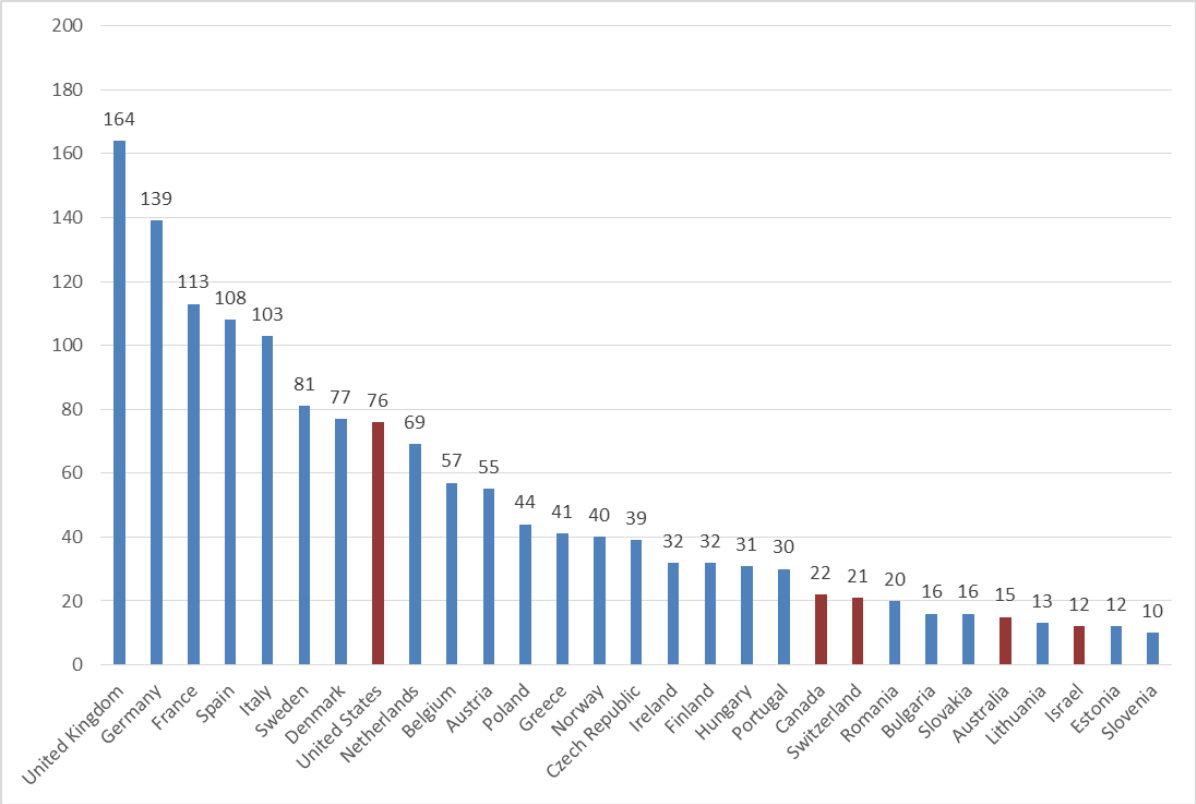
Source: European Medicines Agency, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register.

Figure A8: Regions of the world in which the PASS included in the RMP of medicines authorised in the EU are conducted (n=331)



Source: European Medicines Agency, ENCePP register.

Figure A9: Number of PASS included in the RMPs of products (authorised in the EU) conducted in the different countries worldwide



Source: European Medicines Agency, ENCePP register. Note: the bars corresponding to the EU countries are in blue. The bars corresponding to the non-EU countries are in dark red. The countries in which less than 10 studies are conducted are not included in the graph.

Interviews with pharmacovigilance experts

As of the 15th May 2017, 153 EU qualified persons for pharmacovigilance (EU QPPV) were located in the UK out of 1205 EU QPPV across the EEA. The role of a QPPV could change substantially as a result of Brexit, hence we interviewed three QPPVs for their expert opinions and views. The view of pharmacovigilance experts was that the loss of the expertise of the MHRA to the EU27/EEA may weaken or disrupt the EU system of supervision of medicines for human use both in the EU27/EEA and in the UK. In particular, the experts insisted that the UK regulatory agencies (the MHRA and its predecessor, the Medicines Control Agency, MCA) are major contributors in the field of pharmacovigilance and drug safety, and have been since the creation of the European Medicines Agency (initially called the European Medicines Evaluation Agency, EMEA) and the centralised procedure in 1995. The UK has been at the forefront of major initiatives in the field of pharmacovigilance, for example, the development of:

- Pharmacovigilance databases (with their expertise with the Adverse Drug Reactions Online Information Tracking system [ADROIT] database), and medical terminologies (Medical Dictionary for Regulatory Activities [MedDRA]);
- Statistical methods of signal detection (Evans et al. 2001); and
- Pharmacovigilance planning and risk management activities (Waller and Evans, 2003).

Interviewees indicated that the MHRA is also extensively involved in major pharmacovigilance initiatives including:

- The Innovative Medicines Initiative PROTECT[26] and WEB-RADR[27] projects;
- The SCOPE (Strengthening Collaboration for Operating Pharmacovigilance in Europe) joint action.[28]

The experts additionally highlighted that the UK was at the forefront of the coordination of the scientific pharmacovigilance evaluation in the EU since 1995: most of the CPMP/CHMP Pharmacovigilance Working Party chairpersons were working for the MCA or the MHRA, and the current PRAC Chairperson is also a member of the MHRA. The loss of the MHRA from EU public health activities could thus be detrimental for all parties.

The experts emphasised that the convergence of the future UK requirements with the EU requirements will be important for minimising the additional burden put on the companies: for example, the MHRA could still recognise the European reference date list for the exact submission date for the submission of PSURs. However, differences in scientific requirements (for RMPs, PASS for example) or in the assessments (PSURs, signal detection and management, results from studies) might complicate the management (leading to parallel procedures for signals, PSURs, RMPs and PASS for example), may require the implementation of different possibly conflicting requirements and could lead to parallel and non-coordinated communication of pharmacovigilance information in the future. This could create some confusion for companies, doctors and patients.

In conclusion, the experts expressed various concerns about the public health consequences of the withdrawal of the UK from the EU. Both in terms of resources and from a public health perspective, the withdrawal of the UK from the EU was seen as a step backwards, away from cooperation and coordination in the EU and world-wide pharmacovigilance activities. They believe the sudden withdrawal of the MHRA from the EMA pharmacovigilance activities could have important public health implications in both the UK and the EU. The experts considered that a transition phase allowing a smooth implementation of any changes after 30 March 2019 would be important to minimise and mitigate these potential negative consequences. Further views and opinions from the experts are reflected in the scenario analysis that follows.

A4.2.4. Incident and crisis management

The EMA is currently responsible for the coordination of the management of incidents associated with the use of medicinal products in the EU regardless of their procedure of authorisation (centrally or decentrally authorised, mutually recognised or nationally authorised products). The objectives of the EU Regulatory Network Incident Management Plan (EMA, 2017) are:

- To continuously monitor such events and new information, to review their public health impact, and to take the necessary routine measures to remedy the situation;

[26] See Innovative Medicines Initiative project PROTECT website http://www.imi-protect.eu/ (accessed on 14 July 2017).
[27] See WEB-RADR website https://web-radr.eu/ (accessed on 14 July 2017).
[28] See SCOPE joint action website http://www.scopejointaction.eu/ (accessed on 14 July 2017).

- To request further analysis under the form of the Preliminary Risk Analysis when routine measures are not considered sufficient to address the incident;
- To, undertake in case of a confirmed crisis, the initiatives necessary to manage and control the situation, whereby urgent and coordinated action within the EU Regulatory Network is necessary.

The incident and crisis management plan can be triggered in the event of new information which may be related to quality (for example problems of viral contamination with biological products, GMP compliance issues or batch defect with possible implications for public health), efficacy, or safety concerns (e.g. new pharmacovigilance information, detection of a signal with potential serious public health impact, triggering of a referral procedure to the PRAC). In a limited number of situations, commonly described as "crisis" situations, the management of the large majority of emerging public health concerns related to the use of medicines requires specific measures to allow for an efficient management of the risk to public health (identification of the risk and communication between the EU regulatory authorities, assessment of the risk and implementation of regulatory measures including precautionary measures, external communication). For that purpose, the EMA has established an EU regulatory network incident management plan for medicines for human use (EMA, 2017). The procedure can be triggered by the EC, a National Competent Authority (NCA) or the EMA as appropriate.

Based on the review of the "European Union regulatory network incident management plan for medicines for human use", incident or crisis management relies on two elements:

- The exchange of information relevant to the quality, safety and efficacy of medicines via the pharmacovigilance and rapid alert and non-urgent information and via the quality defect rapid alert systems;
- The management of the crisis by an incident management structure which involves representatives of the EC, EMA and its scientific committees and representatives from the Heads of Medicines Agencies to trigger the incident management procedure until the closure of the crisis.

Regulators from outside the EU are not part of this communication network. EMA collaborates with regulators outside the EU in the area of pharmacovigilance. The primary goal of this cooperation is to exchange information on risk assessments (with special focus on emerging safety concerns, including those assessed in EU referral procedures) and informing the participating parties of anticipated regulatory action, including public communication, prior to decision-making and publication. Currently, the EMA collaborates mainly with the US FDA, Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency and Swiss Agency for Therapeutic Products (Swiss Medic) and the Swiss Federal Department of Home Affairs with which the EMA has negotiated confidentiality arrangements which cover the exchange of information relevant to the incident management.

In order to estimate the number of incidents or crises our review of the EMA Annual Reports found that the PRAC completed 11, 5 and 6 referral procedures in 2014, 2015 and 2016, respectively. The EMA reported that between 147, 164 and 181 quality

defects were reported in 2014, 2015 and 2016.[29] Of these, 2, 1 and 3 Class 1 recalls due to a defect which presents a life-threatening or serious risk to health were performed in 2014, 2015 and 2016, respectively (EMA, 2014, EMA, 2015, EMA, 2016) (Table A8).

Table A8: Number of referral procedures completed by PRAC and Class 1 recalls, 2014-2016

Year	Referral procedures completed by PRAC	Class 1 recalls
2014	11	2
2015	5	1
2016	6	3

Source: EMA Annual reports 2014, 2015 and 2016.

The EMA does not maintain any public registry of the incidents and crises managed by the EU regulatory network, therefore, it was not possible to estimate the frequency or seriousness of these crises. However, based on the number of referral procedures and Class 1 recalls, the EMA may use the incident management plan at least 9-10 times a year on average with different levels of intervention. However, this estimate is probably conservative since incidents and crises can arise from other issues than those analysed in our study. For example, in the past, the Agency had to deal with incidents which arose in clinical trials conducted with interventional medicinal products, recent examples taken from the EMA annual reports also involved investigational medicinal products, in particular in first-in-man studies conducted with TGN1412 in England and with BIA 10-2474 in France (EMEA, 2007; EMA, 2016).

Therefore, by analogy with the management of safety signals detected and communicated by a regulatory authority from a third country (US FDA), we assume that the withdrawal of the UK from the EU is likely to induce some delays in the exchange of 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. While, it is not possible to estimate the impact of these incidents in terms of public health of any delay associated with the exchange of information and with the management of these incidents, recent pharmacovigilance issues that occurred with medicinal products authorised in the EU (sodium valproate, benfluorex, domperidone, etc.) have been shown to have significant public health impacts. It is estimated that the number of deaths attributed to benfluorex in France is between 500 and 2000 over the 33 years during which benfluorex was authorised (Fourneir & Zureik, 2012). Similarly, one study estimated that 231 additional deaths could have been attributed to domperidone in 2012 (Hill et al., 2011). In France, between 2150 and 4100 children since 1967 are suspected of having a birth defect following an exposure to valproate in utero (ANSM, 2017). Although estimates of deaths or harm attributed to adverse effects of medicinal products need to be made with caution since they are usually obtained from observational studies which rely on major assumptions (e.g. case definition, incidence of the reaction and uncertainty of this

[29] Incidents that may be caused by product quality problems are usually dealt with in accordance with another separate procedure. The Incident Management Plan involving the Incident Review Network will be triggered only in the cases when there is a major public health impact relating to the safety, efficacy and/or availability of medicinal products.

incidence estimate), given the potential public health impact of recent pharmacovigilance issues which occurred with these products and their perception by the general public, any delayed exchange of information could result in delayed regulatory action and therefore impose public health damage in the country(ies) in which the risk was not primarily identified and communicated.

A4.2.5. Public health threats (pandemic influenza)

The EMA supports global efforts to respond to existing and emerging public health threats such as antimicrobial resistance, the risk of falsified medicines, biological and chemical threats and emergencies such as an outbreak or a pandemic (including for example Ebola, pandemic influenza and Zika virus outbreaks).[30] In that respect, the EMA is also providing scientific opinions to WHO via the Article 58 procedures on medicinal products for human use that are intended exclusively for markets outside of the EU (such as vaccines used in the WHO Expanded Programme on Immunisation or for protection against a public health priority disease, as well as medicines for WHO target diseases such as HIV/AIDS, malaria, or tuberculosis).

The European Commission is coordinating the preparedness and response in the event of pandemic influenza in collaboration with European public health institutions (these include the EMA, the ECDC and the member state's own public health agencies) in collaboration with the agencies of the United Nations (WHO, the Food and Agriculture Organization and with the OIE-World Organisation for Animal Health) (Commission of the European Communities, 2005).

Concerning its role in the management of the pandemic influenza, the EMA gives the scientific opinions which support the granting of marketing authorisations to influenza vaccines (e.g. Celvapan, Focetria and Pandemrix) and antivirals (oseltamivir) authorised according to the centralised procedure. The EMA has put mechanisms in place to accelerate authorisation of pandemic vaccines, these include in particular better coordination of the supply of strains and reagents; standardisation of clinical trial protocols to ensure timely initiation of trials and earlier data availability; facilitation of ethics approvals, which are locally managed in the EU, particularly for the conduct of studies in children and pregnant women. The EMA has also undertaken discussions with ECDC and WHO concerning the earlier availability of data on the virus strain, disease severity, innate population-based immunity to the new strain and cross-protection of seasonal and other influenza vaccines to direct the choice of vaccine and vaccination strategy. In particular, the communication with WHO is essential considering that two bottlenecks in the vaccine-production process are the availability of knowledge about strains. The EMA is responsible for the coordination of the monitoring of the benefit/risk balance of the vaccines and medicinal products used to fight pandemic influenza. It closely monitors the safety profile of influenza vaccines which are centrally authorised, to ensure a timely detection of safety signals (e.g. signal of narcolepsy detected in 2009) (EMA et al., 2009)[31]. During a pandemic, the EMA communicates with the European (national) Public Health Agencies via a group co-ordinated by the European Commission

[30] See EMA Public health threats http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/general/general_content_000788.jsp&mid=WC0b01ac05809db683 (accessed on 10 August 2017).

[31] See also the pandemic influenza pharmacovigilance updates published on a weekly basis during the 2009 pandemic influenza available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000246.jsp&mid=WC0b01ac058004bf57 (accessed on 10 August 2017).

(EMEA, 2006). Discussion with Public Health Agencies on the choice of vaccine at specific time points pre-, during and post-pandemic and the respective target groups for vaccination are essential in planning a suitable regulatory strategy. The MHRA would have to put similar measures in place to ensure the timely choice of and availability of influenza vaccines in the UK. The multiplication of stakeholders involved in the discussions with WHO and with the pharmaceutical companies manufacturing influenza vaccines could lead to some confusion or disruption in the manufacturing, authorisation and supervision of medicines used during the pandemic influenza (due in particular to different, possibly conflicting advice or requirements). In order to promote equitable access to vaccines against pandemic influenza, the European Commission has established a process for the joint procurement of pandemic influenza vaccines with those member states that have expressed an interest to participate. This also includes the possibility of resale between member states of any excess amounts of vaccine. The withdrawal of the UK from the EU will make this option unavailable to the UK.

In conclusion, based on the review of the guidelines and procedures related to the preparedness and response planning in case of pandemic influenza, we are anticipating that the loss of collaboration between the MHRA and the UK public health institutions involved in the management of pandemic influenza could have some negative public health consequences in terms of communication with the international stakeholders involved in the management of the pandemic, timely availability of the vaccines in the UK, monitoring of the safety profile of the products administered to large amount of the population. This loss of collaboration would occur in a situation where population mortality can increase quickly as the pandemic progresses in the world.

A4.2.6. Supply and possible shortages of medicines

Literature

Several different reasons have been identified to explain drug shortages in the world. A study conducted by the FDA in 2012 has shown that failures in product or facility quality is the primary factor leading to disruptions in manufacturing (in 64% of cases). Not every production disruption leads to a medicinal shortage, but virtually all shortages are preceded by disruptions in production. The majority of production disruptions resulted from product-specific quality failures (in 27-31% of cases) or efforts to remediate or improve a problematic manufacturing facility (in 35-37% of cases). The lack of availability of raw materials account for approximately 25% of the shortages. Quality or manufacturing concerns can involve issues that could pose extreme safety risks to patients (i.e. septic risk). Other reasons include increased demand, the loss of a manufacturing site, or a discontinuation of the product. Other issues can compound these shortages (FDA, 2013; Woodcock and Wosinska, 2013).

Drug shortages have recently increased in the EU (EMA, 2013). Shortages have affected several classes of medicines including injectable chemotherapy agents, anaesthetic agents, intravenous nutrition and electrolyte products, enzyme replacement products (enzyme replacement therapies for Fabry's disease and Gaucher's disease) and radio-pharmaceuticals. Manufacturing issues have been put forward to explain drug shortages in the EU (EMA, 2013). Importantly, the role of the parallel export trade market has also been pointed out as a source of shortages in the UK (Barron et al, 2012).

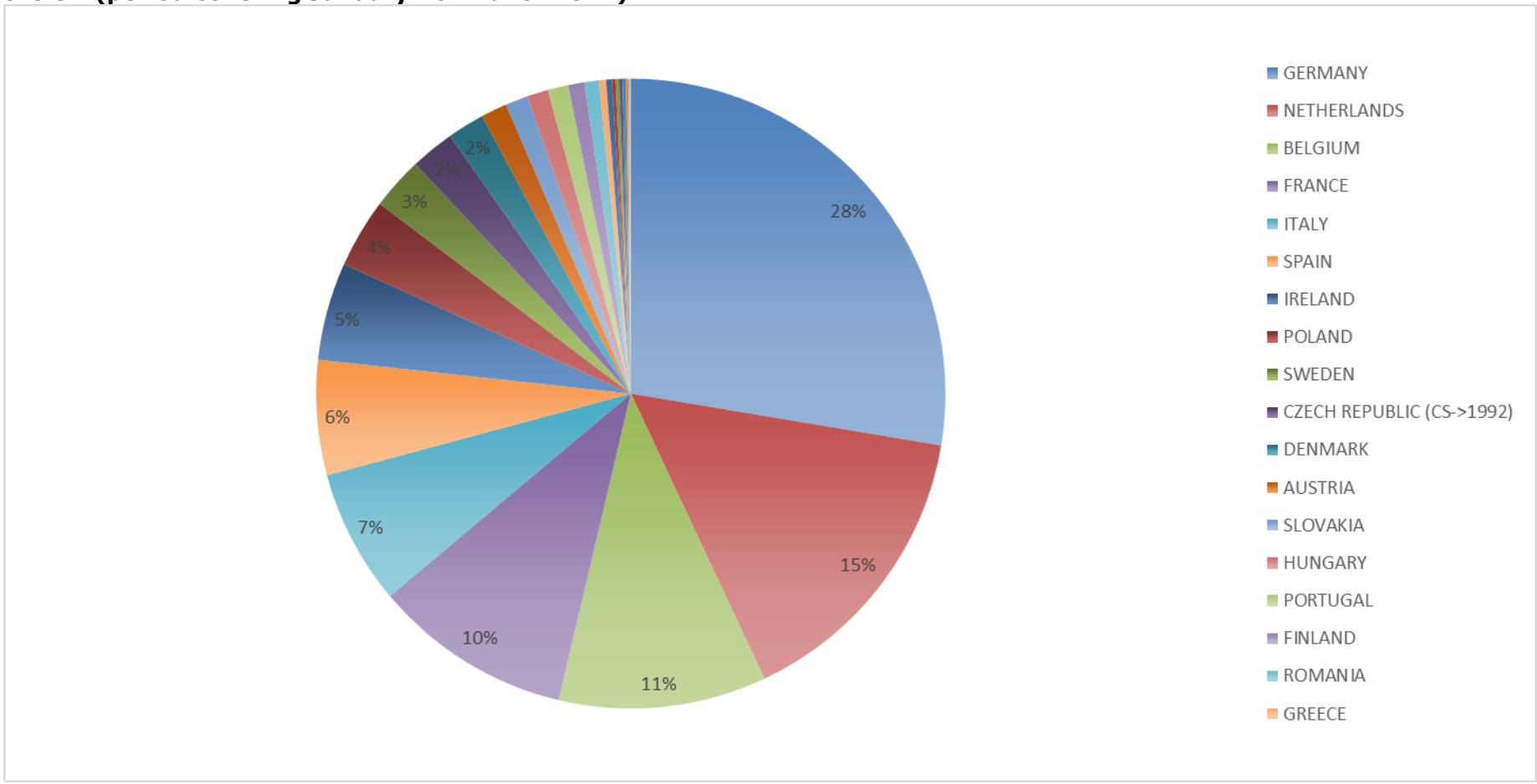
Imports and exports

The EU (including the UK) was by far the largest world trader in medicinal and pharmaceutical products (SITC division 54) in 2016. Its main trading partners were the United States and Switzerland.[32]

In 2016, the UK exported twice the amount (in monetary value) of pharmaceutical products (€15,816million) than it imported (€7,768million).[33,34] UK exports of pharmaceuticals accounted for 11% of the EU exports (Germany has the highest share, 25% of EU exports, for the average EU country the share is 4%).[35] The SITC classification makes it very difficult to know precisely what types of products are exported and imported in the UK (Eurostat, 2017). The UK exports an average €65 billion worth of chemical and related products (not elsewhere specified, SITC) which includes pharmaceutical products (average for period 2014-2016). Annually on average the share of exports going to the EU27/EEA is 53%. The data from Eurostat show that the UK imports around 54% of its pharmaceuticals from Germany, the Netherlands and Belgium (Figure A10), and exports 48% of its medicines to three EU countries: Germany, the Netherlands and France (Figure A11). Between January 2014 and March 2017[36], the UK imported in total more pharmaceuticals from the EU27/EEA than it exported (UK imports from the EU27/EEA: €20.6 billion; UK exports to the EU27/EEA: €12.2 billion, total for the period).

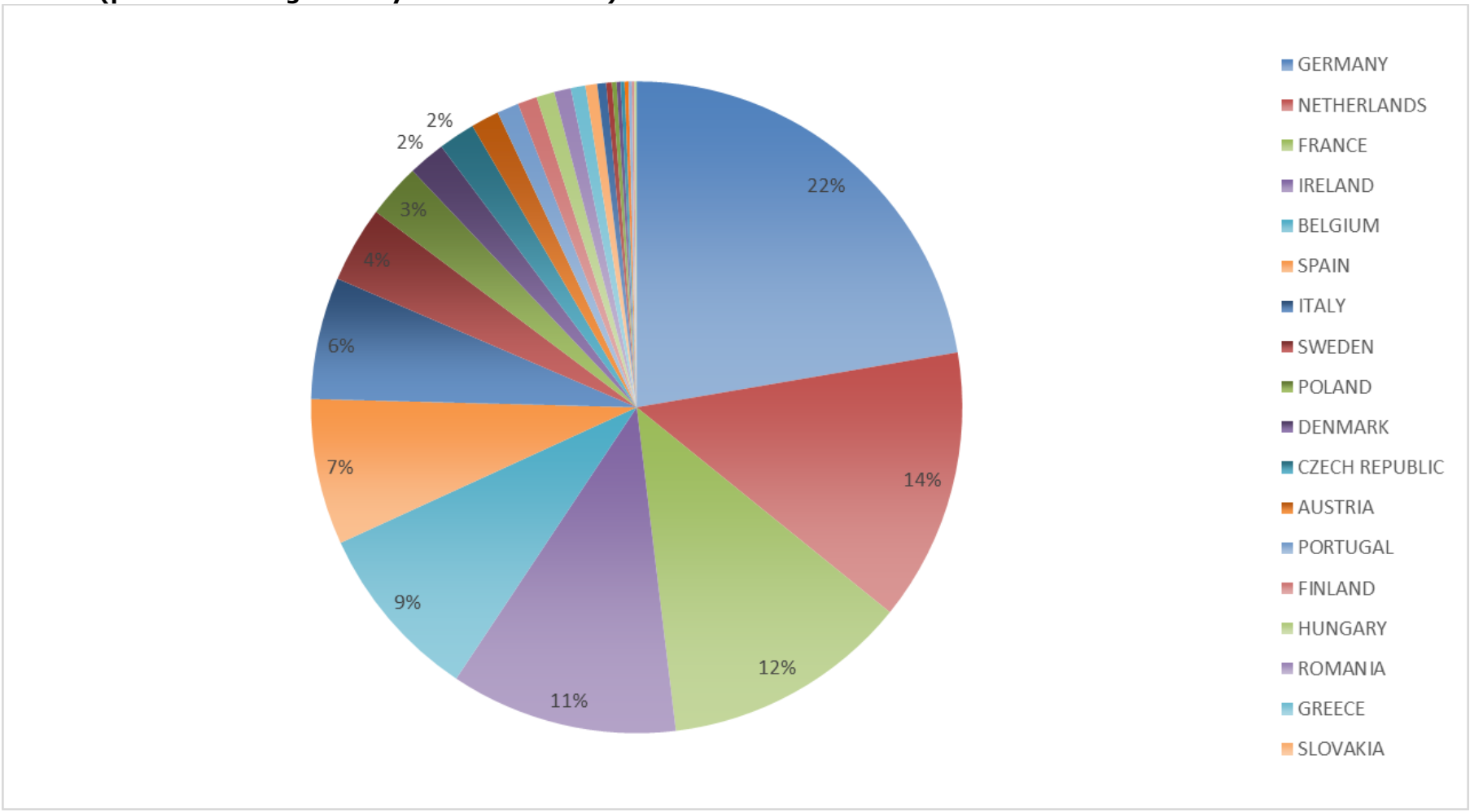
[32] http://ec.europa.eu/eurostat/statistics-explained/index.php/File:Extra-EU-28_trade_in_medicinal_and_pharmaceutical_products,_top_10_trading_partners,_2001,_2006,_2011_and_2016_(EUR_million)-T1.png
[33] Note this is extra-trade only, that with non-member countries.
[34] http://ec.europa.eu/eurostat/statistics-explained/index.php/International_trade_in_medicinal_and_pharmaceutical_products#Further_Eurostat_information
[3535] http://ec.europa.eu/eurostat/statistics-explained/index.php/File:Extra-EU-28_trade_in_medicinal_and_pharmaceutical_products,_by_Member_State_(EUR_million)-T2.png
[36] Eurostat data for Q1 2017 (Jan-Mar) are provisional and will be revised and changed.

Figure A10: Proportion of imports (in euros) of pharmaceuticals (SITC codes 541 and 542) from the EU27/EEA countries to the UK (period covering January 2014 until 2017)



Source: Eurostat database http://ec.europa.eu/eurostat/web/international-trade-in-goods/data/database (accessed on 11 July 2017).

Figure A11: Proportion of exports (in euros) of pharmaceuticals (SITC codes 541 and 542) from the UK to the EU27/EEA countries (period covering January 2014 until 2017)



Source: Eurostat database http://ec.europa.eu/eurostat/web/international-trade-in-goods/data/database (accessed on 11 July 2017).

GMP sites

The number of GMP sites certified by EU competent authorities is shown in Table A9. The results shows that the UK hosts the second highest number of GMP sites (684) and manufacturing sites (444), second to Germany (969 and 695 sites, respectively). The UK hosts the third highest number of sites involved in batch certification operations (231 sites), after France (321) and Germany (302). Finally, the UK has the highest number of sites certified to import pharmaceuticals from third countries (357), ahead of Germany (262). The results show that the UK, like Germany, France, Spain, Poland and The Netherlands, hosts an important number of sites specialised in the 3 types of GMP operations. Our analysis confirms the status of the UK as a major importer, manufacturer and batch certifier of medicinal products in the EU, along with France and Germany. Note that the GMP certificate for the importation of products is an authorisation to import these products from third countries, the information contained in the GMP certificates does not include any information whether the products imported from a third country and/or manufactured in the UK are subsequently exported to other member states in the EU27/EEA.

The analysis of the type of products involved in the manufacturing operations conducted in the UK is provided in Table A10. These data show that most of the GMP sites in the EU are involved in the:

- Manufacturing of aseptically prepared and non-sterile medicinal products;
- Importation of non-sterile products; and
- Batch certification of non-sterile products.

Importantly, our analysis shows 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. Our analysis also shows that the UK is specialised in the manufacturing, importation and batch certification of advanced therapy medicinal products (gene and cell therapies).

Our analysis of the EudraGMDP database identified that 296 sites received a certificate to manufacture, import and distribute specific APIs in the UK. Of these, 61 were authorised to manufacture APIs, 105 were authorised to import and 128 were authorised to distribute them (the manufacturing operation was not specified for 2 of these sites). In total, these 296 sites were involved in the manufacturing, importation and distribution of 5883 different active substances. Of these 1793 sites are authorised to manufacture or import APIs from third countries, 539 sites manufacture APIs (30%) and 1253 sites are authorised to import APIs from third countries (70%). The rest of the sites, 4089, are involved in the distribution of APIs (the GMP certificate does not specify the country of origin or the destination of the active substance).

As at March 2017 there were 496 products included in the WHO list of essential medicines. Cross-linking this list with the active substances manufactured (APIs), imported or distributed in the UK, identified that 37% of the active substances processed in the UK are included in the WHO list of essential medicines. In particular, we estimate that 28% of the substances manufactured and 41% of the substances imported in the UK are included in this list (Table A11).

Table A9: GMP certified sites involved in the manufacturing, batch certifications and importing of medicinal products

Countries	Number of sites which received an EU GMP certificate	Manufacturing	Batch certification (manufactured and imported)	Importation of products from third countries
Australia	61	50	54	0
Austria	167	116	99	46
Belgium	158	113	91	49
Brazil	17	17	2	0
Bulgaria	53	46	24	11
China	90	90	6	0
Croatia	29	20	23	13
Cyprus	25	19	15	9
Czech Republic	144	107	103	29
Denmark	130	82	55	49
Egypt	10	10	0	0
Estonia	10	7	6	3
Finland	32	28	8	8
France	391	328	321	140
Germany	969	695	302	262
Greece	75	44	55	44
Hungary	116	96	42	23
India	320	320	12	0
Ireland	164	125	77	61
Italy	193	191	30	1
Japan	39	39	17	0
Latvia	25	15	10	9
Lithuania	17	11	3	5
Malta	29	11	12	22
Mexico	11	11	0	0

Netherlands	237	125	178	85
Norway	30	21	14	6
Poland	377	344	166	27
Portugal	48	42	23	11
Republic of Korea	25	25	0	0
Romania	58	38	21	21
Russian Federation	16	16	4	0
Serbia	14	14	2	0
Singapore	15	15	1	0
Slovakia	32	24	20	12
Slovenia	43	16	31	17
Spain	351	332	219	83
Sweden	68	52	43	21
Turkey	45	45	1	0
United Kingdom	684	444	231	357
United States	324	324	8	0

Source: European Medicines Agency EudraGMDP database
http://eudragmdp.ema.europa.eu/inspections/displayWelcome.do;jsessionid=e8AO_2UuSrZFay8C_Y8MjiNrxiTjHGLx_voN1kltBFdToDzAT0L0!-444695058
(accessed on 12 July 2017).

Table A10: Type of products involved in manufacturing, batch certification and importing operations at UK GMP sites

Operation	Type of medicinal product	Number sites located within the UK	Proportion of sites located in the UK	Number of sites located outside the UK	Proportion of sites located outside the UK	Proportion of UK sites relative to other EU sites
batch operations	biotechnology products	42	0.016	332	0.019	0.859
batch operations	blood products	19	0.007	114	0.007	1.131
batch operations	cell therapy product	15	0.006	75	0.004	1.358
batch operations	immunological	42	0.016	305	0.018	0.935
batch operations	non-sterile products	218	0.086	2416	0.140	0.612
batch operations	sterile products	138	0.054	1717	0.099	0.546
importation	biotechnology medicinal products	102	0.040	311	0.018	2.226
importation	blood products	41	0.016	83	0.005	3.353
importation	cell therapy products	44	0.017	41	0.002	7.285
importation	gene therapy	51	0.020	46	0.003	7.526
importation	immunological products	85	0.033	223	0.013	2.587
importation	non-sterile products	415	0.163	1395	0.081	2.019
importation	sterile medicinal products	294	0.115	961	0.056	2.077
manufacturing	API	69	0.027	776	0.045	0.604
manufacturing	aseptically prepared	182	0.071	1882	0.109	0.656
manufacturing	biotechnology products	73	0.029	439	0.025	1.129
manufacturing	blood products	25	0.010	551	0.032	0.308
manufacturing	cell therapy products	36	0.014	112	0.006	2.182
manufacturing	gene therapy	32	0.013	50	0.003	4.344
manufacturing	immunological products	80	0.031	436	0.025	1.246
manufacturing	non sterile medicinal products	450	0.177	4005	0.232	0.763
manufacturing	terminally sterilised	93	0.037	1007	0.058	0.627
manufacturing	tissue engineering	1	0.000	12	0.001	0.566

Note: The proportion of UK sites relative to other EU countries is the ratio of the proportion of the sites in the UK performing this operation compared to the EU27/EEA. A ratio <1 (>1) indicates that UK contains a lower (higher) proportion of sites performing this operation compared with the rest of the EU. Source: European Medicines Agency EudraGMDP database.

Table A11: Number of API (including active substances) manufactured, imported or distributed in the UK and included in the WHO list of essential medicines

Operation	WHO essential list	Number of API	Total	Number of sites performing the operation	Percentage of sites operating on APIs included (or not) in the WHO essential list
Distribution	Yes	1490			36%
Distribution	No	2599	Total number of distribution sites	4089	64%
Importation	Yes	510			41%
Importation	No	743	Total number of importation sites	1253	59%
Manufacturing	Yes	151			28%
Manufacturing	No	388	Total number of manufacturing sites	539	72%
Unspecified	No	2	Total number of unspecified sites	2	
Total	Yes	2151			37%
Total	No	3732	Total number of distribution, importation and manufacturing sites	5883	63%

Source: European Medicines Agency EudraGMDP database.

A4.2.7. Supply chain

A4.2.7.1. Scenario 1

Impact of regulatory changes

Under Scenario 1, no changes to the supply chain are required. This scenario is thus used as the benchmark, against which changes to the supply chain that arise in Scenarios 2 to 4 are assessed. Figure A12 shows all UK-EU27/EEA interactions covered by the MRA under Scenario 1.

Note that, whilst the supply chain will not need to change, some implementation activities may be required. Scenario 1 implies the negotiation of an MRA, or the harmonisation and coordination of the information systems between NCAs of the UK and the EU27/EEA. For example, Swiss and EU Official Medicines Control Laboratories (OMCL) are entitled to interchange and share information and individual analytical results of a batch (see Doc. Ref.: EMEA/MRA/22/03). This sort of information sharing

between the UK's OMCL (NIBSC) and its European counterparts would need to be implemented in order to achieve mutual recognition under this scenario.

Impact of changes to trade agreements

Negotiation of FTAs with the EU and adoption (or 'grandfathering') of all FTAs the EU27/EEA has currently in force or ongoing with third countries, as assumed in Scenario 1, would mean that no changes to supply chains would be required. Figure A13 captures how trade between the UK and the EU27/EEA would function in this scenario.

Under this scenario:

- UK manufacturers of APIs and FPs will be able to export their products into the EU27/EEA (or third countries) without incurring additional costs due to customs duties or WTO tariffs;
- EU27/EEA (or third country) manufacturers of APIs, and FPs will be able to export their products into the UK without incurring in additional costs due to custom duties and WTO tariffs;
- Manufacturers of FPs and market authorisation holders from the UK, the EU27/EEA (and third countries where relevant) will be able to use their established supply chains, as if they still were part of the single market.

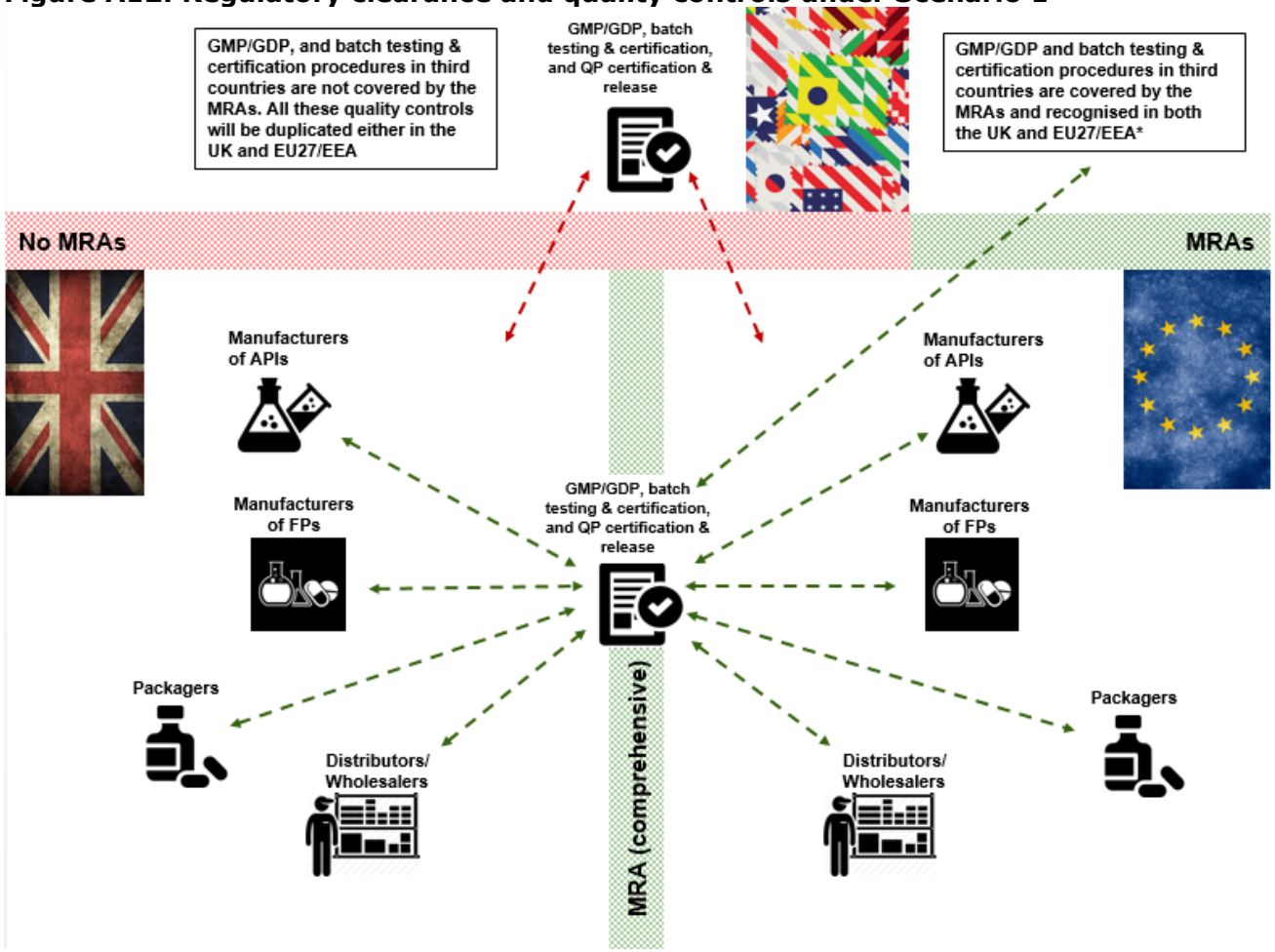
Under the auspices of the comprehensive MRA both, the EU27/EEA-based manufacturer of APIs and intermediate inputs, the UK-based manufacturer of finished medicines and packagers have to comply with the standard GMP qualification and being certified by the corresponding NCA.[37] Certifications of GMP issued and inspections carried out by the MHRA or any other NCA of EU27/EEA member states will be mutually recognised. Therefore, certifications of GMP in the countries where the products are exported to or imported from should not be duplicated. As a consequence companies would be allowed to manufacture in the same plants as before Brexit because GMP regulations would remain centralised for the EU27/EEA plus the UK.

Distributors/wholesalers will also have to comply with the standard GDP qualification which under the auspices of the comprehensive MRA. Certifications issued and inspections carried out by any NCA of the UK and/or the EU27/EEA will also be mutually recognised. Therefore no duplications on the GDP certifications and inspections would be expected and companies' supply chain of medicines regarding the distribution/ wholesale stage across UK plus EU27/EEA would remain equal.

Additionally, certificates for batches compliance with GMP and MA specifications are allowed to be issued indistinctly in the UK or in the EU27/EEA. Furthermore, the location of the QP can also be the UK or the EU27/EEA. Therefore, a comprehensive MRA (Scenario 1) will keep all regulatory procedures of the supply chain including GMP, GDP, QP certifications, and batch release, centralised for the UK plus EU27/EEA. Scenario 1 (our most optimistic case) will result then in an identical regulatory functioning as before the UK's withdrawal from the EU.

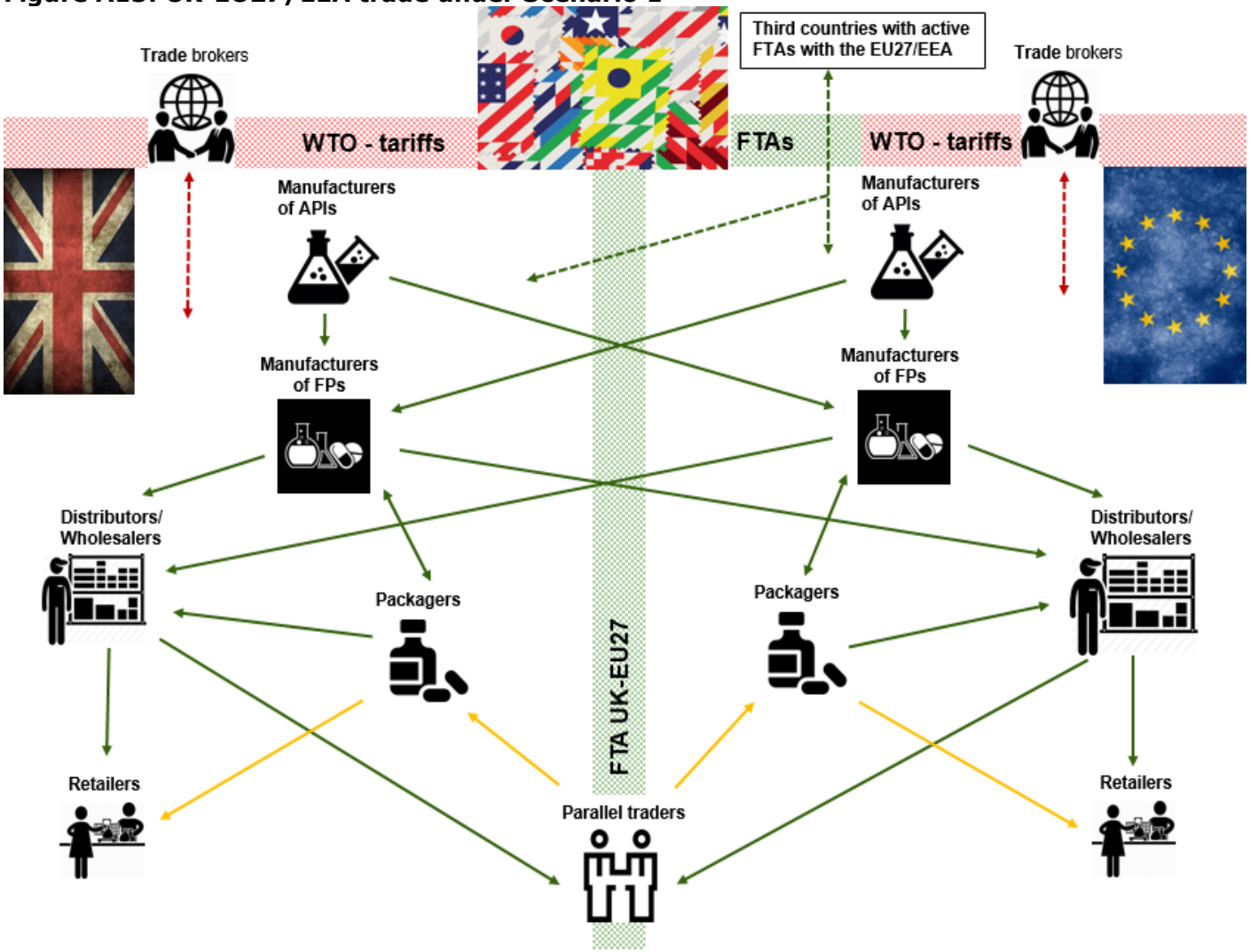
[37] Information about the GMP accessible at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001205.jsp&mid=WC0b01ac0580027088

Figure A12: 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 testing and release activities performed by the NCAs of the UK and EU27/EEA are also mutually recognised. The full quality control and regulatory clearance process is centralised and recognised by both, the UK and EU27/EEA. Green dashed lines going from centralised regulatory processes to stakeholders reflects the centralisation as opposite to red dashed lines which reflect duplication of the same in third countries where there is no active MRA.
*Countries with which the EU has currently active MRAs are Australia, New Zealand, Canada, Japan, Israel, Switzerland and the US.

Figure A13: 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.

Finally, under this scenario we assume that parallel trade will retain the same impact/role after Brexit as before the UK's withdrawal from the EU. Under Scenario 1, the extent to which parallel trade will continue at the same level between the UK and the EU27/EEA as before Brexit[38] will depend on the UK's government and NHS' appetite to access medicines at lower prices. It is reasonable to assume this will be unchanged. The total value of parallel imports will however also depend on the Euro to Pound Sterling exchange rate.

Specific impacts for stakeholders in the UK manufacturer of finished pharmaceuticals example

Figure A14 illustrates the impact of Brexit (under Scenario 1) from the perspective of an UK-based manufacturer of finished medicines.

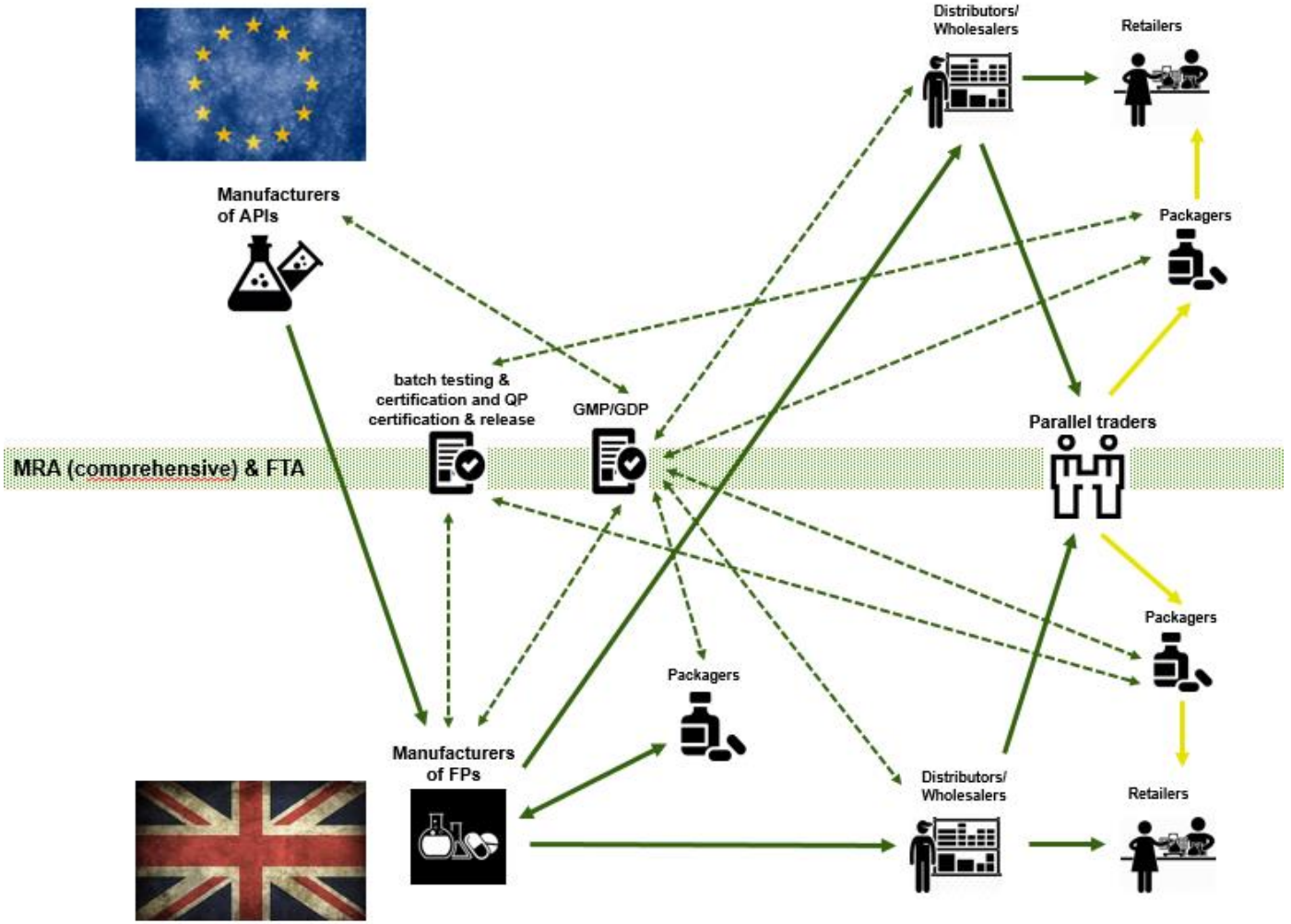
Based on this example:

1. Manufacturers of APIs:
   - Must be GMP certified by the host country's NCA, in line with EMA standards. Inspections would also be carried out by the NCA. Due to the agreed MRA, the MHRA would recognise the validity of certification and inspections conducted by other NCAs (no duplication needed);
   - With an FTA in force, exportation of APIs to the UK would not be subject to tariffs, custom duties, or other non-tariff measures.
2. Manufacturer of FPs:
   - Must be GMP certified by the MHRA in the UK. Inspections of compliance with GMP would also be carried out by the MHRA. Both certifications and inspections would be recognised by the EMA and consequently by NCAs of the EU27/EEA's member states;
   - Batch testing and certification taking place in the UK would be recognised by the EMA and all the NCAs of the EU27/EEA member states;
   - The QP would remain located in the UK and batch release facilities would not need to be duplicated and they would remain located in the UK (or the EU27/EEA) as they were before Brexit;
   - Under an FTA, materials imported into the UK for manufacturing, including APIs, excipients, intermediate inputs, would not be subject to WTO tariffs, custom duties, or non-tariff measures.
3. Packagers:
   - MHRA would control the GMP certification and compliance of packagers in the UK. GMP certificate and inspections would be recognised by the EU27/EEA due to the agreed MRA;
   - Parallel trade would be allowed between the UK and the EU27/EEA which involves repackaging of parallel imports/exports. Currently any repackaging of a batch of medicines that has already been released must be reviewed and approved by the NCA. Prior to certification by the NCA, the QP should confirm compliance with the national requirements for parallel importation and EU rules for parallel distribution, as well as certify that the repackaging has been performed in compliance with the marketing authorisation (MA) specifications and GMP.

[38] Parallel trade value amounted to €5.5bn in 2016, from which a 20% (€1.1bn) correspond to the UK (QuintilesIMS, 2017).

4. Distributors/wholesalers:
    - GDP certifications and inspections will be carried out by the NCAs of each country – the MHRA in the UK or the corresponding NCA of member states of the EU27/EEA – and will be mutually recognised by each other as covered by the MRA;
    - The agreed FTA would ensure that the imported medicines from UK-based manufacturers into the EU27/EEA would not be subject to tariffs, custom duties, or to non-tariff measures;
    - Distributors/wholesalers continue dealing with parallel traders to parallel import and export finished medicines across EU27/EEA countries and the UK.
5. Parallel trade:
    - With both an FTA and a MRA in force, we assumed that parallel traders would still be allowed to buy medicines from distributors/wholesalers in low-price countries and resell to retailers in higher-price countries;
    - For parallel importation and distribution, any repackaging carried out on a batch that has already been released must be approved by the NCA of the importing country. The QP should confirm compliance with national requirements for parallel trade and EU rules for parallel distribution as well as certify that the repackaging has been performed in accordance with the MA specifications and GMP.

Figure A14: Supply chain of an UK-based manufacturer of FPs under Scenario 1



Note: Dashed lines reflect regulatory procedures involved in the supply chain as per Scenario 1. Solid lines reflect economic and trade transactions inter- and intra-country. Green lines reflect no impact of Brexit in such specific part of company's supply chain. Parallel trade is reflected by yellow lines to point out that it is an arbitrage activity affecting prices, access and affordability which is not essential for the supply of medicines from the manufacturer of FPs perspective.

A4.2.7.2. Scenario 2

Impact of regulatory changes

The key change from Scenario 1 is the scope of the MRA. Under Scenario 2, the releases of batches conducted in the UK and in the EU27/EEA would not be mutually recognised, the same would apply to the official batch release. Figure A15 shows UK-EU27/EEA interactions under Scenario 2.

Under this scenario, batch testing, batch release and QP certificates of compliance with GMP and MA specifications must be conducted separately for the EU27/EEA and the UK. This means that, for UK-based companies, batch sample testing facilities within the EU27/EEA (or within the UK if EU27/EEA-based) must be acquired. Companies have estimated the cost of establishing each new sample testing facility in the UK or the EU27/EEA (including hiring QPs, transfer facilities, new investments) in the range of £10-£20 million (see Annex 5).

The EU27/EEA's MRAs with third countries would be adopted by the UK, but batch release would still need to be conducted in the UK.

Impact of changes in trade agreements

This is the same as in Scenario 1.

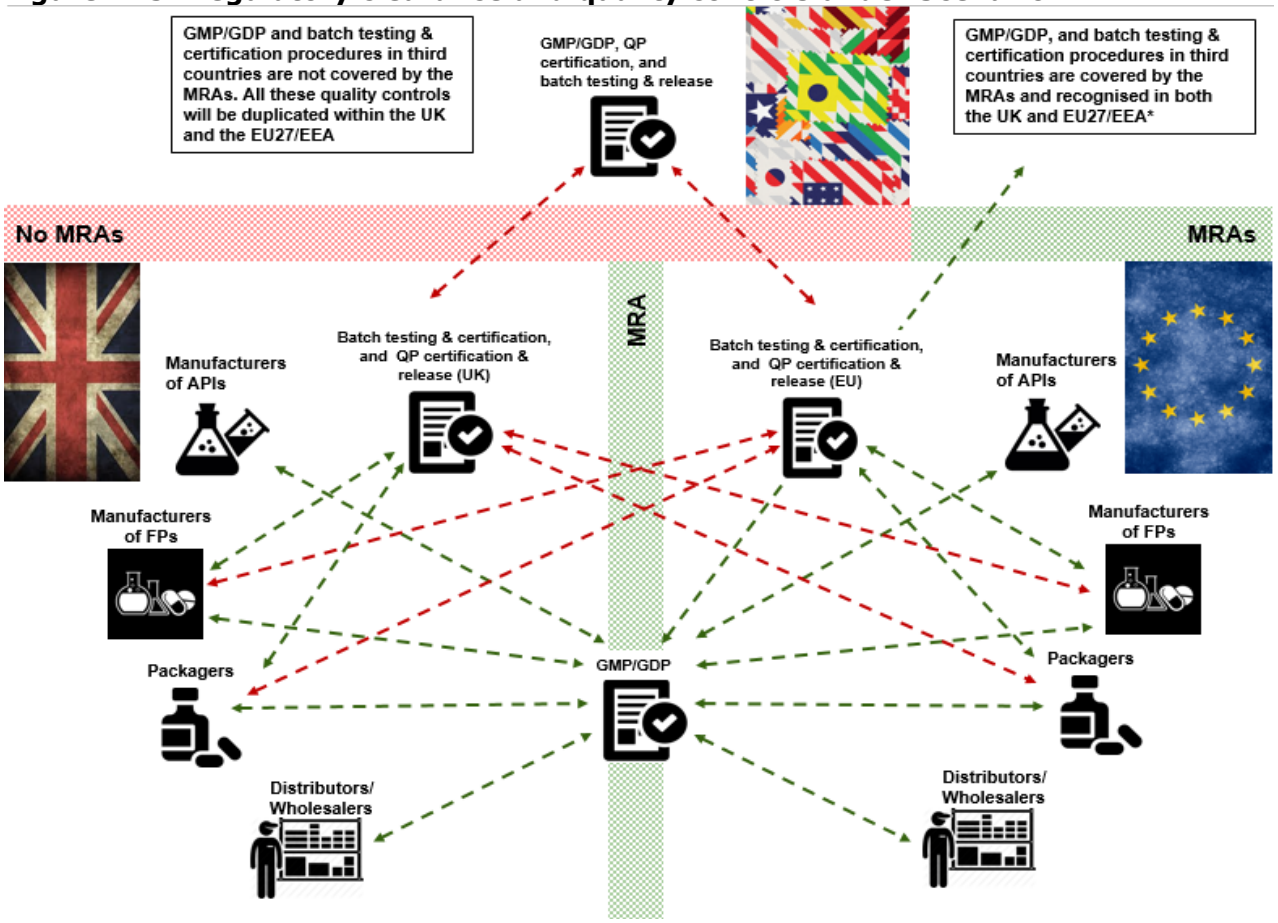
Specific impacts for stakeholders in the UK manufacturer of finished pharmaceuticals example

Figure A16 shows the supply chain of a UK-based manufacturer of finished products that imports APIs and intermediate inputs from the EU27/EEA, and exports the finished medicines to the EU27/EEA.

Using Figure A16 we can infer the following:

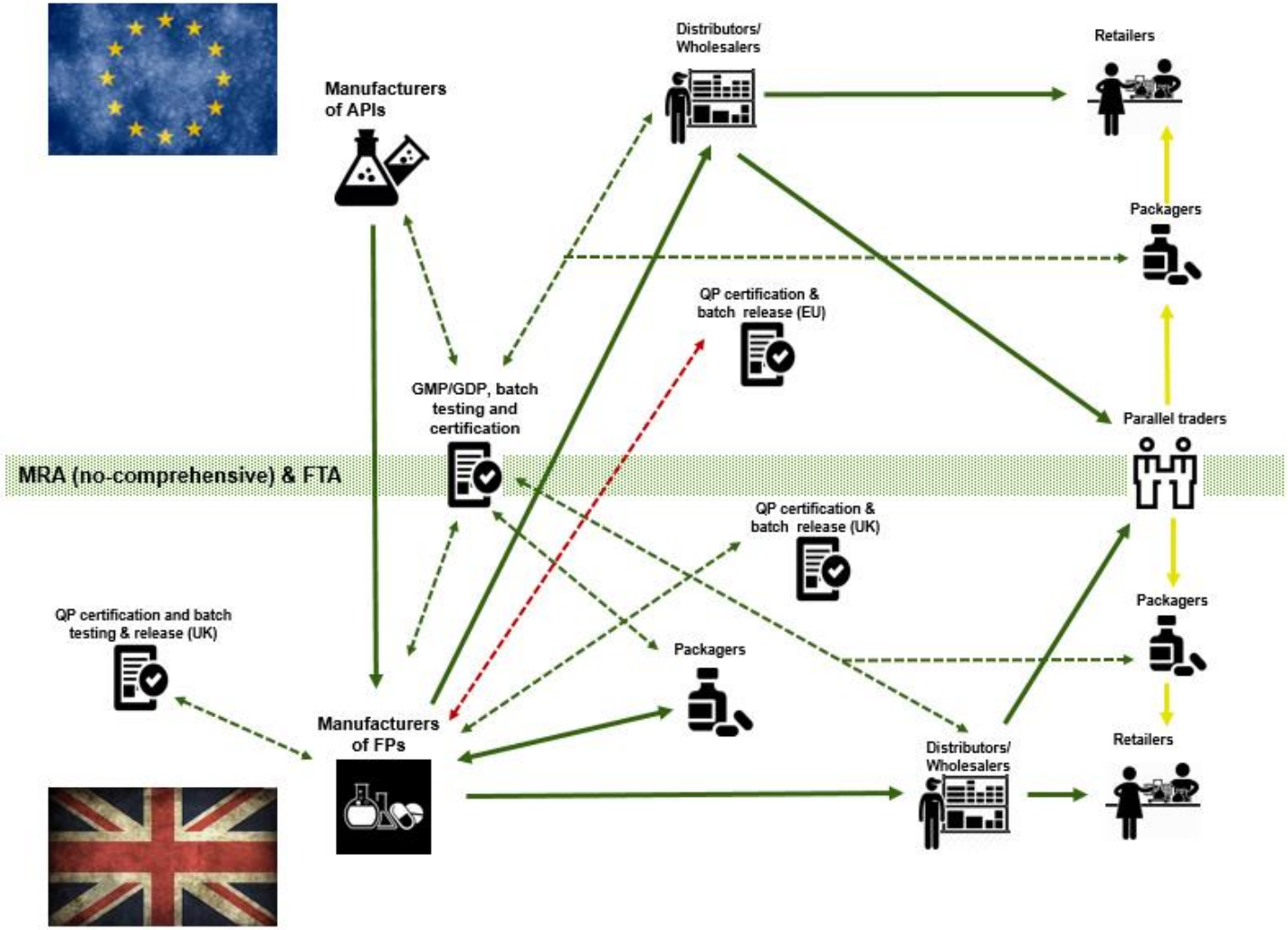
1. Manufacturer of APIs: no change from Scenario 1.
2. Manufacturer FP:
    - Batch testing, QP certification and batch release facilities would have to be established in the EU27/EEA for the official batch release of batches of finished products exported from the UK. The company must also retain batch testing, QP and batch release facilities within the UK for official batch release if MHRA requires. All batch release procedures are thus duplicated.
3. Packagers:
    - The QP should confirm compliance with national requirements for parallel importation and EU rules for parallel distribution. The QP also must certify that any repackaging of an already released batch with parallel trade purposes, has been performed in compliance with the MA specifications and GMP. Under Scenario 2 the QP doing the review of the repackaging must be located where the repackaging is completed (UK or EU27/EEA).
4. Distributors/Wholesalers: no change from Scenario 1.
5. Parallel trade:
    - 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.

Figure A15: 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 recognized) performed internally within the UK (EU27/EEA) for finished medicines manufactured and distributed within the UK (EU27/EEA). Red lines however, reflect quality control and regulatory procedures that must be duplicated under Scenario 2 when companies export finished medicines from the UK/EU27/EEA to EU27/EEA/UK. In Scenario 2 this involves the 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.
*Countries with which the EU has currently active MRAs are Australia, New Zealand, Canada, Japan, Israel, Switzerland and the US.

Figure A16: Supply chain of a UK-based manufacturer of FPs under Scenario 2



Note: Dashed lines reflect quality controls and regulatory procedures involved in the supply chain as per Scenario 2. Solid lines reflect economic and trade transactions within and between countries. Green lines reflect no impact of Brexit; red lines reflect changes due to Brexit (under Scenario 2); parallel trade is shown by yellow lines.

A4.2.7.3. Scenario 3

Impact of regulatory changes

No change from Scenario 2.

Impact of changes in trade agreements

Under Scenario 3, trade between the UK and the EU27/EEA would be regulated by the WTO MFN agreements with no transitional adoption of the existing EU27/EEA FTAs. Trade would thus be subject to WTO tariffs and custom duties, as well to other important non-tariff measures. Furthermore, UK trade with third countries which under the previous scenarios had been covered by FTAs, would no longer be covered by FTAs.

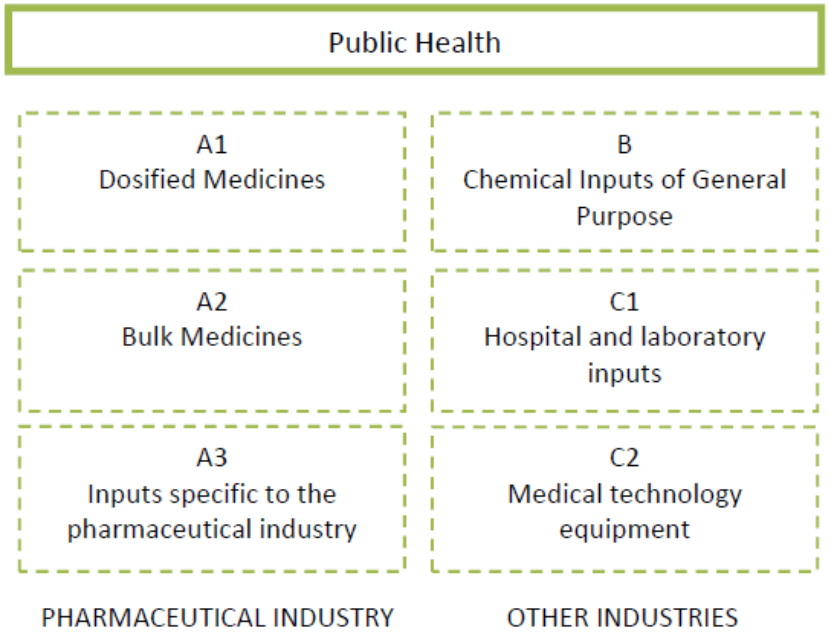
Figure A18 shows the trade relationships under Scenario 3.

The impact to pharmaceutical companies from switching to application of the WTO MFN rules (from FTAs) comes from two different sources:

- Tariff measures: the potential increase of costs by tariffs and custom duties;
- Non-Tariff measures: the threat of protectionist measures or of an additional administrative burden to arise at custom clearance stage.

Both tariff measures and non-tariff measures can be considerable for the pharmaceutical industry[39]. They affect different types of products in different ways. To analyse the effects we adopt the classification system presented by Helble (2012), in which products relevant to public health are split into six categories. Figure A18 shows the different product categories involved. The focus of this study are groups A and B.

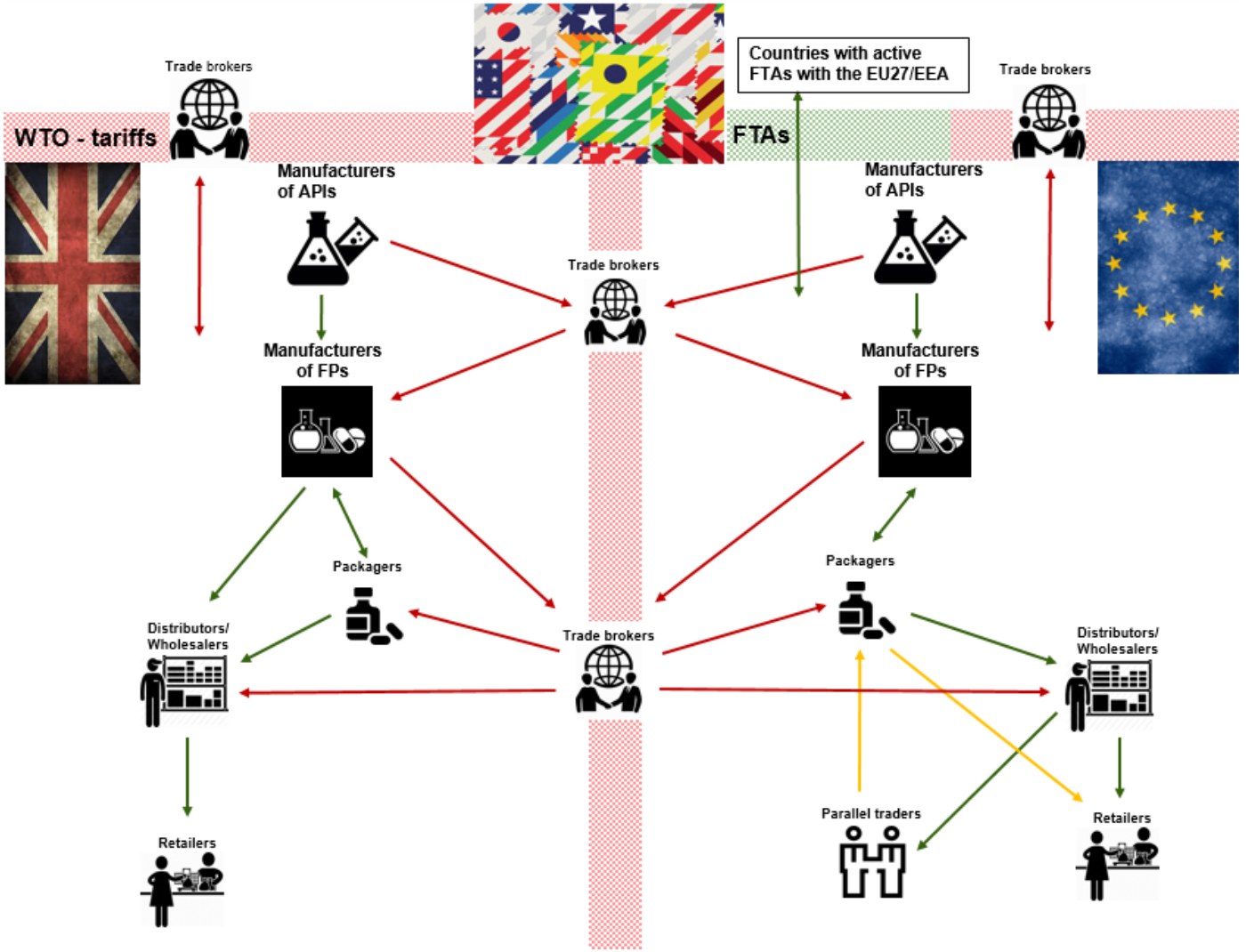
Figure A17: Product groups related to public health



Source: Helble (2012)
Note: the six groups of the table are the result of grouping the 207 within the Harmonised System subheadings containing products which can be directly linked to health purpose.

[39] Baker McKenzie (2017) estimate the total additional cost of trade for the UK Health Care sector (tariff and non-tariff measures) of £0.3 billion. Non-tariff measures represent 57% of the total.

Figure A18: Trade under WTO 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.

Tariff measures will impose additional costs for manufacturers importing APIs and intermediate inputs (groups A3 and B) (the WTO tariff for APIs is within the range of 6%-15%). The trade of finished medicinal and pharmaceutical products (groups A1 and A2) is regulated by the Pharmaceutical Tariff Elimination Agreement (PTEA), under which all parties signing the agreement[40] have committed to eliminate tariffs on all finished pharmaceutical products (Helble, 2012).

Non-tariff measures affect groups A and B and can be grouped into the following five categories:

- sanitary and phytosanitary measures (e.g. restrictions to additives, contaminants, disease-causing organisms),
- technical barriers to trade (e.g. labelling requirements, quality standards, requirements of product size, import testing requirements),
- customs formalities,
- contingent protection (antidumping, safeguards, and countervailing duties),
- quality and quantity control measures (such as licenses or quotas) (Helble and Shepherd, 2017).

The EU is currently applying technical barriers to trade to all pharmaceutical products imported from third countries under WTO rules, and applying sanitary and phytosanitary measures to 28% of pharmaceutical products that are imported from third countries under WTO rules (Helble and Shepherd, 2017). Non-tariff measures like technical barriers to trade and sanitary and phytosanitary measures may lead to delays in accessing markets, additional costs for importers and patients, and additional costs of storing, administrative paperwork and custom clearance for companies.

Finally, there will also be an impact on parallel trade under Scenario 3. Parallel imports to the UK would no longer be available due to the application of different intellectual property rights and patent policies in relation to products moving between the UK and the EU27/EEA. This would affect the distributors/wholesalers business and may involve medicine shortages, at least initially, and increased pharmaceutical expenditures to the NHS.

Specific impacts for stakeholders in the UK manufacturer of FPs example

Figure A19 shows the supply chain of our illustrative UK-based manufacturer under WTO trade rules (Scenario 3).

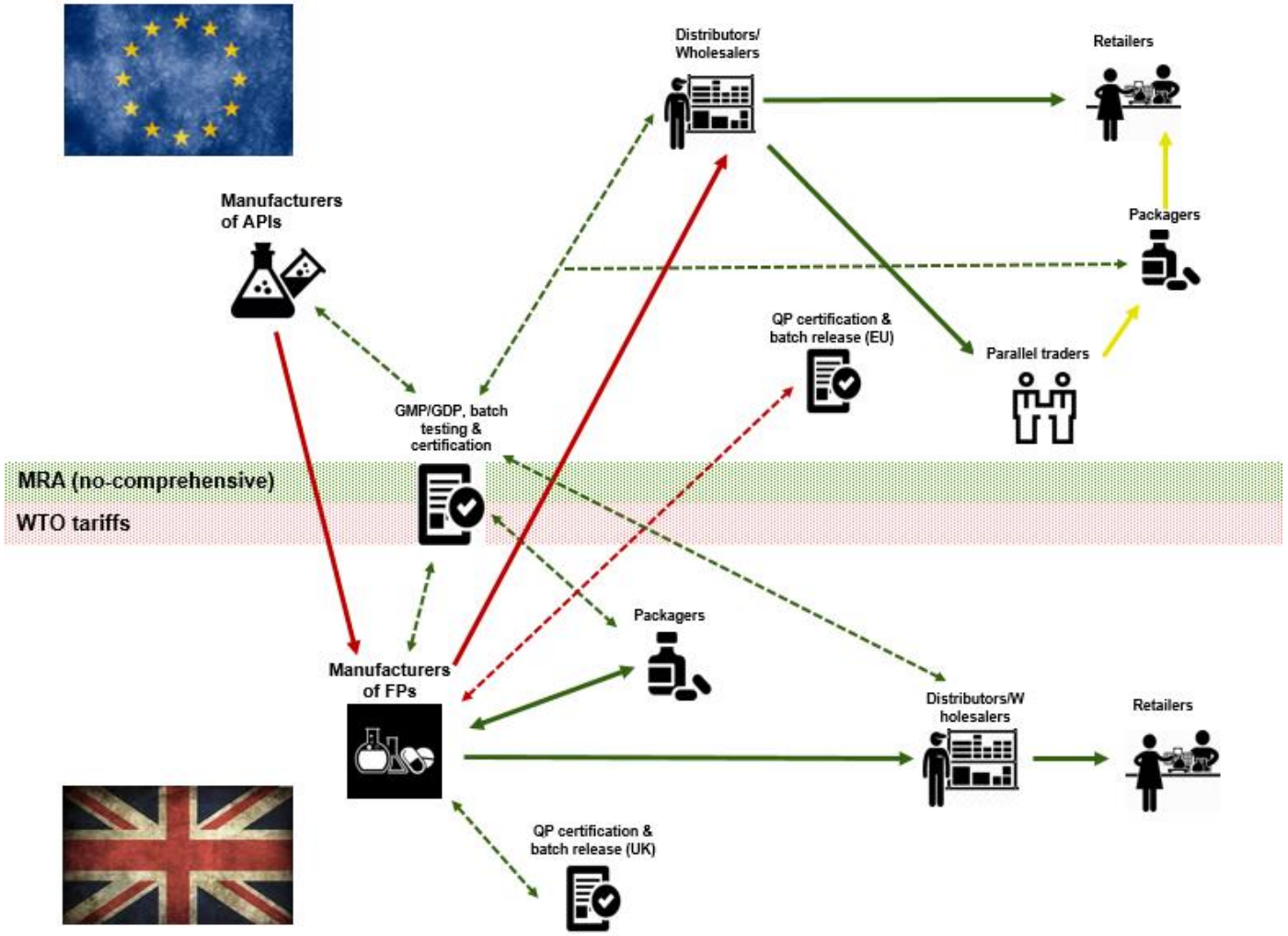
The following impacts for stakeholders are on top of those outlined in Scenario 2 (related to changes in regulation):

1. Manufacturer of APIs:
    - EU27/EEA based, they now export APIs to the UK, which may be subject to tariffs and custom duties. This may put them under a competitive disadvantage compared to a UK-based Manufacturer of APIs;
    - Non-tariff measures that the UK may impose on imports of APIs and intermediate inputs could lead to delays in supplying products and additional costs at the custom clearance stage.

[40] PTEA signatories at its inception were the European Union, US, Switzerland, Japan, Canada, Norway, Czech Republic, Slovak Republic and Macau.

2. Manufacturer of FPs:
    - Tariff measures applied to APIs and intermediate inputs imported from the EU27/EEA will increase the costs of manufacturing;
    - Finished pharmaceutical products are free of tariff measures in the EU27/EEA therefore no additional costs/impact should be incurred;
    - Non-tariff measures could lead to delays and shortages of APIs and other intermediate inputs that need to be imported to the UK;
    - Non-tariff measures may also be applied to exported finished products. Non-tariff measures may delay the supply of the medicines to external markets and may also increase the costs of storage, administrative paperwork and logistics for exporting Manufacturers of FPs.
3. Packagers: no change from Scenario 2.

Figure A19: Supply chain of an UK-based manufacturer of FPs under Scenario 3



Note: Dashed lines reflect quality controls and regulatory procedures involved in the supply chain as per Scenario 3. Solid lines reflect economic and trade transactions inter- and intra-country. Green lines reflect no impact of Brexit in such part of company's supply chain. Red lines reflect the impact of Brexit (Scenario 3) on the reflected stakeholder. Parallel trade is reflected by yellow.

4. Distributors/wholesalers:
    - Parallel trade with the UK would no longer be available. This will have a large impact on UK-based distributor/wholesalers;
    - Distributors/wholesalers supplying the medicine within the EU27/EEA member states may face the consequences of non-tariff measures. This may cause supply shortages and delays as well as additional administrative costs.
5. Parallel traders:
    - Parallel trade will no longer be available with the UK. This represents the loss of a market for parallel traders.

A4.2.7.4. Scenario 4

Impact of regulatory changes

Under Scenario 4, there is no MRA between the UK and the EU27/EEA. Figure A21 shows the supply chain changes under Scenario 4.

The main implication of the lack of an MRA is that all quality controls applied to the supply chain of medicines will be duplicated: no regulatory activity performed in the UK will be recognised in the EU27/EEA, or vice versa. The following regulatory activities will be duplicated:

- GMP and GDP certifications by NCAs in the UK and EU27/EEA member states;
- Regular inspections of compliance with GMP and GDP standards, also by NCAs in both the UK and EU27/EEA member states;
- QP certification of batches of finished medicines certifying batch compliance with MA specifications and GMP;
- Batch testing and release.

Impact of changes in trade agreements

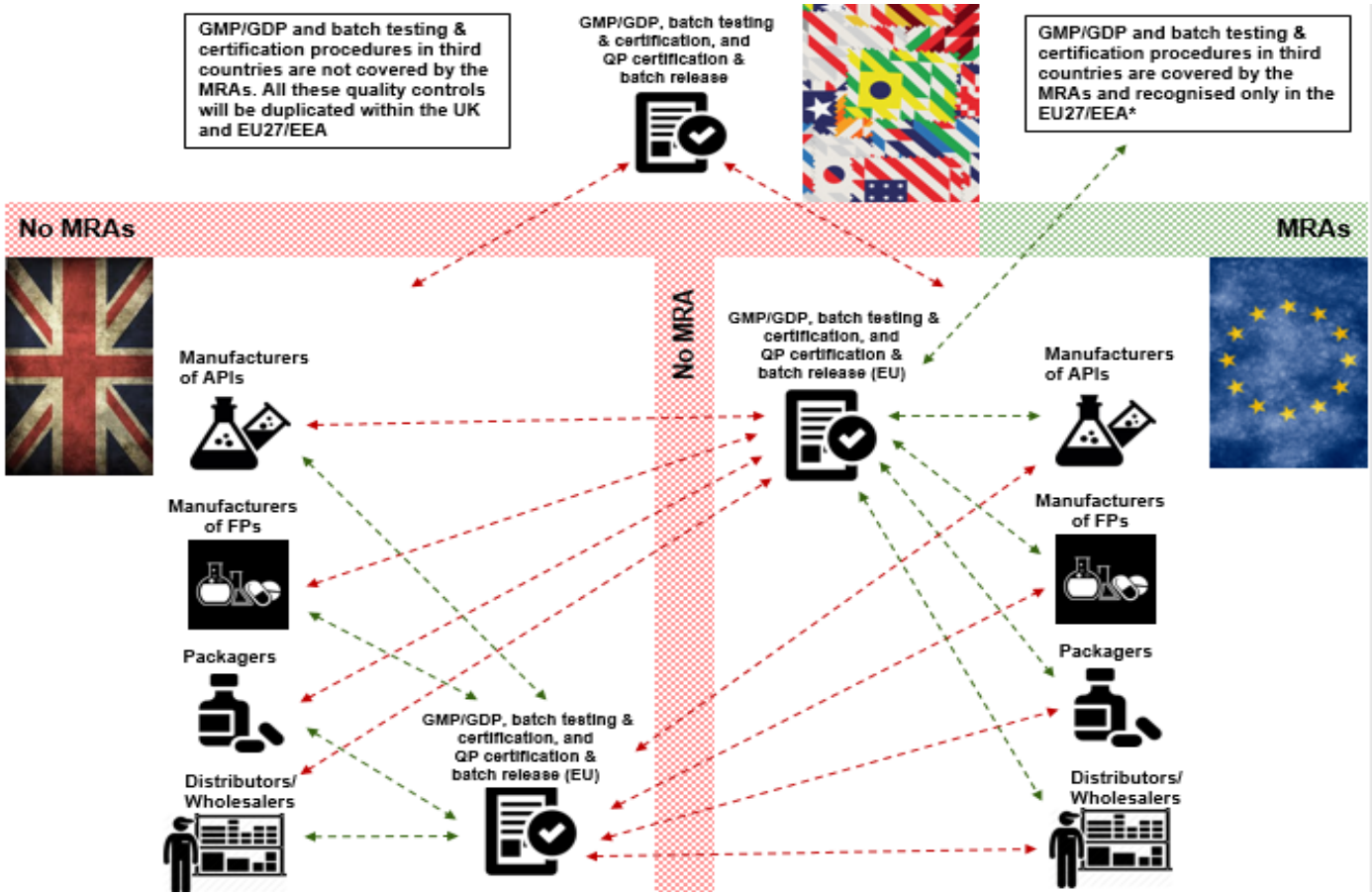
- No change from Scenario 3.

Specific impacts for stakeholders in the UK manufacturer of FPs example

The following impacts are in addition to those identified for Scenarios 2 and 3:

1. Manufacturer of APIs:
    - Any EU27/EEA-based manufacturer of APIs shall accompany active substances with a written confirmation from the EU27/EEA NCAs specifying that the plant manufacturing the exported APIs is subject to a GMP control equivalent to those in the UK. Additionally the QP of the UK-based manufacturer of FPs must certify the validity of such written confirmation. This would be a duplicated cost that would affect manufacturer of APIs in the EU27/EEA but could also be transferred in part to the manufacturer of FPs in the UK.
2. Manufacturer of FPs:
    - Manufacturers of finished medicines based in the UK would need to be GMP certified by bothMHRA and EMA (through a NCA of a member state) in order to supply medicines internally within the UK and export medicines to the EU27/EEA.. This duplication would give rise to additional costs.
    - Inspections of GMP compliance would also be performed separately by in the UK and the EU27/EEA, requiring further duplication and associated costs.

Figure A20: Lack of MRA between the UK and the EU27/EEA



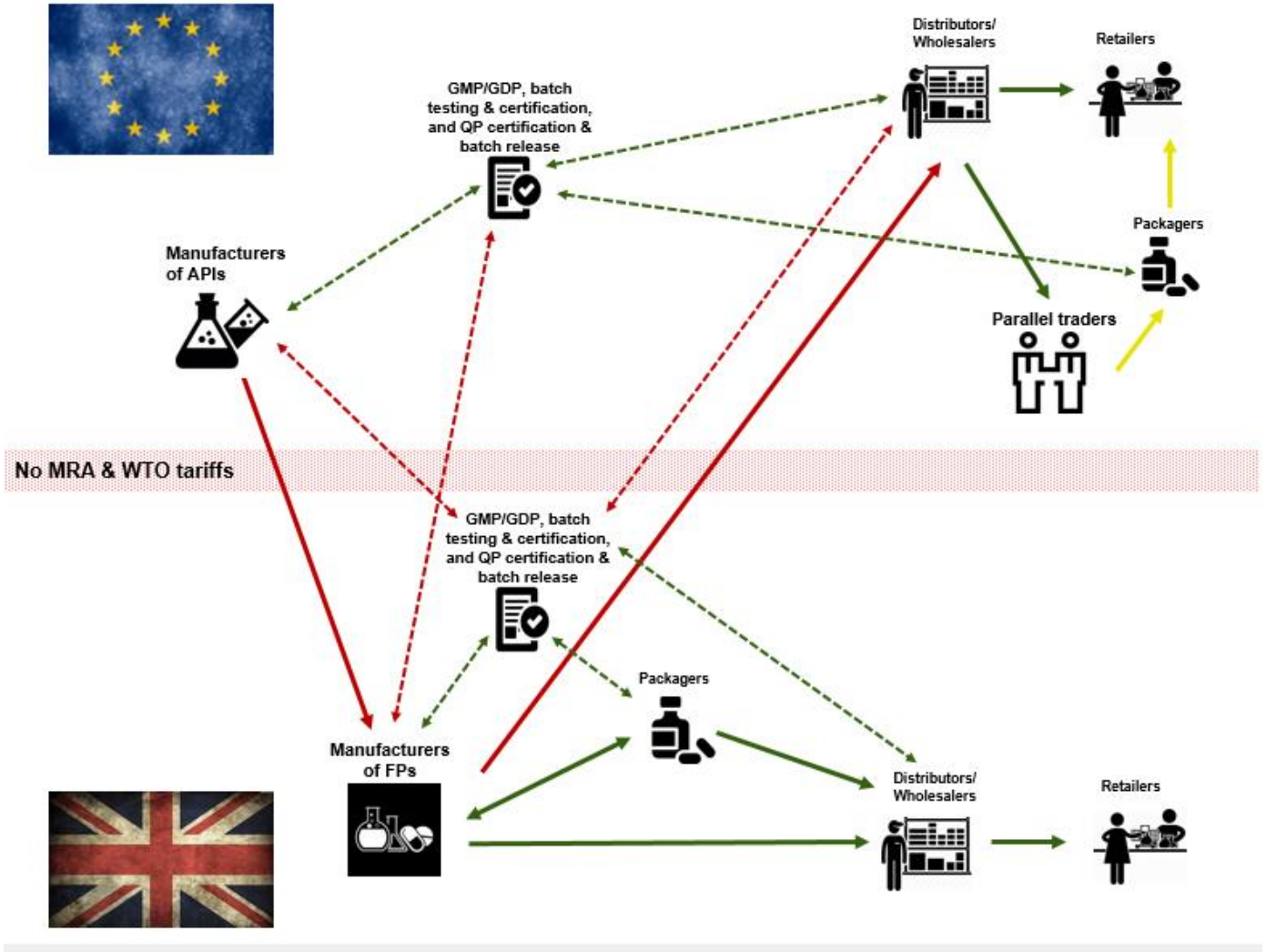
Note: Green lines reflect all quality controls and regulatory procedures performed intra-country to allow the supply of medicines within the domestic market. Red lines reflect quality controls and regulatory procedures performed between countries (UK and EU27/EEA) for the supply (export/import) of medicines. 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.
*Countries with which the EU has currently active MRAs are Australia, New Zealand, Canada, Japan, Israel, Switzerland and the US.

3. 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 require further duplication and associated costs.
4. Distributors/wholesalers:
   - UK based distributors/wholesalers supplying medicines to the domestic market would only need to be GDP certified by the MHRA in the UK and would not be affected by the lack of an MRA.
   - EU27/EEA-based distributors/wholesalers importing medicines from the UK and supplying retailers within the EU27/EEA must be GDP certified by the MHRA within the UK and the EMA (through a NCA) within the EU27/EEA. This involves a cost duplication for them.
   - In absence of MRA and FTA, it may be unlikely that a UK-based distributor/wholesaler is able to export pharmaceuticals directly to a EU27/EEA retailer and vice versa.
5. Parallel traders: no change from Scenario 3.

A4.2.7.5. Summary of supply chain effects

It is evident that depending on the trade agreements and MRAs that are negotiated, there are many possible (often costly) changes to the supply chain that could be required following Brexit. Table A12 provides a summary of the possible impacts.

Figure A21: Supply chain of an UK-based manufacturer of FPs Scenario 4



Note: Dashed lines reflect quality controls and regulatory procedures involved in the supply chain as per Scenario 4. Solid lines reflect economic and trade transactions within and between countries. Green lines reflect no impact of Brexit. Red lines reflect the impact of Brexit (Scenario 4) on the reflected stakeholder. Parallel trade is reflected by yellow lines.

Table A12: Summary of impacts of Brexit 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.

ANNEX 5: ECONOMIC IMPLICATIONS FOR PHARMACEUTICAL COMPANIES

A5.1. Methods

We identified the different drivers of cost by considering the following sources of evidence:

- *Relevant literature* including UK Government and European Commission white papers, EMA and MHRA publications, papers and documents shared by the ABPI and the BIA, and by their member companies, as well as scientific peer reviewed papers;
- *Interviews* with a variety of member companies of the ABPI and the BIA. We purposely sampled companies to cover the widest possible range of typology across the industry – UK, EU27/EEA and third country/global manufacturers supplying medicines to both the UK and the EU27/EEA, large and medium sized, generic and branded products;
- *Internal cost estimates* produced by companies were requested as well as external reports of costs they expect Brexit may impose;
- *Interaction with ABPI team* members for feedback and advice:
    - Mike Murray (Association of British Pharmaceutical Industry);
    - Magda Papadaki (Association of British Pharmaceutical Industry);
    - Rick Greville (Association of British Pharmaceutical Industry);
- *Indicative supply chain diagrams* were presented at the joint ABPI and BIA Brexit Deep Dive for Trade (Medicines) meeting in June 2017 and feedback was incorporated into the analysis.

The MHRA has conducted a survey with companies. In this survey, companies provided estimates of some of the costs that Brexit will impose, specifically in relation to the EMA/MHRA licensing and quality control procedures. For our purpose of estimating the cost to companies, OHE Consulting received, from two large-size, global-pharmaceutical companies, copies of their responses to this survey.

Additionally, companies have also been asked to participate in a survey conducted by the European Federation of Pharmaceutical Industries and Associations (EFPIA). OHE Consulting has received a copy of the questionnaire. This has been informative for identifying the different cost drivers. Note that at the time of writing the EFPIA survey is still open and the companies we engaged with had not completed the survey and so could not share their responses.

The total cost to companies of Brexit is determined by a number of different drivers. Brexit could impact on: the complexity of clinical development processes; marketing authorisation routes and regulations; manufacturing and supply chains of medicines; and compliance with international trade regulations. This expands the number of cost drivers to a long list. Given such a range of potential impacts, our effort in assessing the cost to companies has been focused on a twofold task:

- Identifying and classifying all sources of additional cost that Brexit may involve;
- When possible, estimating the cost to companies of each source, both to a "typical" individual company, and to the industry in total.

An initial classification that helps to understand and assess the cost of Brexit to companies is to separate costs into (i) implementation costs (one-time or adaptation costs to a new context), and (ii) maintenance costs (ongoing or recurrent costs of the new context). All implementation and maintenance costs identified have also been grouped into three different sources of costs: (a) clinical development and market authorisation costs, (b) manufacturing and supply chain costs, and (c) trade costs.

A5.2. Results

A5.2.1. Implementation costs

Implementation costs represent the costs incurred by pharmaceutical companies to comply with the immediate legal and regulatory requirements associated with the withdrawal of the UK from the EU.

Table A13: Implementation costs

Category	Implementation costs
Clinical development & market authorisation	1. Transfer of the legal representative of the sponsor 2. Transmission of SUSARs from UK/EU27/EEA to EU27/EEA/UK 3. Transfer of MA holders from UK/EU27/EEA to EU27/EEA/UK 4. Establishing facilities to supply investigational medicinal products and support clinical trials in (UK/EU27/EEA) 5. Retroactive submissions of applications/procedures to MHRA 6. Pharmacovigilance: a. Recruitment/relocation of the QPPV b. Relocation of the pharmacovigilance masterfile c. Adaptation of pharmacovigilance system 7. Retroactive update of product information a. Labelling information b. Packaging 8. Retroactive adaptation of the RMP a. Adaptation of the RMP activities 9. Retroactive recognition of orphan designations and paediatric implementation by the MHRA 10. Additional project management and support resources for a transitional period
Manufacturing & supply chain	1. GMP and GDP certification of sites (MHRA) 2. Transfer batch release facilities for authorised products: a. Transfer of methods and technology b. Built sites for Batch release c. Increase warehousing capacity for sampling, quarantine and hold products with special requirements d. Potential increase of inventory of finished products to maintain supply over implantation period e. Costs associated with extra Stock Keeping Units due to splitting UK/Irish packs 3. Recruitment of QP for batch release: a. QP for clinical trial products batch release b. QP for authorised products batch release 4. Additional project management and support resources for a transitional period

Trade	1. Capital tie up due to the necessary investments to increase inventories at borders (avoid delays)

Table A13 presents a comprehensive list of implementation costs that have been identified from the literature search, interviews with companies, and the request for companies' internal data and information.

The extent (and magnitude) of these costs depend on the scenario which will occur after 30 March 2019. Based on our different scenarios, no cost would be incurred in Scenario 1 (maintaining the status quo), whilst companies would face all costs in in Scenario 4 (worst case scenario). With respect to implementation costs (one-time costs), full cooperation between MHRA and the EMA through a negotiated *comprehensive* MRA between the UK and the EU27/EEA would remove all implementation costs associated with the clinical development and marketing authorisation, and manufacturing and supply chain (i.e. the majority of implementation costs). Only trade implementation costs would remain if full cooperation was reached.

Evidence gathered from our sources have provided some estimates for the costs listed above. Unfortunately, given the complexity of the impact that the UK withdrawal from the EU represents, together with its acute and unexperienced nature, we have been unable to source all the costs in the list. Companies are still in the process of predicting and estimating the impact and they have only been able to provide an incomplete set of implementation cost estimates. We have asked companies for estimates of implementation cost for changes in clinical development and marketing authorisation (see Annex 5) but few companies have been able to provide these as they have not yet performed any internal work to anticipate these costs. Estimates of the implementation costs of manufacturing and supply chain activities are more readily available. Note we have not been provided with any estimate of the total capital tie up resulting from increased inventories at borders.

A5.2.2. Maintenance costs

The maintenance costs represent the costs incurred by pharmaceutical companies associated with the duplication of work and existence of the parallel procedures across the UK and EU27/EEA. The costs companies will face will depend on the degree of cooperation after 30 March 2019. A comprehensive list of all potential maintenance costs identified is provided in Table A14.

Costs of maintenance are also scenario dependent: it is estimated that Scenario 1 (status quo) would not involve any additional maintenance cost, while Scenario 4 would incur all the costs included in Table A14. As above the negotiation of a MRA between the UK and the EU27/EEA would help to avoid the majority of maintenance costs, however, in comparison with the implementation costs, maintenance costs as a result of an absence of an FTA are much more substantial.

We have collected evidence and estimates of the costs in Table A14 from the three sources previously mentioned. Again the data gathered are incomplete, and estimates of several costs have either not been found or not been reported. Companies may well not to date have undertaken any estimation of them.

Table A14: Maintenance costs

Category	Maintenance costs
Clinical development & market authorisation	1. Duplication of the clinical safety reporting and submission activities (e.g. DSURs, PSURs, individual case safety reports, PASS/PAES) 2. Duplication of MA/Applications/submissions a. Preparation of (electronic) common technical documents submissions b. Variations applications c. Application and variation application fees d. Evaluation procedures and documents e. Submission of post-approval commitments f. Delays accessing the UK as standalone market 3. Duplication of GDP and GMP inspections (regular to certified sites) 4. Duplication of Pharmacovigilance activities a. Master file management b. Inspections c. Procedures (e.g. referrals) 5. Duplication of RMPs: a. Submission b. Implementation 6. Duplication of artwork product information: a. Labelling b. Packaging
Manufacturing & supply chain	1. Duplication of GMP and GDP inspections (regular to certified sites) 2. Duplication of the analytical batch testing and official batch release in the UK and the EU27/EEA 3. Duplication of the OMCEL and NIBSC analytical batch testing and official batch release in the UK and the EU27/EEA for vaccines and biological medicines 4. Duplication of regulation on Registration, Evaluation, Authorisation and restriction of Chemicals (REACh) for any chemicals used in the production process for medicines which do not appear in the finished medicine (UK and EU27/EEA) 5. Duplication of regulation on Classification, Labelling and Packaging of substances and Mixtures (CLP/CHS)
Trade	1. WTO tariff measures for finished pharmaceuticals 2. WTO non-tariff measures for finished pharmaceuticals 3. WTO tariff measures for APIs and intermediates 4. WTO non-tariff measures for APIs and intermediates 5. VAT due at import (cash flow impact) 6. Supervision of trade moving across borders and compliance processes (rules of origin, Union Custom Code, Custom officials) 7. Broker fees

A5.2.3. Case studies

We acknowledge the lack of estimates is a caveat to quantitatively assess Brexit's cost to companies. However, using the available information we provide (incomplete) estimates of the total cost to companies in the form of several case studies using both quantitative estimates and qualitative responses.

The four case studies are:

1. Large US-based manufacturer accessing EU (the UK included) mainly through EU27/EEA;
2. Large UK-based manufacturer accessing the EU27/EEA through current UK's member state status;
3. UK-based SME developer of biological medicines;
4. Large European manufacturer of generic and biosimilar medicines exporting to and selling in the UK.

The four case studies correspond to the four companies we have interviewed. Additionally, we have collected information from other companies and sources, as well as from the literature and the media. Additional data have been used to confirm or complement the information we have obtained from interviews.

Case Study 1: Large global manufacturer accessing EU (the UK included) mainly through EU27/EEA

This is a global company with over 90,000 employees, a quarter of whom are based in Europe (including >2,500in the UK). The company markets medicines across most countries globally and global sales are in the tens of billions. The UK market is one of the biggest markets in Europe commercially, however the company has a relatively small manufacturing presence there compared to other EU27/EEA countries. The company does manufacture and undertake release activities in the UK: 16 CMOs including manufacturing four active substances.

The transfer of marketing authorisations to a EU27/EEA legal entity including changes in labelling and establishing the new UK-EU27/EEA clinical supply network, and the transfer of batch release testing facilities are considered to be the major costs to this company. Both involve implementation (one-time) costs and maintenance (ongoing) costs. Based on 2016 data the company reports the following estimates and impacts[41]:

- Implementation costs:
  - Approximately £6.75 million to transfer necessary batch testing methods and facilities into the UK for imported finished products from EU27/EEA;
  - Approximately £19.3 million for establishing an EU27/EEA distribution operation for investigational medicinal products to supply clinical trials;
  - Approximately £0.6 million to transfer necessary batch release methods and facilities into the EU27/EEA for exported products from the UK;
  - Approximately £21 million to transfer MAs to EU holder, and maintain the 600 MAs in the UK regulatory area, without considering the label changes (more than 2000 products);
  - Approximately £8.6 million to change all the artwork (e.g. labelling, packaging) associated with MAs updates;
  - Approximately £0.4 million for GMP/GDP registering and certificating for UK CMOs – EFPIA estimate per certificate is £26,500, which has been multiplied by the 16 UK-based CMOs.
- Maintenance costs:

[41] Where the company reported estimates in its local currency (US $) the figure was converted to pounds sterling using the exchange rate of 29th of August of the Bank of England (see http://www.bankofengland.co.uk/boeapps/iadb/Rates.asp).

- Approximately £17 million annually for testing finished products imported into the UK from the EU27/EEA;
- Approximately £1.9 million annually for QP batch certification of products imported into the UK from the EU27/EEA;
- Approximately £3-6 million annually for sample management and personnel resources (including QPs) required for the batch release of products imported from the EU27/EEA into the UK, and UK products and active substances imported into the EU27/EEA
- Approximately £3 million annually of testing finished products exported to the EU27/EEA from the UK.

The company's QPPV function is outside of the UK, so this has not been included in cost impact estimations for the company. The cost of trade under WTO agreements has also been estimated by the company internally. An initial estimate of increased Customs Duty expense (globally) for company as a result of Brexit (based on 2016 figures) will be around £7 million, which can be broken down as follows:

- UK inbound from EU27/EEA: £1 million
- UK outbound to EU27/EEA: £3.8 million
- UK direct trade preference shipments: £2.2 million

The assumptions behind the estimations of Customs Duty expense are:

- That full WTO MFN duty rates would apply post Brexit.
- EU FTAs or similar understandings would no longer apply to the UK post Brexit .
- The UK remains party to the WTO Zero-for-Zero Tariff Agreement post Brexit. The Agreement removes tariffs for finished products (but not APIs and intermediate inputs) in signatory countries.

Other costs could include:

- VAT relief at customs *"could result in millions of additional costs"*, but only a cash flow impact
- Company also reported that *"(…) contract resources for project management and support would be required to supplement internal resources for a period of several years, given the extent and complexity of changes needed if there is no EU/UK medicines regulation agreement (…). The costs for these additional resources could be millions of pounds, but cannot be easily estimated at this stage".*

Other non-easily quantifiable issues have also been reported by the company. One of the most important is the burden that trading under WTO rules may cause. The company is concerned not only about the cost of potential re-imposition of tariffs if the UK were to 'fall out' of some EU FTAs, but also about less-quantifiable impact; *"(…) Value taken from FTA is the rules framework rather than the exact numbers. Driver for global norms, clarity in market access and procurement rules."*

The company's representative also noted that *"[we] don't think there will be a large custom/tariff cost impact. But delays are more likely to be a problem".* Another important concern of the company is the switching of batch testing methods and release facilities to the UK *"(…) that would be a disaster. Cost is unreasonable".* A final concern worth a mention is if the UK were to withdraw from serialisation of medicines that is

planned under the EU Falsified Medicines Directive *"(…) this will cause a major further layer of complexity",* given that the timelines for implementation are very close to the Article 50 deadline and the volume of artwork changes and submissions for both companies and health authorities.

Case Study 2: Large UK-based manufacturer accessing the EU27/EEA through the UK's current member state status

UK-based global big pharmaceutical company with manufacturing sites within the UK. Global sales are approximately £11.5 billion[42] from which approximately a 12%, around £1.4 billion, are from sales in the EU. Key export markets include Europe, Russia, the US and Japan, with others like China, Middle East and Latin America significant and growing.

Estimates provided by the company are mainly refer to trade under WTO rules scenarios. The interviewee reported that estimates about duplication and implementation costs for regulatory clearance are currently being estimated.

The three most important sources of cost as reported by the company representative are (in order of importance):

- The cost of regulatory clearance which involves creation and duplication of batch testing and release facilities, recruitment of QP and transfer of MAs holder – *"(…) without this we cannot supply the medicines. (…) wastes time and requires development of facilities and recruitment of expertise";*
- The delay at the border (e.g. error on paperwork, customs questions, traffic queues, physical examination) – *"(…) might need to increase inventory held in the EU. This has a cost of tying up capital";*
- Custom duty and VAT – *"(…) UK doesn't have a system where you put on the VAT return, so there is a significant cash flow issue".*

No estimates of the costs of regulatory clearance have been provided for either implementation or maintenance. Estimates for costs of trading under WTO rules were provided. These are 100% maintenance costs based on the company's 2016 activity.

1. Maintenance costs[43]:
   - Approximately a cost of £24 million annually in additional duty on current transactions;
   - Approximately a cost of £4 million annually in additional duty on imports of APIs to the UK;
   - Approximately a cost of £200,000 annually in broker fees.

The data provided in the interview were consistent with the estimates provided by the company in Case Study 1.

Additionally, as for Case Study 1, other immeasurable costs were reported qualitatively. The main concern of the company is to avoid the risk of being unable to supply medicines to the EU. A plan to create facilities for the batch testing and release, as well as, to recruit skilled personnel (i.e. QPs) has been initiated. However, *"In terms of*

[42] Originally in US dollars ($15 billion). Converted to pounds sterling using the exchange rate of 29th of August of the Bank of England (see http://www.bankofengland.co.uk/boeapps/iadb/Rates.asp)

[43] All figures presented in the list were originally in provided in US dollars. They have been converted to pounds sterling using the exchange rate of 29th of August of the Bank of England (see http://www.bankofengland.co.uk/boeapps/iadb/Rates.asp)

building capacity, some of this work would need to be outsourced in the first instance as the time scale is too short. We need premises, people, equipment, etc. and putting this together in a short time frame is difficult".

There would be a cash flow issue due to the VAT imposed on importing to the UK. The company representative reported this to be a significant impact in the instance that the *"(…) the tax treatment between the UK and the EU is not expected to be structured to allow for any VAT due at import to be accounted for on the taxpayers' VAT return, as happens in some EU countries, rather than by payment to HMRC".*

The interviewee also reported that *"At the moment it looks like the cost of moving production elsewhere in the EU probably outweighs the savings from benefiting from an FTA"* and that apart from the figures of additional trade costs provided, the impact is *"(…) also delays, not just financial. This will depend on the new customs declaration system being up and running and operating efficiently (it is not planned to be in operation until beginning of 2019 so we don't really know) and the cost of brokers not operating efficiently".*

Case Study 3: UK-based SME developer of biological medicines

UK-based private biotech company of 400 employees. Developing biological products. They have a very diverse workforce with employees from over 40 different countries.

It currently has a novel biologic in clinical trials as well as other products in the development pipeline, as such they are manufacturing only for supplying clinical trials. It expects the product to launch in the next two to three years.

The company's main concerns with respect to Brexit are, in order of priority:

- Freedom of movement of people and employees to guarantee access to a skilled labour market;
- Creation of manufacturing capacity: the UK was the first option but now considering to move/locate to the EU27/EEA;
- Regulatory and quality control impact including the creation of batch testing and release facilities.

It reported a £15.5 million[44] implementation cost of creating batch testing and releasing facilities in a standalone country (the UK or any EU27/EEA member state), consistent with figures reported by big pharmaceutical companies in case studies 1 and 2.

Additional (qualitatively stated) impacts were also reported. The most important impact from the company's perspective is the staffing issue. The company foresees difficulties in hiring QPs in the UK because of the constraint of limited skilled people *"this would be a significant impact. A break down in the ability to manage data for approval in the UK and EU".* Recruitment issues will affect skilled workers for the manufacturing activities as well *"(…) greater abundance in the EU (particularly Ireland)"*. Costly recruitment and difficulties accessing markets would have an impact on income and sales, *"If the right to work is not kept post-Brexit, staffing issues would be a significant negative impact for*

[44] Originally in US dollars ($20 million). Converted to pounds sterling using the exchange rate of 29th of August of the Bank of England (see http://www.bankofengland.co.uk/boeapps/iadb/Rates.asp)

the company – this would increase the likelihood of the company locating manufacturing facilities in the EU27/EEA rather than in the UK".

Another important concern around manufacturing site location is the tariffs that may be applied to the company's exports after Brexit if no FTA is reached between the UK and the EU27/EEA, but also due to the customs duties the company will face when importing inputs for its manufacturing process.

A further concern was the post approval commitments with HTAs and regulatory bodies and most importantly, the impact on clinical trials, which was reported to be positive, *"(…) Brexit could have a positive impact by creating savings in clinical development. The UK can become competitive in clinical trials".*

Finally the company also identified possible difficulties in accessing capital markets and venture capital. This would bring the *"(…) risk of disappearance for small-medium sized suppliers of substances and products to big pharma and result in increased cost for them".* The company representative further noted that Brexit comes with the risk that *"ideas, innovation and research outcomes created in the UK will go abroad which means a loss of export income outside the UK".* Start-up companies may migrate abroad and generate value outside the UK.

Case Study 4: Large European manufacturer of generic and biosimilar medicines exporting to and selling in the UK

A global producer of generic medicines. The company's global portfolio comprises more than 1,000 molecules of which around 200 to 300 products are marketed in the UK.

The company's UK business provides medicines to the NHS for use in primary and secondary care, with the main distribution route for medicines to the NHS being through wholesalers. The company does not have manufacturing facilities in the UK but has a significant presence in regulation, distribution, sales and support teams.

The main impacts of changes to imports and exports arising from Brexit that created concern included:

- The potential for regulatory divergence between the UK and EU and potential delays to patient access, including the potential need to transfer or otherwise amend MAs so that they continue to be valid in both the UK and the EU27.
- The lack of a national regulatory pathway for biosimilar medicines if the EU pathway is not available or does not lead to MAs which cover the UK.
- An end to mutual recognition with regards to regulatory approvals, quality audits and batch release will drive up the need to recruit more QPs *"(…) which is not easy - there are a limited number. The cost of recruiting a Qualified Person will no doubt increase as there is already a known capacity shortfall in the UK market".*
- Increased import and VAT costs which negatively impact short term cashflow and that *"(…) could be millions of dollars".*

No absolute measures about implementation costs and maintenance costs were provided in the interview. The company provided some percentage estimates:

- Approximately a 5-10% increase of the cost of supplying to the UK related to managing an increased administrative burden and duplication of quality release procedures (including testing and certification).

- An unknown and therefore unquantifiable increase in the cost of supplying the UK from additional administrative burden linked to custom declarations.
- Approximately 15-20% increase in the stock of medicines held in the UK, and subsequent cost, to ensure supply continuity in the event of border delays in Q1/Q2 2018.

The company has concerns about the cost of developing infrastructure to deal with UK border delays that will arise if trade between the UK and the EU27 is regulated by the WTO tariff system. This will be a new cost *"(…) there could be delays at the border (…) could stockpile, but there is a cost to this as well".*

Generic manufacturers generally operate in low margin environments. Absorbing the potential costs of Brexit will have a disproportionate impact on the company's profitability as compared to an Originator *"(…) the UK market for generics is very competitive – margins are very low. This would make the UK less attractive for investment".*

A5.2.4. Insights from the analysis of cost to companies

The major concern of companies is the impact of Brexit on complying with all legal conditions for regulatory clearance required to distribute and supply medicines in the EU27/EEA and the UK post-Brexit. The transfer of batch testing methods and batch release facilities (QPs included) and the transfer of MAs holder to EU27/EEA/UK from UK/EU27/EEA are the main concerns of companies.

The implementation cost of creating batch release facilities and transfer batch testing methods for a standalone regulatory country has been estimated to be around £15.5 million regardless of the size of the company.

Transferring the MAs holder into the UK/EU27/EEA may involve a £19 million implementation cost to a large global company. However the magnitude depends on the size and the number of MAs a company currently has.

While additional trade costs due to the lack of a FTA seem to be significant, companies appear to be more concerned about the impact that adapting to the new legal obligations may have on their supply chain. This is due to several reasons:

Firstly, if no MRA is agreed between the EU27/EEA and the UK it would be necessary to assume duplicated regulatory requirements to distribute and supply medicines in both the UK and the EU27/EEA. In the absence of this companies would not be allowed to access both markets and would lose revenue and profits.

Secondly, even though some guidance has been published by the EC and the EMA[45], companies' are concerned are about the absence of information on the new legal obligations of the MAH in the UK. Companies are also concerned by the uncertainty surrounding the progresses and outcome of the Article 50 negotiations. Costs involved by transferring batch testing methods and facilities and MAs holder are significant but

[45] See "Questions and Answers related to the United Kingdom's withdrawal from the European Union with regard to the medicinal products for human and veterinary use within the framework of the Centralised Procedure". No equivalent guidance had been published by the Department of Health / MHRA at the date of completion of our study.

they would only be necessary in the case that no MRA is adopted.[46] However, according to the guidance published by the European Commission and EMA, companies do need to start planning for these changes as soon as possible if they want to be able to comply with the new legal obligations and distribute and supply medicines in both the UK and the EU27/EEA to avoid any disruption and medicines shortages on 30 March 2019. Companies interviewed have expressed their concern that the period of time given to companies to comply with the new legal obligations might be too short, particularly for products like biologicals or ATMPs (including products under clinical development). Finally, a possible divergence of requirements after the withdrawal of the UK from the EU might further complicate this problem. This is a difficult uncertainty to deal with that outsourcing/contracting batch testing and release activities may only partially resolve.

Thirdly, fast and efficient adaptation of companies' supply chains to the UK/EU27/EEA standalone regulatory context is crucial. If they do not adapt, shortages of medicines, with consequential public health impact, would be expected, as well as lost profit.

An additional issue is the negative effect that Brexit may have on recruitment and retention. Without free movement of people, companies will struggle to hire skilled people for manufacturing sites and particularly QPs for batch testing and batch release activities. Skilled personnel are scarce in the UK and two effects are expected from this scarcity; difficulties in hiring and higher costs of recruitment.

A trade relationship of the UK with the EU27/EEA and the rest of the world regulated by WTO tariffs and rules would have a large impact in terms of monetary costs, but mostly in terms of potential delays. The latter will require capital investment to increase inventory capacities in target countries (the UK or member states of the EU27/EEA).

From the perspective of generic producers (high volume, low margin) and global companies (UK a low volume market) the increasing costs due to the worst case scenario (Scenario 4) might have an impact on their portfolio of products sold in the UK. They will consider not marketing products in the UK if it is no longer a profitable market.

The SME we interviewed reported that some SMEs in the UK depend on accessing to capital markets and attracting venture capital so they could be at risk of disappearing. This will have a wider impact as SMEs are frequent suppliers of substances and innovation to the global companies based in the UK and the EU27/EEA. Furthermore, promising innovation and research outcomes developed in the UK may be sold 'offshore' to such that the return of the investment (e.g. value created, tax, knowledge, and access to innovation) will be not received in the UK.

In summary the greatest priority of our four companies is for an MRA which keeps the MHRA and EMA fully aligned to avoid the uncertainty and potential cost derived from its absence. A second priority would be the implementation of a transitional period which would give to these companies sufficient time to comply with their new legal obligations.

[46] A MRA is negotiated between the third country, the EMA and the European Commission on behalf of the EU Member States (i.e. to agree on the products covered and excluded, the territorial applicability, the activities covered by the MRA and the exchange of information). Once agreed the MRA has to be published in the Official Journal of the European Union before coming into effect. The negotiation of a MRA is therefore a process which can require a substantial amount of time.

ANNEX 6: SIGNALS DETECTED BY THE MHRA AND DISCUSSION AT THE PRAC

Date of the PRAC	International non-proprietary name	Medicinal product invented name	Regulatory action
02-05 May 2017	Insulin aspart; insulin bovine; insulin degludec; insulin degludec, insulin aspart; insulin degludec, liraglutide; insulin detemir; insulin glargine; insulin glulisine; insulin human (rDNA); insulin human, insulin isophane; insulin lispro; insulin porcine	Novomix, Novorapid, Tresiba, Ryzodeg, Xulthopy, Levemir, Abasaglar, Lantus, Lusduna, Toujeo, Apidra, Actraphane, Actrapid, Insulatard, Insulin human winthrop, Insuman, Mixtard, Protaphane, Humalog, Liprolog	Update of the product information
03-06 Feb 2014	Interferon beta 1a; interferon beta 1b	Avonex, Rebif; Betaferon, Extavia	Update of the product information and risk management plan and health care communication (DHPC)
10-13 June 2014	Ipilimumab	Yervoy	Routine pharmacovigilance / monitor within periodic safety update reports
28 Oct/01 Nov 2016	Methylphenidate	N/A	Update of the product information
08-11 Sept 2014	Natalizumab	Tysabri	Update of the product information
10-13 June 2013	Orlistat	Xenical, Alli	Routine pharmacovigilance / monitor within periodic safety update reports
09-12 March 2015	Palifermin	Kepivance	Routine pharmacovigilance / monitor within periodic safety update reports

Date of the PRAC	International non-proprietary name	Medicinal product invented name	Regulatory action
03-06 Nov 2015	Palifermin	Kepivance	Update of the product information
07-10 Oct 2013	Pandemic H1N1 and seasonal trivalent influenza vaccines		Routine pharmacovigilance / monitor within periodic safety update reports
06-09 Jan 2014	Pazopanib	Votrient	Update of the product information
03-06 Nov 2014	Radium-223 dichloride	Xofigo	Routine pharmacovigilance / monitor within periodic safety update reports
24-27 Oct 2016	Riociguat	Adempas	Update of the product information and risk management plan and health care communication (DHPC)
07-10 July 2014	Rivaroxaban	Xarelto	Routine pharmacovigilance / monitor within periodic safety update reports
29-31 Oct 2012	Short-acting beta agonists: hexoprenaline; fenoterol; ritodrine; salbutamol; terbutaline	N/A	Referral: restriction of use
07-10 Apr 2014	Simvastatin	N/A	Update of the product information
07-10 Apr 2015	Sodium containing formulations of effervescent, dispersible and soluble medicines	N/A	Update of the product information

Date of the PRAC	International non-proprietary name	Medicinal product invented name	Regulatory action
07-10 July 2014	Tacrolimus; Febuxostat	Advagraf, Protopic, Modigraf; Adenuric	Routine pharmacovigilance / monitor within periodic safety update reports
06-09 Jan 2014	Tapentadol	N/A	Update of the product information
10-13 June 2013	Tiotropium bromide	N/A	Update of the product information
04-07 Feb 2013	Tolvaptan	Samsca	Update of the product information and health care communication (DHPC)
03-06 Feb 2014	Ustekinumab	Stelara	Update of the product information and risk management plan and health care communication (DHPC)
03-05 Sept 2012	Varenicline	Champix	Update of the product information
08-11 Apr 2013	Adalimumab	Humira	Routine pharmacovigilance / monitor within periodic safety update reports
07-10 Apr 2014	Adalimumab	Humira	Update of the product information
05-08 Oct 2015	Adalimumab	Humira	Routine pharmacovigilance / monitor within periodic safety update reports

Date of the PRAC	International non-proprietary name	Medicinal product invented name	Regulatory action
07-10 Sept 2015	Bisphosphonates: alendronic acid; alendronic acid, colecalciferol; clodronic acid; etidronic acid; ibandronic acid; neridronic acid; pamidronic acid; risedronic acid; tiludronic acid; zoledronic acid; Denosumab	Prolia, Xgeva, Zometa, Aclasta, Fosavance	Update of the product information
08-11 Sept 2014	Chlorhexidine	N/A	Update of the product information
07-10 Apr 2014	Clindamycin	N/A	Update of the product information
24-27 Oct 2016	Cobicistat containing products: cobicistat; cobicistat, atazanavir sulfate; cobicistat, darunavir; cobicistat elvitegravir, emtricitabine, tenofovir alafenamide; cobicistat elvitegravir, emtricitabine, tenofovir disoproxil fumarate	Tybost; Evotaz; Rezolsta; Genvoya; Stribild	Update of the product information
07-10 Sept 2015	Digoxin	N/A	Routine pharmacovigilance / monitor within periodic safety update reports
06-09 July 2015	Donepezil	N/A	Update of the product information
01-04 Oct 2012	Erlotinib	Tarceva	Routine pharmacovigilance / monitor within periodic safety update reports
01-04 Oct 2012	Erlotinib	Tarceva	Update of the product information

Date of the PRAC	International non-proprietary name	Medicinal product invented name	Regulatory action
03-06 Feb 2014	Etanercept; Adalimumab; Infliximab	Enbrel; Humira; Remicade	Routine pharmacovigilance / monitor within periodic safety update reports
06-09 Oct 2014	Exenatide	Byetta	Routine pharmacovigilance / monitor within periodic safety update reports
26-29 sept 2016	Fluoroquinolones ciprofloxacin, enoxacin, flumequine, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin, rufloxacin	N/A	Routine pharmacovigilance / monitor within periodic safety update reports
11-14 Apr 2016	Fulvestrant	Faslodex	Update of the product information
06-09 Jan 2015	Gadodiamide; Gadopentetic acid; Gadoversetamide	Optimark	Update of the product information
03-06 Mar 2014	Goserelin	N/A	Update of the product information

ANNEX 7: LIST OF THE UK PHARMACOPEIDEMIOLOGY CENTRES LISTED IN THE ENCEPP RESOURCES DATABASE

Name of the Centre of Pharmacoepidemiology	Date entered in the ENCePP database
Adelphi Real World http://www.adelphirealworld.com/	05/08/2016
Biologic Studies Group - University of Manchester	09/10/2013
Centre for Health Informatics (CHI) - University of Manchester http://research.bmh.manchester.ac.uk/healthinformatics	23/06/2017
Clinical Practice Research Datalink (CPRD) www.cprd.com	25/01/2016
Cambridge Real-Life Research Organisation (CRO) www.cro-uk.com	06/10/2015
Cegedim Strategic Data Medical Research UK (CSD MR UK) http://csdmruk.cegedim.com	19/11/2012
Cancer Epidemiology Unit, University of Oxford http://www.ceu.ox.ac.uk/	22/07/2013
Clinical Trials Unit & Epidemiology and Biostatistics - Imperial College London	14/06/2010
Drug Safety Research Unit www.dsru.org	07/03/2016
Evidera www.evidera.com	13/10/2016
FV&JK Consulting	02/10/2015
Gillian Hall	10/05/2017
Health Information Research Unit (HIRU) - Swansea University http://www.swansea.ac.uk/medicine/ils/healthinformationresearchunit/	13/03/2014
INC RESEARCH INCRESEARCH.COM	03/10/2016
International Primary Care Respiratory Group (IPCRG) www.theipcrg.org	17/06/2014
LA-SER Research (Real World Studies) www.LA-SER.com	23/03/2012
London School of Hygiene & Tropical Medicine, LSHTM Pharmacoepidemiology Group http://www.lshtm.ac.uk/research/areas/index.php	18/06/2012
Medicines Monitoring Unit (MEMO) - University of Dundee	20/07/2016
Centre for Maternal, Fetal and Infant Research (MFIR-Ulster) - University of Ulster http://www.science.ulster.ac.uk/inr/mfir.php	14/10/2016
Medpace Holdings www.medpace.com	20/11/2014

National Perinatal Epidemiology Unit (NPEU) - University of Oxford www.npeu.ox.ac.uk	19/03/2010
Numerus 1010 Statistics and Pharmacoepidemiology www.numerus.com	12/06/2017
Observational and Pragmatic Research Institute Pte Ltd (OPRI Pte Ltd) www.opri.sg	23/11/2016
PAREXEL PACE (PAREXEL International Corporation) http://parexel.com	17/11/2011
Pope Woodhead & Associates (PWA). Drug safety, Risk management & regulatory Practice. www.popewoodhead.com	25/11/2014
Patients Direct www.patientsdirect.org	07/10/2014
Pharmatelligence http://www.pharmatelligence.co.uk/	10/04/2015
Quintiles Late Phase www.quintiles.com	03/09/2015
The Wolfson Centre for Personalised Medicine - University of Liverpool http://www.liv.ac.uk/research/research-themes/personalised-health/	29/10/2014
UCL School of Pharmacy, University College London http://www.ucl.ac.uk/pharmacy	21/04/2015
University of Bath, Pharmacy & Pharmacology www.bath.ac.uk	14/05/2014
Worldwide Clinical Trials (WCT) Evidence www.wwctrials.com	19/01/2016
Wolfson Unit, Newcastle - Newcastle University http://www.nyrdtc.nhs.uk/	01/05/2014
Yellow card Centre Scotland www.yccscotland.scot.nhs.uk	06/11/2014
inVentiv Health Clinical http://www.inventivhealthclinical.com/	04/10/2013

ANNEX 8: LIMITATIONS AND FURTHER RESEARCH

A8.1 Limitations

There are some important limitations of our study that must be acknowledged.

Firstly, we could not obtain information concerning the number of submissions of applications for medicinal products authorised according to the decentralised and mutual recognition procedures in the EU and other third countries. These represent a large number of medicinal products. Similarly we have no information on the location of the MAH, qualified persons and batch release sites. In addition, the analysis concerning the submission of new marketing authorisation applications to Australia, Canada and Switzerland was conducted under the current regulatory framework, any delays that will ultimately happen may be influenced by other mechanisms or incentives which may be put in place after Brexit. Therefore, our estimates concerning the delays of submission of applications for new products require caution when extrapolating.

Secondly, the use of the type of regulatory action we employed to address specific signals has some limitations. However, as described in the Module IX of the Good Pharmacovigilance Practice, this choice is made by the PRAC following an impact assessment and prioritisation of the signals (HMA and EMA, 2012). Therefore, our approach was the best option to estimate the public health impact of the signals validated by the PRAC.

Thirdly, given that the EMA does not maintain a public list of incidents and crises management events, we could not estimate accurately the frequency and the public health impact of these events.

Fourthly, when understanding the possible impact of Brexit on medicines shortages we could not obtain a definitive list of medicinal products for human use exported and imported between the UK and the EU27/EEA. In particular the SITC codes do not allow such a specific query. The same comment applies to the information extracted from EudraGMDP, we could not obtain a complete and precise list of the type or class of products manufactured, imported or distributed in the UK. In particular, our data extracts did not contain exhaustive information on biotechnology or biological medicinal products, nor did it contain information on the investigational medicinal products which are subject to similar testing and batch release rules as the other products. Therefore, we could not estimate the impact of Brexit on the manufacturing, testing, imports and exports for investigational medicinal products.

Additionally, we have assumed that despite the loss of access to the single market that parallel imports of medicines would still be allowed under the terms of a FTA negotiated in Scenarios 1 and 2. This assumption is strong since the existence of the parallel import of medicinal products across the EU countries is a core principle of the EU and linked to the freedom of goods within the single market. Therefore, the persistence of a parallel trade allowing medicinal products to move freely between the UK and the EU27/EEA, despite the withdrawal of the UK from the single market, depends on the outcome of the Article 50 negotiations. We acknowledge that the parallel trade could disappear when the UK leaves the EU.

Unfortunately, it is not possible to accurately quantify the public health effects of Brexit given that the effects associated with the non-availability of a specific medicine or due to delays in regulatory decisions are highly situation dependent. The studies conducted to

quantify the public health impact of new risks associated with medicines for human use are observational in nature and often yield divergent or contradictory results. Even if the UK does not cooperate with the EU network of authorisation and supervision of medicines for human use, our study shows that the delays between regulatory decisions made by the EU authorities and the US FDA do not exceed a couple of months (2-5 months). Therefore, for that reason, the relevance of pharmacoepidemiology studies to assess the public health impact of Brexit is limited. However, recent examples of public health issues associated with medicines which occurred in various EU countries have shown that this impact can be significant and can lead to major public health crises, often relayed in the media (e.g. benfluorex, domperidone, sodium valproate, TGN1412).

Finally, it was impossible to quantify one important effect of Brexit which is the loss of expertise (particularly in terms of expertise related to supervision and pharmacovigilance activities) from both sides. Instead, we provided metrics that we were able to calculate, for example the numbers of signals detected in each region, used to indicate relative levels of expertise. We did not attempt to predict the impact of this loss of expertise on signal detection going forwards.

With respect to estimating the effects on the supply chain and the cost to companies we acknowledge that the pharmaceutical industry is extremely heterogeneous, thus an 'average' company does not exist and the costs incurred and effects of Brexit are very dependent on the nature of a company's organisation, their research and development strategy as well as their manufacturing processes. Our cost estimates are indicative only. We were also unable to source some cost estimates, this is likely due to the uncertainty of the nature of Brexit and companies not yet being at a stage in their planning with respect to determining how they react (or not). Our estimates therefore are likely underestimates of the cost to companies. Finally, it is worth noting that as companies continue to refine their plans and estimates, the numbers from the case studies presented above will be subject to change.

A8.2 Further research

It is possible that some public health consequences of Brexit in some scenarios could be mitigated, such as the absence of, or delays in, submissions to the MHRA of marketing authorisation applications for new medicinal products. To aid this mitigation it may be valuable to try to understand some of the mechanisms underlying this effect (type of medicinal products, size of the company, orphan status, etc.) so that incentives could be put in place to minimise the consequences of Brexit.

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