Brexit:
Possible regulatory impacts on the pharmaceutical industry and marketing authorisation holders in Europe

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AMG	German drug law (‘Arzneimittelgesetz’)
API	Active pharmaceutical ingredient
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CA	Competent authority
CADREAC	Collaboration Agreement of Drug Regulatory Authorities in European Union Associated Countries
CEP	Certificate of Suitability to the Monographs of the European Pharmacopoeia
CETA	Comprehensive economic and trade agreement
CH	Switzerland
CHMP	The Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition Procedures and Decentralised Procedures - Human
CMS	Concerned member state
CP	Centralised procedure
CTA	Clinical trial application
DCP	Decentralised procedure
EC	European commission
ECJ	European Court of Justice
EDQM	European Directorate for the Quality of Medicines & HealthCare
EE	East European
EEA	European Economic Area
EEC	European Economic Community
EMA	European Medicines Agency
EPAR	European public assessment report
EPO	European Patent Office
EU	European Union
FMD	Falsified Medicines Directive
GCP	Good clinical practice
GDP	Good distribution practice
GMP	Good manufacturing practice
GVP	Good pharmacovigilance practices

ICH	International Conference on the Harmonisation
MAH	Marketing authorisation holder
MHRA	Medicines & Healthcare products Regulatory Agency
MRA	Mutual recognition agreement
MRP	Mutual recognition procedure
NCA	National competent authority
PI	Parallel import
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PIL	Patient information leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance system master file
PSUR	Periodic safety update reports
QP	Qualified person
QPPV	Qualified person for pharmacovigilance
R&D	Research and development
RDP	Regulatory data protection
RMS	Reference member state
SMEs	Micro, small and medium-sized enterprises
SmPC	Summary of product characteristics
SPC	Supplementary protection certificate
TEU	Treaty on European Union
TFEU	Treaty on the Functioning of the European Union
UK	United Kingdom
UPC	Unified Patent Court
VAR	Variations
WHO	World Health Organization

1 Introduction

On 29 March 2017, the United Kingdom (UK) decided to leave the European Union (EU) and the UK government triggered Article 50 of the Treaty on the EU, officially starting the two-year period of negotiation before the exit [1]. The process, known as 'Brexit', will presumably lead to profound changes to the broadly harmonised field of medicinal products. At present, it is widely reported that the UK government intends to pursue a 'hard break' from the EU, which would consider the UK outside of the single market [2].

Although the UK government has stated its desire to retain a close working partnership with respect to medicines regulation after the UK leaves the EU, the Brexit decision has caused much uncertainty throughout the pharmaceutical industry. Moreover, the interests of public health and safety are affected [3]. However, the government's latest position paper *'Continuity in the availability of goods for the EU and the UK',* outlines the UK's objectives of providing legal certainty and enabling a smooth and orderly withdrawal in order to avoid disruption in the availability of goods [4].

A quote from the European Medicines Agency (EMA) website states that *'[n]o Member State has previously decided to leave the EU, so there is no precedent for this situation'* [5]. This has led to an urgent need for guidance regarding various regulatory topics. In their notices to marketing authorisation holders (MAHs), the European Commission (EC), EMA and Co-ordination Group for Mutual Recognition and Decentralised Procedures – human (CMDh) have indicated that MAHs will *'need to act sufficiently in advance and must be ready to take the necessary steps to enable undisrupted supply of their medicines for the benefit of patients'* [6,7]. Furthermore, it must be the goal of all stakeholders to avoid a delay in the approval of important new drugs in the UK and Europe.

The aim of the present master thesis is to provide an overview of various regulatory aspects to consider when making a strategic decision concerning the consequences of Brexit. To decide on a strategy regarding Brexit without prejudice to the outcome of the withdrawal negotiations, it principally focuses on the assumption that the UK will become a third country as of 30 March 2019, when the UK will cease its membership in the European single market and acquire full control of its own law-making. This 'hard Brexit' is the chosen scenario to run through the preparation of this master thesis because it was also the assumption of regulatory authorities to give guidance regarding the worst-case scenario [6,7]. Furthermore, only with this assumption can a gap analysis cover all areas and steps to consider. Regardless, other scenarios could be implemented which would lead to more flexible options.

However, for the pharmaceutical industry, there is a strong business aspect in the background of this regulatory strategy with regard to the required investments in terms of time, money and resources. It is therefore imperative to thoroughly assess and analyse key issues which could potentially impact the business activities within a company in order to ensure continuous validity of marketing authorisations.

After a summary of the principles and legal basis for the withdrawal of a member state from the EU, the following thesis provides an analysis of the status of approved marketing authorisations. The next step presents and discusses the regulatory consequences

of the abolition of the UK as a reference member state (RMS) for authorisations from the decentralised or mutual recognition procedure (MRP) and as a rapporteur for central approvals.

Based on a presentation of the current regulatory environment and recently published information for companies from EMA and CMDh, an assessment is made in terms of areas for which future regulations will need to be found and which require arrangements by MAHs, sponsors and drug manufacturers. This key section describes different aspects of the following areas affected in the lifecycle of a medicinal product:

- Research and development (R&D) (clinical trials, orphan designation and SME status)
- Post-approval Activities (change of MAH, variation and renewals, pharmacovigilance)
- Manufacturing (GMP and inspections, manufacturing sites, batch release, qualified person (QP) status, import and export)
- Further aspects such as legal issues in the surrounding of regulatory affairs, including parallel distribution, IP-rights, falsified medicines and fundings.

Since EMA is based in London and must leave its present location, the consequences of relocation are also part of the discussion.

Even though an EU country has never left the EU before, the regulatory environment has already experienced co-operation with other countries outside the EU as well as with the integration of new member states to the EU. In order to propose possible solutions regarding a transitional phase, past and present regulatory collaboration models and their potential as templates for future co-operation of regulatory bodies with the Medicines & Healthcare products Regulatory Agency (MHRA) are presented. In a further step, the models will be under discussion regarding practical aspects and possibilities for their use in similar or “reversed” ways.

Most chapters are accompanied by current statistics illustrating the position of the UK in the described context.

It should be noted that medical devices and veterinary medicines are not within the scope of this master thesis.

2 Principles and legal basis

To assess regulatory aspects of Brexit, it is necessary to recall some basic facts concerning the Article 50 (Treaty on the EU) process steps, the 'EU Withdrawal Bill' and the legal framework that governs medicinal products for human use.

2.1 Article 50 process steps

On 23 June 2016, the UK held a referendum on whether the UK should remain in the EU, and a modest majority of 51.89% voted to leave [1]. On 29 March 2017, the UK notified the European Council of its intention to leave the EU, thus formally triggering Article 50 of the Treaty on the EU, which gives member states the possibility to voluntarily withdraw from the EU [8,9]. Article 50 establishes the process for a Member State to leave the EU '*in accordance with its own constitutional requirements'* [10]. The following figure illustrates the main process steps of the exit procedure [11]:

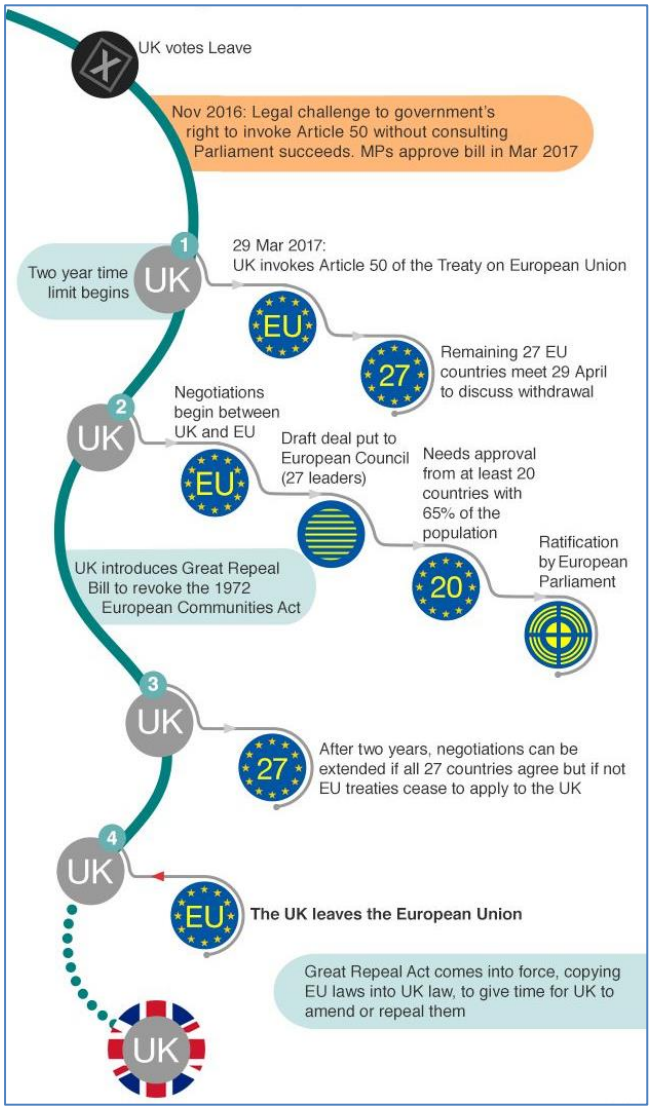

Figure 1: Steps to UK departure from the EU

Once triggered, Article 50 allows for two years to negotiate two agreements. The first is a withdrawal agreement treaty concerning the details of the exit, and the second is a separate framework agreement '*taking account of the framework of the future relationship with the Union*' [10]. This must be done according to Article 218 Treaty on the Functioning of the EU (TFEU), which details how negotiations should be opened and concluded and regulates the conclusion of international agreements by the EU [12]. At the present stage, the divorce and the negotiation of the future relationship are sequential, not parallel [13].

The withdrawal agreement will cover immediate issues, such as the rights of EU citizens living in the UK and of UK citizens living in the EU, the UK's financial commitments undertaken as a member state, border issues, the seat of the EMA and other agencies, and international commitments undertaken by the UK as a member state [14]. As Article 50 states, the final withdrawal agreement would need to be ratified by the UK and approved by the European Parliament as well as by at least 20 of the 27 member states represented in the council by a qualified majority [10].

The agreement on the future framework will describe the conditions for co-operation on a wide range of issues and include e.g. the UK's degree of access to the single market in terms of goods, services and people. Furthermore, requirements in terms of financial contributions, adherence to EU laws and influence over EU rules and regulations will be part of this agreement [14]. Therefore, with a view on the pharmaceutical regulatory and pharmaceutical industry, a key section will be the agreement to the basis for future trade and a framework for the co-operation with regard to certain objects of regulation. This agreement on the future framework will require the unanimous support of council members and a simple majority vote of the European Parliament and must also be approved by all member states. It must then be ratified by all remaining 27 member states and the UK government [14].

In view of the wide range of legal, economic and political links between the UK and the EU, a deadline of two years for the conclusion of an exit agreement appears almost impossible, as a glance at the actual negotiation practice has revealed. The negotiations between the EU and Canada regarding the CETA Treaty lasted eight years (2009-2017), and national parliaments have still not ratified it [15]. Similarly, the EU and Switzerland needed five years for the first tranche of more than 120 individual agreements (1994-1999) [16].

It should be noted that if no deal regarding Article 50(2) sentence 1 TEU is reached within this two-year period, there are two options: the negotiating period can be extended by unanimous agreement of the European Council in agreement with the withdrawing member state or the UK leaves the EU with no withdrawal agreement in place. The EU treaties would cease to apply to the UK, with no arrangement for managing the transition [9]. This second option would create significant uncertainty for e.g. UK citizens living in the EU, UK businesses trading with EU states and UK organisations that are reliant on EU funding. For example, if no trade relations agreement is achieved, the country will be obligated to trade with the EU under WTO rules. A transitional agreement will almost certainly be necessary to ensure businesses can continue to trade with the EU, and it

would allow them to conduct negotiations in a less pressured environment, which benefits all concerned parties. According to Article 50(3) TEU a formal renewal of the deadline would require unanimity in the European Council [17]. Even if long-term negotiations are expected, the risk of an unregulated withdrawal of the UK from the EU will remain in the case of a politically indisputable and unanimous decision of the council. On the other hand, if the period of withdrawal is extended, both parties are protracted a time of legal uncertainty.

2.2 The EU regulatory system for medicines

A large body of legislation determines access to medicinal products for the European market, which has been harmonised for many years. Therefore, in the EU, authorities control the applied standards, whose uniform design and application in the member states is supervised by the European Court of Justice. The year 2015 marked the 50th anniversary of the adoption of the first law on the authorisation of pharmaceuticals at the EU level, which set a foundation for certain key principles that are still valid today [18]. The unique European medicines regulatory system is based on a network of around 50 regulatory authorities from the 31 European Economic Area (EEA) countries [19].

Article 288 TFEU explains several legal acts of the EU. The following summary reveals the various tools of the EU legislation:

- *'A **regulation** shall have general application. It shall be binding in its entirety and directly applicable in all Member States.*
- *A **directive** shall be binding, as to the result to be achieved, upon each Member State to which it is addressed, but shall leave to the national authorities the choice of form and methods.'*
- *A **decision** shall be binding in its entirety. A decision which specifies those to whom it is addressed shall be binding only on them.*
- ***Recommendations** and **opinions** shall have no binding force'* [20].

Directive 2001/83/EC, the so-called 'Community code relating to medicinal products for human use' and Regulation (EC) No 726/2004, specifies the requirements and procedures for the marketing authorisation for medicinal products for human use as well as the rules for the constant supervision of products after they have been authorised. These furthermore concern harmonised provisions in related areas, such as manufacturing, wholesaling or advertising of medicinal products for human use [21,22].

Additionally, community legislation provides rules for the conduct of clinical trials in the EU, indicated in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 [23]. On 27 May 2014, the new Clinical Trials Regulation EU No 536/2014 replacing Directive 2001/20/EC was adopted and published in the Official Journal [24]. Although the regulation entered into force on 16 June 2014, it will apply no earlier than the end of 2019 [25].

Furthermore, the European Parliament and Council of Ministers adopted new provisions for pharmacovigilance in December 2010. Many of the new provisions contained in the

legislation have been effective since July 2012. The legislation is outlined in Regulation (EU) No 1235/2010 and Directive 2010/84/EU and is accompanied by the implementing regulation (EU) No 520/2012, which the EC published in June 2012 [26,27,28]. This implementing regulation details the operational aspects of the legislation.

Further directives were implemented to address special fields of regulation, such as Regulation (EC) No 141/2000 on orphan medicinal products [29], Regulation (EC) No 1901/2006 on products for paediatric use [30], Regulation (EC) No 1394/2007 on advanced therapy medicinal products [31] and Directive 2004/24/EC regarding traditional herbal medicinal products [32]. Directive 2011/62/EU, which aims to prevent falsified medicines the EU, came into force on 21 July 2011. This directive informs several legislative implementation measures for the commission to carry out [33]. For example, the Commission Delegated Regulation (EU) 2016/161, which describes detailed rules for the safety features appearing on the packaging of medicinal products for human use, was adopted on 2 October 2015 and published on 9 February 2016 following scrutiny by the European Parliament and the council. The delegated regulation will apply as of 9 February 2019 [34].

The next chapter describes how the UK will maintain this EU law and transpose directly applicable EU law into UK law.

2.3 The EU Withdrawal Bill

With the withdrawal, the ‘treaties’ – and thus the entire union law, or ‘Aquis-Communautaire’ – would no longer be applicable in the UK [35].

To ensure a smooth transition on the day after Brexit, the UK government published a white paper on the ‘Great Repeal Bill’ on 30 March 2017 [36]. Following this white paper, the British government introduced the EU Withdrawal Bill into parliament. This bill, published on 13 July 2017, would officially repeal the European Communities Act 1972, initially converting directly applicable EU law (EU regulations) into UK law and preserving all domestic legislation based on EU law, such as directives. Thereby, all existing EU-derived domestic legislation and direct EU legislation will form part of domestic UK law after Brexit day and current corpus of EU law remains in force [37].

According to House of Commons research services, which conducted an analysis of the Eur-lex database, there are presently around 19,000 EU legislative acts in force. Many of these instruments, mainly around 5,000 EU regulations and 900 EU directives, are valid in the UK [38, 39]. These laws are to be examined to change or abolish them if necessary. The current UK government intends to implement this review and possible changes to the law without parliamentary approval [37]. After Brexit, the UK would no longer be obliged to follow future EU law. On-going legislative proposals will only be valid in the UK if finalised before the end of Article 50 negotiations. Thus, all EU directives and regulations that enter into force after the official Brexit will no longer be applicable in the UK [38,39]. However, the UK has the option to follow future EU regulations and create similar legislation.

The future role of the European Court of Justice (ECJ) decision is still open. It was initially planned to end the jurisdiction of the ECJ with Brexit, but a white paper has revealed that ECJ will still be relevant. It states that only the direct jurisdiction of the ECJ ends with Brexit; its judgments could therefore continue to be used as a guideline for legal disputes affecting the UK [40].

3 Approval of MR/DC/CP authorisations - Status quo after Brexit

There are currently four routes to obtaining marketing authorisation in the UK:

i) The ‘centralised procedure’ (CP) by making one application to the EMA (a single marketing authorisation is obtained);
ii) The ‘decentralised procedure’ (DCP) by making multiple applications to each individual EU member state where marketing authorisation is sought (separate national authorisations are obtained);
iii) The ‘MRP’, whereby a medicine is authorised in one EU member state and a later application is submitted for this authorisation to be recognised in other member states (separate national authorisations are obtained);
iv) The ‘national procedure’ (only possible if the medicinal product is not yet registered in any other EU MS) [41].

Following Brexit, the UK will separate from the EEA and will have to adopt a new system for independent marketing authorisation approval. New rules will need to be established for the participation of the UK in European marketing authorisation procedures for new medicines.

The following chapters summarise the status of existing marketing authorisations after Brexit. The pure national procedure is not part of the discussion, as Brexit has no consequences on the procedure itself.

3.1 Status of central marketing authorisations after Brexit

Central marketing authorisations are commission decisions [41]. Under Article 288 TFEU, an EU decision is binding on those to whom it is addressed, and in the case of marketing authorisation, it is directly applicable [20]. Without the EU Withdrawal Bill, a commission decision as a legal instrument of the EU would be invalid in the UK after the withdrawal, but would remain valid for the remaining 27 EU countries. However, at first, the “acquis communautaire”, will remain valid, as described in Chapter 2.3, and the recognition of centralised marketing authorisations of medicinal products is therefore highly likely. This is also noted in the Position Paper of the UK, which states, ‘Continuity in the availability of goods for the EU and the UK’. This indicates that the UK government aims to recognise the validity of approvals, registrations and authorisations that are issued for these products [4].

Nevertheless, the UK must immediately create fixed national rules for maintaining its central marketing authorisation. For the already existing approvals by the commission, a possible scenario is that the UK could acknowledge central approvals through a national act and make it binding for the UK. However, Brexit would result in a technical change to the way that new centralised marketing authorisations take effect as a national licence in the UK. Rather than the commission decision granting the EU marketing authorisation automatically applying in the UK, the UK would have to take steps to give effect to it, for example by granting a national marketing authorisation to mirror the EU approval. The

question in place is if the UK would also automatically adopt commission decisions on variations after Brexit.

Considering the UK that is departing from the EU, MAHs will have to apply for two authorisations after Brexit: one for the central marketing authorisation in the EU and one for the same product as national authorisation in the UK. This would lead to additional charges, and the approval process in the UK could take longer. The MAH could choose when to apply for the licence which would lead to a preference in the central approval, as this is in most of its market share.

To avoid a delay in the approval process, it would be preferable if the MHRA and EMA would work up a recognition process and guidelines for a (mutual) recognition process to acknowledge the central marketing authorisation, with the EU as rapporteur and the UK accepting all decisions. The EMA could act as a consultant for regulatory and scientific questions as part of this process. Such an agreement would benefit both regulatory authorities by reducing duplication of work. Such a procedure would only work if the UK would also automatically adopt commission decisions on variations, updates and referrals. If not, a drifting apart of the authorisation is possible after Brexit due to national decisions. To set up such procedure, the EMA and the commission must demand certain conditions and clear rules for the 'transfer process'. Because voting rights in The Committee for Medicinal Products for Human Use (CHMP)/EMA decisions for the UK (MHRA) will result in a 'hard Brexit', it is unclear if the MHRA could have any influence in such a procedure. Chapter 10.1 presents a more detailed proposal for a procedure based on experiences with EU enlargement procedures. From an industry point of view, existing centralised European marketing authorisations of medicinal products should remain principally valid and be recognised by the UK without restrictions.

3.2 Status of MR/DC authorisations after Brexit

Decentralised authorisations (MRP, DCP) are national decisions by the national authorities [41] and are therefore independent of Brexit, irrespective of which authorities are reference member states (RMSs) or concerned member states (CMS). That means that decentralised authorisations remain valid in EU 27 even if the UK authority is an RMS) or if another national authority in an EU country is 27 RMS. However, after the withdrawal, no decentralised process can be operated from the UK as an RMS; the UK as a CMS is also not imaginable. Therefore, procedures with the UK as an RMS must be transferred to the authorities of the EU 27 [42]. Chapter 4.1 highlights this issue in detail.

However, the same questions as for centralised authorisations must be clarified: Can the UK participate in the approval process? And do already existing UK approvals remain in the 'RMS network' regarding variations, referrals etc.? A screening of the MHRA website has offered no advice until now about how the MHRA will handle its national license after Brexit. A divergence from the harmonised authorisation would be the consequence. As DCP and MRP procedure is a work-sharing procedure, there is strong demand for elaboration of a guideline for a mutual recognition process for the approval and recognition of variations and referral procedures. Otherwise, an increased workload will generate a

significant challenge for the MHRA. Chapter 10.1 includes a more detailed proposal for a procedure.

Another aspect must be discussed for the status MR/DC authorisations with a reference medicinal product approved in the UK for gaining a generic licence. Procedural advice of CMDh defines the ‘repeat-use’ procedure as follows: ‘*A Marketing Authorisation Holder (MAH) can use the Mutual Recognition Procedure (MRP) for the same authorisation more than once after completion of a first MRP or a Decentralised Procedure (DCP) for the recognition of a marketing authorisation by other Member States (MS)*’ [43]. Reference medicinal products approved by the MHRA will no longer be acceptable in the EU, as a marketing authorisation for an RMP must be issued by the competent authorities of a member state in the EU, as defined in Article 10 (referring to Article 6) of Directive 2001/83/EC [21]. Therefore, a repeat-use procedure after Brexit is no longer possible with a reference medicinal product approved in the UK. Overall, the subject of RMPs approved in the UK leads to a strong need for guidance regarding their recognition in case of repeat use procedure.

4 The UK in running and finished MR/DC/CP procedures

The UK plays an important role as an RMS for authorisations from the decentralised or MRP and as a rapporteur for central approvals, as the following chapters demonstrate. The EC describes the national authority in the function of the RMS or rapporteur as '*the privileged interlocutor of the applicant and continues to play this role, even after the marketing authorisation has been granted'* [43]. The following chapters describe impacts of Brexit regarding the UK as an RMS or rapporteur in running and finished MR/DC/CP procedures and the preliminary steps to consider for MAHs with respect to upcoming switches.

4.1 Reference member state for an MRP or DCP is the UK

The CMDh 'Best practice guide for the RMS in the MRP or DCP procedure' more precisely defines the RMS as *the 'Member State, which evaluates the marketing authorisation application dossier and prepares the assessment report on behalf of the Concerned Member States in Mutual Recognition Procedure (MRP) and Decentralised Procedure (DCP). RMS has an essential role in both MR and DC procedures; the RMS acts as a scientific assessor of the documentation, as a regulatory advisor to the applicant, and as a moderator in the discussion between the applicant and the Concerned Member States (CMS)'* [43].

According to Directive 2001/83/EC [21], and furthermore stated in the CMDh question-and-answer paper related to the UK's withdrawal from the EU with regard to national authorised medicinal products for human use, *'the evaluating agency (RMS) must be established in a member state of the Union (EEA)'*. Consequently, '*for national authorised medicinal products via MRP/DCP in which the RMS is the UK the marketing authorisation holder will therefore need to change the task of the RMS to an agency of a member state of the Union (EEA)*' [42].

The strong role of the MHRA as the RMS can be proofed through an analysis of the MRI Product Index, which includes medicines approved in the member states of the EU according to the Mutual Recognition or DCP [45]. This database contains a total of 36,938 products with positive outcomes (accessed 12 August 2017). Filtering this database to 'United Kingdom' as the RMS indicates that 5,214 (research date: 12 August 2017) authorisations have the UK as the RMS – in proportional terms, 14.1% of all marketing authorisations (MRP/DCP) in this database.

All those licences must be transferred to other authorities before Brexit, which is 27 but will focus on those member states which are strong RMS and CMS countries, such as the Netherlands, Germany, Portugal and Denmark. The following statistical evaluation, performed by the CMDh in 2016, gives an overview of which countries were strong RMS and CMS countries in the year 2016 [46] in finalised and started procedures.

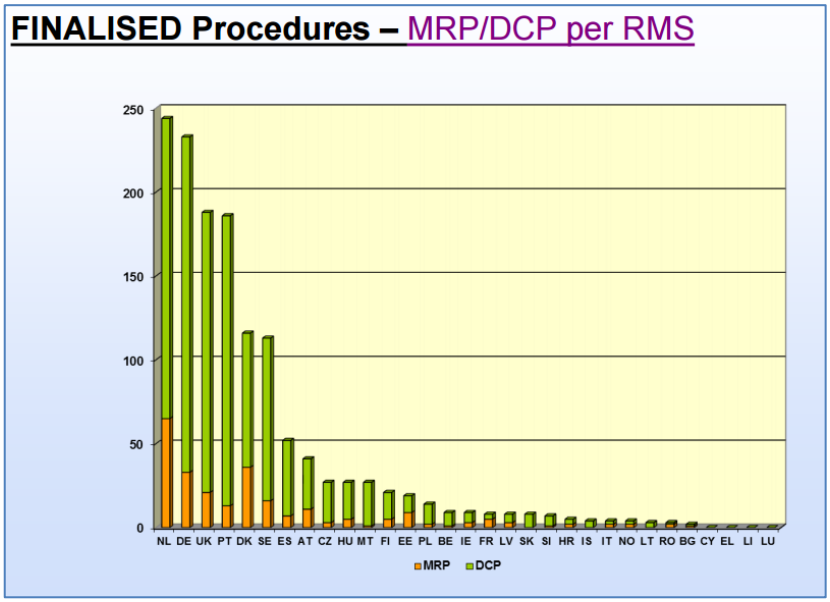

Figure 2: Finalised procedures in 2016 with the indicated countries as RMS

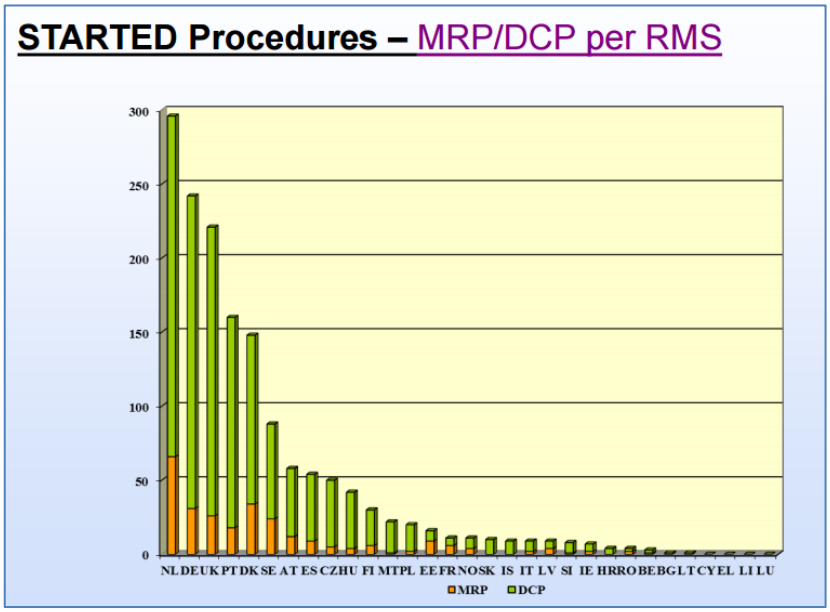

Figure 3: Started procedures in 2016 with the indicated countries as RMS

Figures 2 and 3 clearly demonstrate that the UK was the third-strongest country in started and finalised procedures in 2016, with approximately 240 procedures. It also gives an impression of which other countries are strong RMS countries and which were expected to share the workload of the outstanding RMS changes. It is reasonable that most of MAH's will switch to an already existing CMS for their licence. For example, the overlap with Germany as the CMS is 2,002 marketing authorisations (MRI Product Index accessed 12 August 2017) [45], which means an expected increased workload for the German Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) in case of switching to Germany as the RMS. This increased workload could lead to delays in the assessment and review process.

The procedure and prerequisites to switch the RMS for an authorised medicinal product for human use are outlined in the CMDh procedural advice on changing the RMS. This procedural advice was updated regarding Brexit and considers an '*RMS triggered Article 50 of the Treaty on EU'* to be a justified reason to change the RMS [47]. This procedural advice furthermore indicates that a change of the RMS cannot take place during an on-going procedure. This relates not only to the procedure itself but also to an outstanding renewal, variation, repeat-use procedure e.g. [47]. For companies with an on-going procedure (UK RMS), finalisation is therefore highly recommended before Brexit is effective. If the RMS has already started the procedure, it would make sense to check the timeline and finish the procedure with the UK as he RMS, but switch after completion.

To get an impression of how long the MHRA needs to finish different procedures, the following Figures 4 through 8 reflect licensing time-based performance measures from June 2017. These include the average time to complete the assessment and time to determine the application regarding new marketing authorisations and Type II / Group Variations of the MHRA as the RMS in the last year, excluding time taken by the applicant to provide further information or data required [48].

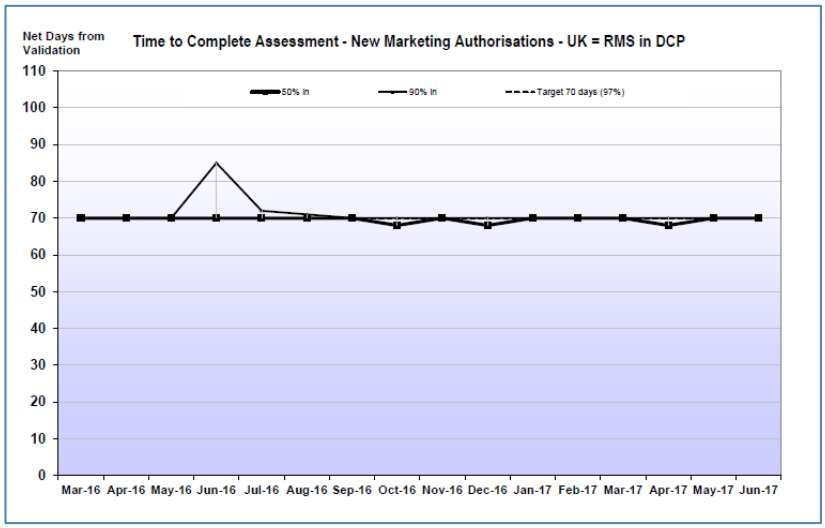

Figure 4: MHRA Statistic 2016: Time to complete assessment – New marketing authorisations

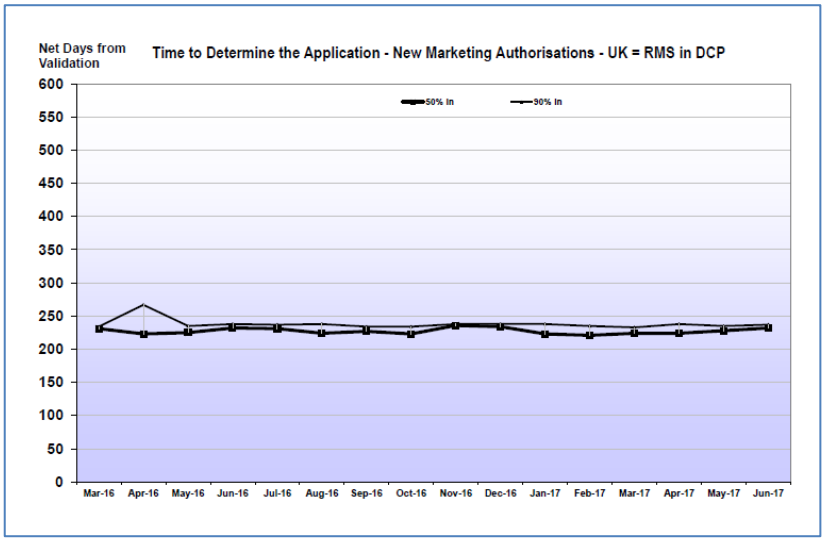

Figure 5: MHRA Statistic 2016: Time to determine the application – New marketing authorisations

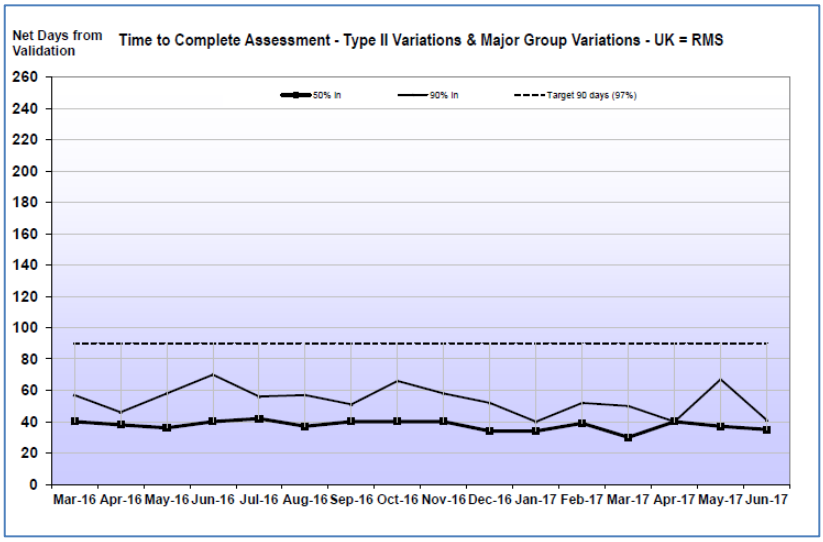

Figure 6: MHRA Statistic 2016: Time to complete assessment – Type II & major group variations

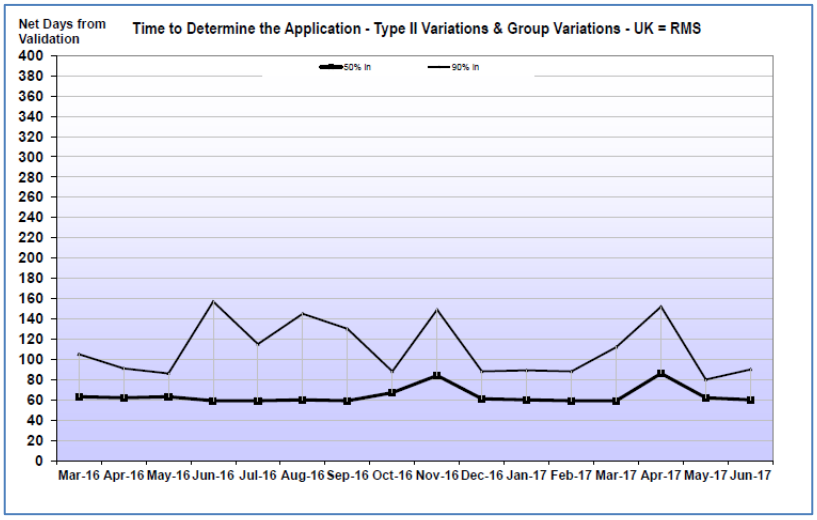

Figure 7: MHRA Statistic 2016: Time to determine the application – Type II & major group variations

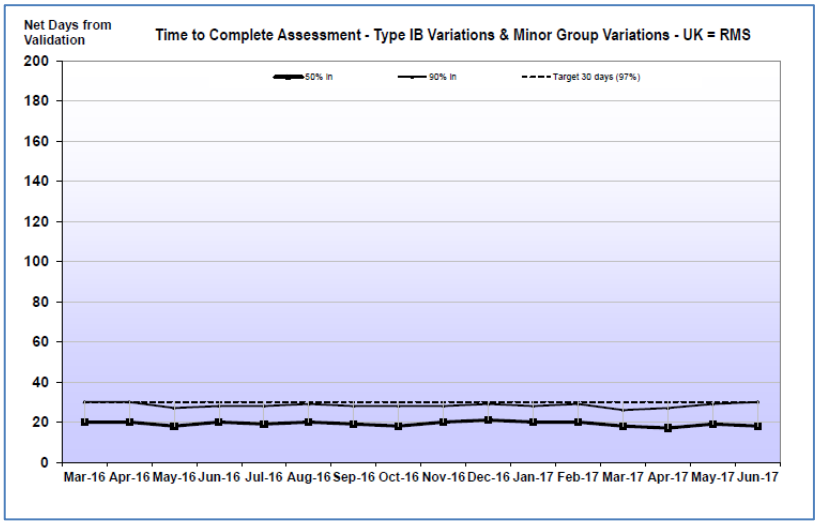

Figure 8: MHRA Statistic 2016: Time to complete assessment – Type IB & minor group variations

These figures are intended to identify the optimal date for a switch. If no extension is achieved on the date 29 March 2019, in the worst case, started procedures with the UK as the RMS cannot be completed. It is therefore not recommended to start a new procedure with the UK as the RMS, although there is still the possibility on the MHRA website to book a DCP submission date to start an application with the MHRA as the RMS. The CMDh statistical evaluation for started procedures from 1 January to 30 June 2017 implies that many MAHs still started a procedure with the MHRA during the first half of the year (see Figure 9) [49]. A decrease in the amount of the procedures cannot be determined in comparison to Figure 3 since the statistic in Figure 9 represents only the evaluation for half a year.

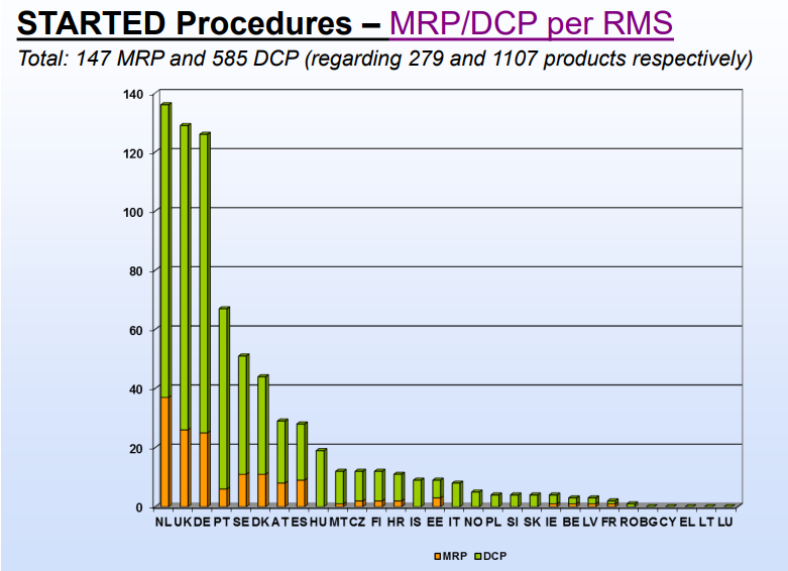

Figure 9: Started procedures from 1 January to 30 June 2017, with indicated countries as the RMS

Companies that have already gained authorisation must decide when and to which member state to switch. It is anticipated that these MAHs faced with a ‘decoupling process’ will need to select an alternative RMS to act on their behalf, and they will contact the

intended RMS to discuss the company's intention to switch the RMS. Choosing the 'appropriate' RMS is the responsibility of the MAH and an important aspect to take into consideration, also if marketing authorisation is already granted. In general, the scientific expertise of the respective national authority is the main driver in choosing the RMS. Good communication with the competent authority of the respective member state is crucial, as are some other aspects, e.g. time until granting national approvals for Type II Variations, as for example timely evaluation or less complicated additional requirements [50]. The change to a new RMS should also be carefully considered since many other MAHs will have to go through this process. It cannot be ruled out that authorities will decline due to increasing workloads. Procedural advice assures authorities the right to refuse the application [47].

Nevertheless, it is recommended that an RMS switch should be discussed with the concerned national competent authorities (NCAs) before any further steps are taken and after agreement to officially notify the MHRA of their intention to change the RMS. From the NCA in the role as new RMS, a new DCP number must be requested by the MAH. Some of the NCAs have established an application form and a fee structure for this process. The MHRA then sends the assessment report (AR) to the intended RMS. No definitive timeline is fixed for this process [47]. The availability of resources at the new RMS will dictate how soon they can assume the new RMS. Finally, it should be noted that the guidance also allows for a switch back to the UK if an exemption is agreed on as a result of Brexit negotiations [47].

4.2 Rapporteur for a CP is the UK

After withdrawal, the MHRA can no longer be rapporteur or co-rapporteur of central procedure and will no longer have voting rights in CHMP/EMA decisions, as this function is reserved for community members [22]. Unlike for the MR/DC procedure, the switch of a rapporteur for a CP is not triggered by the MAH. According to Article 62(1) (EC) No 726/2004, members of the committees appoint a member state to act as rapporteur [51]. The scientific committees of EMA will therefore have to designate new rapporteurs for the central marketing authorisations supervised by the MHRA and will need to organise the transfer from the MHRA to another national regulatory authority. The responsibilities of a rapporteur encompass a broad range of tasks [50]:

- *'Take responsibility for the scientific assessment/evaluation undertaken by the assessment team within the scope of their committee's involvement with the concerned procedure in accordance to the timeframes laid down in the EU legislation and the EMA regulatory procedures*
- *Coordinate input from her/his assessment team*
- *Coordinate input from a variety of fora e.g. Working Parties, Ad Hoc Expert Groups, SAGs(Scientific Advisory Groups), external meetings/conferences*
- *Involve additional expertise as considered necessary*
- *Act as a committee representative/spokesman in liaison with Applicant/MAH*
- *Interact with the EMA product team*

- *Ensure that all her/his activities are performed in a transparent manner (informing accordingly the EMA Secretariat)*
- *Establish contacts with Patient Organisations/Health Care Professional Associations (in accordance with the provisions laid down in Article 78(2) of Regulation (EC) No 726/2004)*
- *Collaborate with the rapporteur from other relevant EMA committees for the medicinal product for human use and ensure comments are taken on board, as appropriate*
- *Conclude rapporteurship with the completion of required documentation as appropriate (Assessment Report, Draft Opinion etc.)'* [50]

This list illustrates the extensive activities of the rapporteur. Given that the EMA is going to move, reallocation will be a huge challenge. Distribution of the workload requires compliance with the legally fixed timelines and maintenance of the quality of the output.

In addition, the MHRA acts as a rapporteur in many centralised marketing authorisation decisions. On the basis of a statistical evaluation from the EMA which was accessed on 29 March 2017 and is specified in Figures 10 and 11, the UK is the rapporteur for 155 authorisations and co-rapporteurs for 71 authorisations that have already been approved and distributed [52]. This implies further aggravation of the situation and reallocation of substantial work to other authorities.

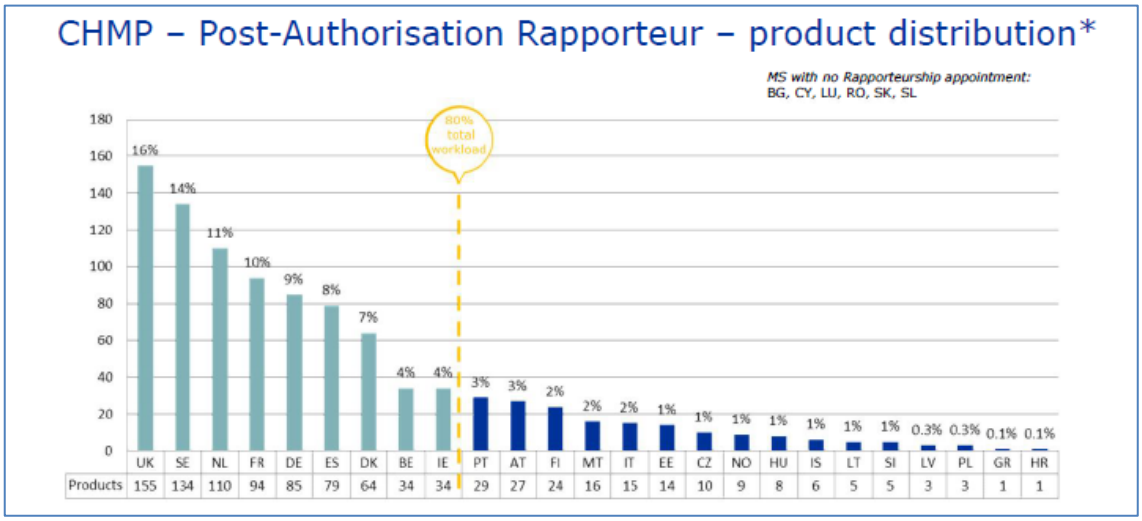

Figure 10: EMA statistics on Rapporteur; UK is rapporteur for 155 products.

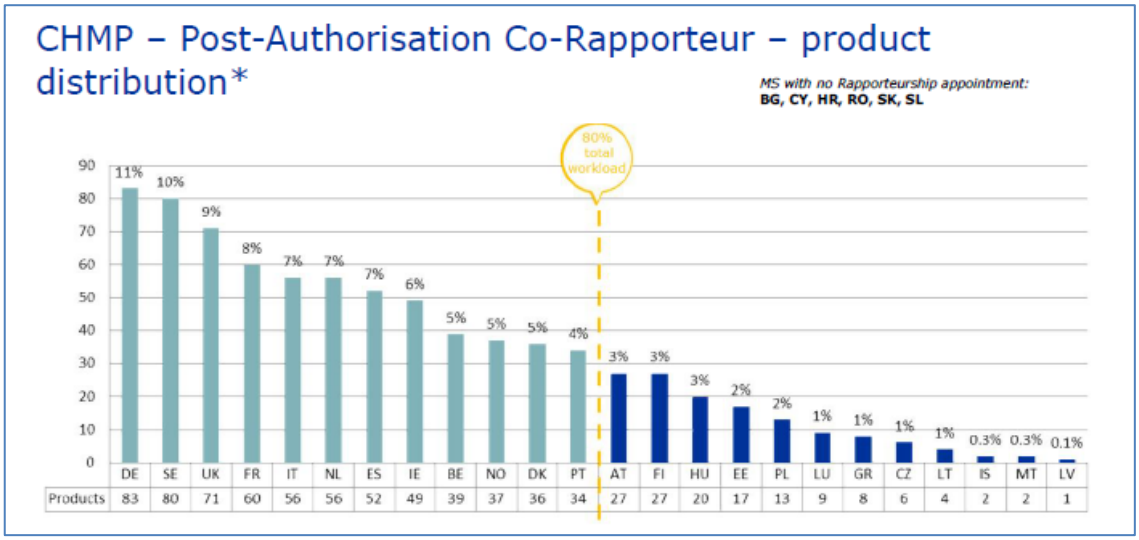

Figure 11: EMA statistics on Co-Rapporteur; UK is co-rapporteur for 71 products

Nevertheless, the business continuity plan of the EMA classifies the scientific assessment as one of the highest-priority activities [53]. To ensure business continuity, the EMA's management board endorsed the mandates of two working groups, one of which focuses on human medicines. This working group will explore options for a robust allocation of the workload across the European medicines regulatory network and will discuss ways to streamline work and further increase capacity in the network [54]. Until now (31 August 2017), no concrete proposal has been published to address how exactly the EMA wants to handle the switch of rapporteurs. This also concerns the work of the Pharmacovigilance Risk Assessment Committee (PRAC) as rapporteur for referrals, which is noted in the PV section (Chapter 8). It raises the concern of delays in the approval process, and it cannot be ruled out that procedures will take longer in the transfer period.

5 Research and development

All new medicines introduced into the market are the result of lengthy, costly and risky R&D conducted by business enterprises and higher education institutions as well as government and private non-profit organisations. In 2015, the pharmaceutical industry invested nearly €336 billion in R&D in Europe [55]. The cost of researching and developing a new chemical or biological entity was estimated at $2.558 billion in 2013 [56].

The following figure depicts key steps in the development of a medicine and specifies the average time for each step. This conveys why it is so important for all stakeholders to clearly define a thoughtful regulatory R&D strategy. By the time a medicinal product reaches the market, an average of 12 to 13 years will have elapsed since the first synthesis of the new active substance [55].

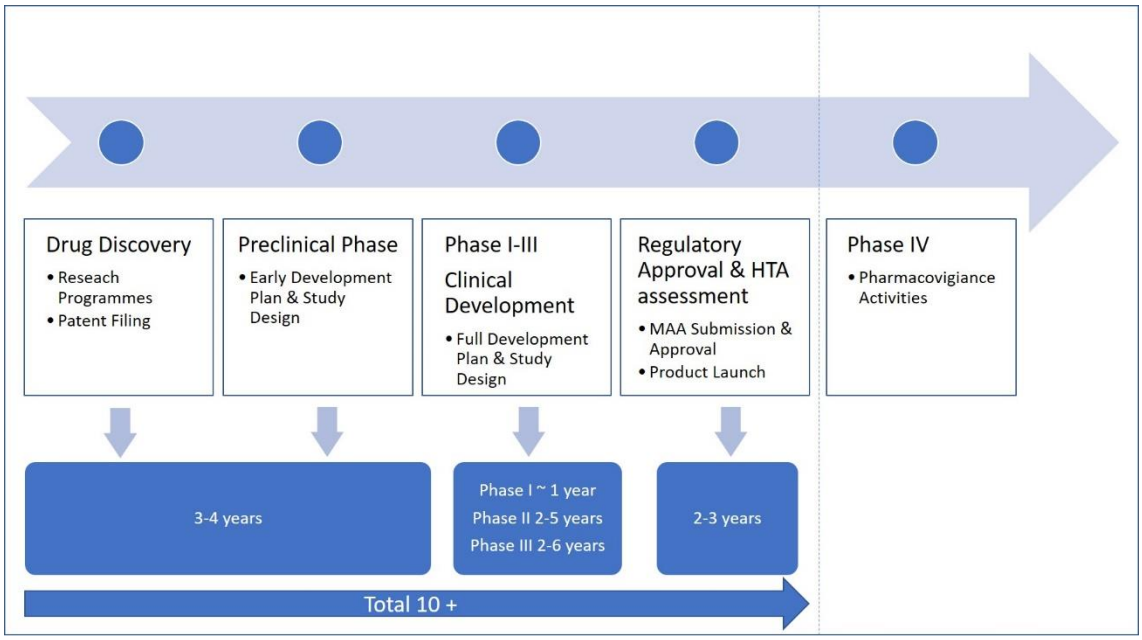

Figure 12: Medicines development process in Europe

The following chapter discusses Brexit's impacts on different regulatory aspects in the development of human medicine, such as the new clinical trial regulation, the support for small and medium entities and orphan designations. This chapter is certainly incomplete given the breadth of this subject, but it focuses on the main concerns. Please note that Chapter 8.5 explains the impact on funding.

5.1 Clinical trials and clinical trial regulation

The UK is currently the most popular location for phase I trials in Europe, and it is second in popularity for phase II and phase III trials, according to an analysis of the Association of the British Pharmaceutical Industry [57]. This is also highlighted through the following figure published in the MHRA statistics, which illustrates the high volume of clinical trial applications (CTAs) received by the MHRA from 2005 to 2016 [58].

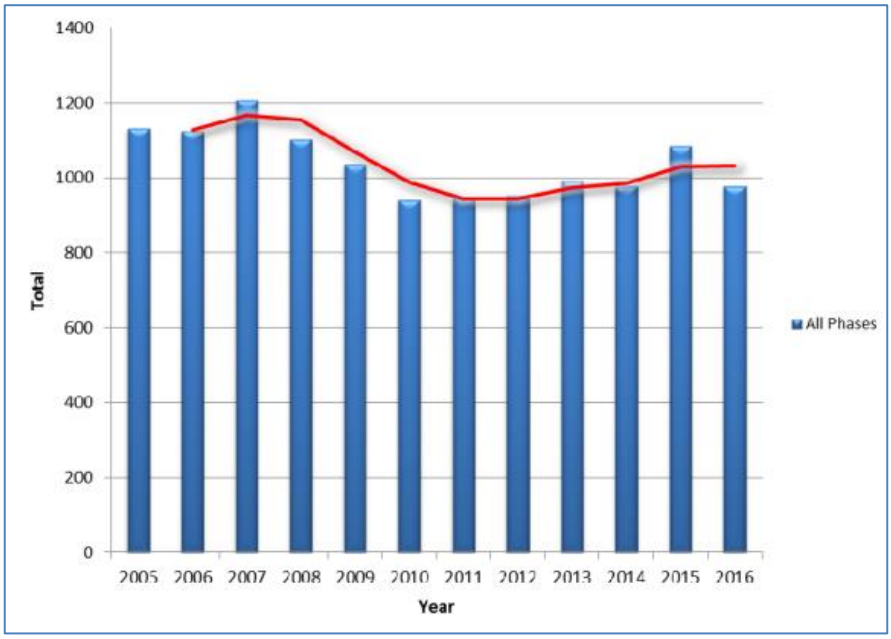

Figure 13: Clinical trial applications 2005-2016 in the UK: authorisation assessment performance of the MHRA (all phases)

According to the MHRA's figures, the number of applications for clinical trials in the UK has declined since 2005, with the lowest ebb in 2010. Recent years have reflected a small recovery in application numbers. It is difficult to predict whether it will be possible to maintain a good position in the field of clinical studies after Brexit, but new clinical trials regulation in the environment of Brexit could influence this position.

The new Clinical Trials Regulation 536/2014 was adopted on 16 June 2014 and replaces the previously valid Directive 2001/20/EC [23, 24]. This directive was implemented in the UK in *'The Medicines for Human Use (Clinical Trials) Regulations 2004'* [59]. Stakeholders often criticised Directive 2001/20/EC for its disharmonised interpretation because members states had implemented the clinical trials directive differently and because it increased associated costs, delays, and the administrative and regulatory burdens of conducting clinical trials in different member states [59,60]. Major advantages of the new regulation include an authorisation procedure based on a single submission dossier via a single EU portal, an assessment procedure leading to a single decision on all aspects per member state, rules on the protection of subjects and informed consent, and transparency requirements. Other aspects include more detailed safety provisions, new indemnity provisions and a category for low interventional trials. A new regulation also intends to make it easier for pharmaceutical companies to conduct multinational clinical trials, which would improve the attractiveness of Europe as a location for clinical research and lead to an increasing number of studies conducted within the EU [62].

The first-time application of the new EU regulation on clinical trials is directly linked to the availability of an EU portal and an associated database on clinical trials, according to Articles 80 and 81 of the regulation, which the EMA must provide. According to Article 82 of the new regulation, the entry into application of the clinical trials regulation is made

dependant on the full functionality of the EU portal, which an independent audit will confirm [24]. Due to technical difficulties, the EMA has stated in a management board press release that it will begin applying during 2019 instead of in October 2018 as previously scheduled [63]. Therefore, any CTA submitted before the 'GO Live' of the new database is still governed by the old Directive 2001/20/EC. The following process in Figure 14 illustrates periods and timelines for the EMA's plan to introduce the new clinical trial database in Europe, specifically noting the time overlap with the Brexit date.

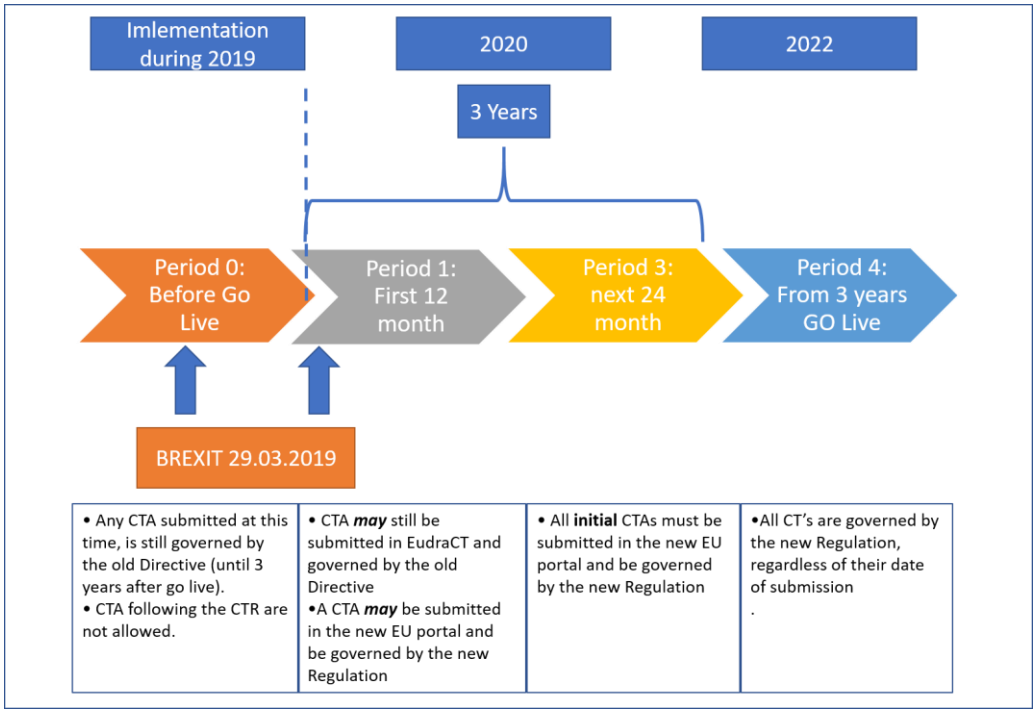

Figure 14: Overview of transition to the new clinical trial system

It increasingly seems that Brexit will occur prior to the implementation of the regulation, in which case the EU Withdrawal Bill would not protect the regulation. The UK would, without any agreement, be excluded from the new clinical trials database, as provisions of the clinical trials regulations are not converted into UK law. Furthermore, after entry into force of the clinical trial regulation, it will also govern clinical trials that have already been approved e.g. regarding substantial amendments, inspections, conduction and termination, which raises the question of the future role of the UK as a reporting member state for clinical trial assessment. It is not clear whether the UK will be able to participate in the 'streamlined' clinical trial approval process that the new regulation introduces. A possible solution is new community legislation which would permit an RMS status for the UK after the withdrawal. However, this could be ruled out after Article 50 EU Treaty of the withdrawal agreement. Thus, the UK must furthermore remain aligned with the EU with regard to data protection.

Regulatory uncertainty and negotiations that do not contain any prospect of a solution lead to the following 'worst-case' implication: the UK cannot play any role as reporting member state. This emphasises the need to regulate the concept of clinical trials regarding Brexit. So, if the UK is excluded from the new clinical trial regulation, the proposal for affected companies is to discuss a repositioning of resources to address the potential

risk of increasing the complexities, administrative burden and cost in conducting clinical research in the UK, as this will necessitate a separate submission outside of the single EU trial portal. Leading healthcare service provider Quintiles IMS has stated that it poses a risk to begin e.g. a complex multiyear trial in the UK because this trials could become misaligned with Europe later in the process. It has also noted that after having already received approval for the wider EU market, it will be too costly and complex to apply and conduct clinical trials in the UK [64].

Since the new regulation is addressed to the member states, it is significant that Article 74 (1) of the Regulation dictates that UK sponsors are obliged to appoint a legal representative in an EU member state who is responsible for locally managing the clinical trial and submitting the CTA [24]. Nevertheless, with the UK as a third country, clinical trials included in applications for marketing authorisation in the EEA and conducted in the UK after Brexit will have to comply with national UK law which is based on Directive 2001/20/EC; thereby, GCP standard and ethical principles are equivalent to those set out in the EEA, including adhering to good clinical practice (GCP). Furthermore, International Conference on the Harmonisation (ICH) GCP Guideline E6(R2) provides a unified standard for the design, conduct, recording and reporting of clinical trials [65].

5.2 Orphan designation

According to orphan drug Regulation No. 141/2000, a pharmaceutical company developing an orphan drug can benefit from several incentives, including market exclusivity for the drug for a period of 10 years, provided it meets the necessary criteria. Currently, the Committee for Orphan Medicinal Products at the EMA receives applications for and assigns orphan drug designation [29].

Article 2 of Regulation (EC) No 141/2000 further notes that the sponsor of an orphan medicinal product designation must be established in the union (EEA) [29]. Therefore, designated orphan medicinal product holders with legal entity in the UK will be affected and must transfer their designation to a sponsor established in the union (EEA) [66]. In the case that the sponsor is a new legal entity or different person, the EMA provides a checklist for the orphan medicinal product designation transfer process, which describes which documents are needed for the application of a transfer [67]. This transfer process is not unusual, as the application is usually carried out early in the development process. Moreover, transfers may arise from various business or regulatory aspects. It should be noted that if a transfer is sought for several orphan designations, an application must be submitted for each designation. The EMA will provide an opinion on the transfer, and the transfer will be accepted from the date of notification of the amended commission decision [68].

It is also possible '*to change place of establishment to a Member State of the Union (or EEA) and submit the corresponding documentation through a change of name and/or address of the orphan designation holder procedure provided the legal entity remains the same'* [66]. This is subject to a different procedure, and the authorities publish a '[g]uideline on the format and content of applications for designation as orphan medicinal

products and on the transfer of designations from one sponsor to another' for this process [69].

5.3 Supporting micro, small and medium-sized enterprises (SMEs)

Commission Regulation (EC) No 2049/2005 was enacted to promote innovation and the development of new medicines for human and veterinary use by companies *'employing less than 250 employees and have an annual turnover of not more than €50 million or an annual balance-sheet total of not more than €43 million*'. Under this commission regulation, SMEs established in the EU or EEA have the option to apply for a reduction of fees as well as to defer the payment of fees during the assessment of applications for marketing authorisation for medicinal products for human and veterinary use. The regulation additionally offers administrative assistance from the EMA, such as for translation of documents that are deemed necessary to issue a marketing authorisation (see Article 9 and 10 of the regulation) [70]. The EMA SME register (accessed on 3 September 2017) contains all companies established in the EEA that have submitted an SME declaration and includes 1,359 companies with activity in human medicinal products, 243 of which are located in the UK [71].

In order to be eligible for financial and administrative assistance, companies must be established in the union (EEA) and meet the definition of an SME [70]. Therefore, all those companies based in the UK will lose their SME status, and new UK-based enterprises cannot apply for SME status after 2019. However, such legal status may be maintained or obtained through two channels. A new legal entity (such as a subsidiary) that is located in the EU or EEA can act as a liaison between the MAH and the EMA or a regulatory consultancy, which makes it possible to indirectly benefit from the SME incentives. In the first channel, the company must submit a copy of the certificate of incorporation in the company's commercial register as proof of establishment. The SME declaration can be submitted in the name of the newly established subsidiary with details of the parent company to be declared. In the second channel, both the regulatory consultancy and the non-EU/EEA-based company must be assigned SME status by the EMA SME office, which requires that they meet its SME criteria (EMA user Guide for SME). In this case, both the regulatory consultancy and the non-EEA based company must submit SME declarations. It must be noted that an SME regulatory consultancy is not allowed to act on behalf of non-SME clients, as this would be contrary to the objectives of the SME regulation. An SME notification would be sent to the regulatory consultancy and the non-EEA based company would be listed in an annex to that notification as an SME client company [66].

On a national basis, payment easements in the UK are only given to small companies. The defining conditions of a small company are specified under the 'small company' heading in Section 382(3) of the Companies Act 2006, namely that the balance sheet total does not exceed £5.1 million and the number of employees is a maximum of 50 [72]. A 'Payment Easements for Small Companies' guideline of the MHRA describes the fee reduction specifications [73].

6 Post-approval activities

The following chapters engage with various topics in post-approval activities and focus on areas which Brexit may impact. These particularly include change of MAH, variations, renewals and the major topic of pharmacovigilance.

6.1 Change of MAH – when required?

According to Directive 2001/83/EC, a MAH needs a legal establishment in the EEA. To maintain market authorisation, MAHs located in the UK with market authorisations throughout Europe will need to transfer their marketing authorisation to a holder established in the union (EEA) before Brexit [21]. The general index on marketing authorisation holders and sponsors for central marketing authorisations in the community register counts 380 MAHs and sponsors (accessed 26 June 2017) [74].

Commission Regulation (EC) 2141/96 describes which elements must be taken into consideration for the transfer. The EMA has published post-authorisation procedural advice for users of the CP that contains a chapter for the transfer of marketing authorisations. The 30-day procedure follows strict rules. In this context, it is important to take into account that a change to elements of the pharmacovigilance system master file (PSMF) summary, e.g. to the qualified person for pharmacovigilance (QPPV) or to the PSMF location, which result from the transfer of the marketing authorisation (can be notified as part of the transfer application without need for a separate variation [75]. The MAH should therefore clarify before the transfer who can take over the task in Europe and which further responsibilities are concerned in the context of the pharmacovigilance system. It is also a key consideration that MAHs should avoid submitting variation procedures in parallel with a transfer of marketing authorisation application. In case a marketing authorisation transfer is needed for several medicinal products, an application must be submitted for each marketing authorisation [75].

Regarding national authorised products through MRP, DCP or national procedure in the EU, transfer of a marketing authorisation is a non-harmonised process among member states and differs greatly from one member state to the next. The marketing authorisation transfer change is outside the scope of the Variation Regulation [76] and is therefore processed individually by the competent authority (CA) that has granted the marketing authorisation on a national basis. Therefore, the national websites must be checked regarding how to proceed with the change.

It has become obvious that the MAH would need two residences: one in the UK for the national licence and one for the marketing authorisation in the other European countries. To organise a registered office in the respective jurisdiction (UK and EU), MAHs therefore need to prepare proactively. A possible solution is to out-license to a regulatory service in the UK; only this approach will maintain the UK market for European pharmaceutical manufacturers and ensure access to medicines for patients.

6.2 Variations and renewals

6.2.1 Variations

After authorisation, any changes made to the approved dossier, including the approved product information, must be reported to the competent authorities of the member states in which the medicinal product is authorised. These changes are defined as variations and are regulated in Commission Regulation (EU) No. 1234/2008 [76].

Since Brexit would lead to various changes to the marketing authorisation if the UK is part of the dossier, e.g. as manufacturer for batch release, PSMF in the UK, etc., the CMDh updated the list of examples of acceptable and unacceptable groupings of variations for MRP/DCP products regarding if member state has triggered an Article 50 procedure of the Treaty on EU. Therefore, Brexit-related formal changes to the finished medicinal products can grouped into one application according to the highest variation type for the single changes. An exemption is the transfer of the marketing authorisation to a new MAH; this application must be viewed independently and according to the respective national regulations [77]. The newly inserted section in the list of positive and negative examples for groupings helps the regulatory affairs department with reducing the workload. Nevertheless, the EMA has not yet updated its procedural advice regarding groupings in the environment of Brexit for CP.

6.2.2 Renewals

The renewal of authorisations granted through the ‘mutual recognition procedure’ (MRP) or ‘decentralised approval procedure’ (DCP) is based on Article 24 Directive 2001/83/EC. For centrally authorised medicinal products, the renewal is based on Article 14 of the EC Regulation No 726/2004. The RMS or rapporteur conducts the assessment, and in most cases, the renewal must be performed once in a lifetime of an authorisation. The renewal application must be submitted at least nine months before the marketing authorisation expiry date [22, 23].

In this context, it is essential to check the date for renewal of the concerned authorisations. If the renewal date is close to Brexit, the timing for submitting the application should be carefully considered. For centralised renewals, the agency will not accept any application earlier than 11 months before the marketing authorisation expiry [75]. Therefore, for renewals around the Brexit date, MAHs should try to submit the renewal application before Brexit in order to avoid the submission of two renewals. In this context, it is also critical that all other changes (e.g. QPPV change, change of MAH) have been completed, as these must be specified during the renewal. Particularly in cases where parts of the dossier have implications for UK companies, e.g. the manufacturer, it is logical to request a pre-submission meeting at the EMA in order to clarify which actions to take and when. This is also true if the rapporteur of the CP is the MHRA and the rapporteur has already switched at the time of the renewal submission (see Chapter 4.2).

For national approvals, however, renewal can also be applied significantly earlier to allow for summarising individual renewal dates and determining a uniform renewal date for all

approvals from a MR/DC procedure [78]. As far as possible, no variation procedures should be initiated immediately before or during the enactment of a renewal procedure. If the UK is the RMS or CMS, it would make sense to have previously changed the RMS since it is unclear during the procedure whether the process can be completed by the MHRA. A previous change of RMS avoids this uncertainty. In this context, the dossier should additionally be checked to identify changes to any further UK functions. It is imperative to remain aware of the timelines of the procedures.

6.3 Pharmacovigilance

Monitoring the safety of medicinal products before and after they receive marketing authorisation is a top priority for regulators and the pharmaceutical industry. This field has reached the highest harmonisation standard throughout Europe. For an introduction, it is important to give a short overview of the current pharmacovigilance legislation, which became effective in July 2012. Due to a pharmacovigilance report from the EMA, this legislation was '*the biggest change to the regulation of human medicines in the European Union (EU) since 1995*' [79]. Placing greater emphasis on surveillance in the post-authorisation setting to improve the monitoring of drug risks in the EU was one trigger for the change in the regulatory approach and the enhancement of the pharmacovigilance procedures and activities. A final key driver of the change in the legislation was the need to enhance the pool of information and the availability of sources such as patients and literature reports [80].

This new legislation had significant implications for applicants and holders of EU marketing authorisations as well as for patients, healthcare professionals and regulators. Directive 2010/84/EC and Regulation 1235/2010 overhauled the EU's pharmacovigilance framework as established by Directive 2001/83/EC and (EC) No. 726/2004. The amendments to the directive and regulation impacted authorisation requirements for a marketing authorisation, such as the introduction of a PSMF instead of a detailed description of the pharmacovigilance system as well as introduction of risk management plans (RMPs). Furthermore, post-authorisation measures were also enhanced with post-authorisation safety studies (PASS) and post-authorisation efficacy studies becoming legally binding. Another aspect is that the EMA and NCAs need to evaluate the effectiveness of risk minimisation measures through the scrutiny of company reporting on its risk minimisation measures and measurement of drug utilisation studies and health outcomes for key benefit risk issues. In addition, new legislation has provided for the development of an EU database that lists all medicinal products authorised in the EU. For pharmaceutical companies, reporting adverse drug reactions (ADRs) has been directed to the EudraVigilance database rather than to NCAs, thus creating a European pool of safety information [80].

Through a further implementing regulation (EU) 520/2012, GVP modules were introduced which contain the practical measures to facilitate the performance of pharmacovigilance in accordance with the legislation available in the guideline on good pharma-

covigilance practices (GVP). Good pharmacovigilance practice applies to marketing-authorisation holders, the EMA and NCAs in EU member states, and it covers medicinal products authorised centrally via the agency as well as medicines authorised at the national level [28]. Through this new legal framework, the concern that EU regulators were acting in disharmony when taking regulatory action on safety issues across all medicinal products irrespective of the approval procedure (CAPs or NAPs) is resolved. But Brexit raises the concern of the risk of a drift apart from harmonised rules.

The main concerns of companies affected by Brexit are that PV conducted in the UK may not be accepted in the EU anymore, and will therefore need to be duplicated elsewhere in Europe, and that they will no longer be obliged to carry out PV in the UK and may not ask UK PV providers to carry out PV tasks. The following chapters explain the legal obligations and preparatory steps regarding these obligations. Furthermore, from a regulatory point of view and in PV legislation, the future roles of the UK and MHRA in pharmacovigilance procedures is not yet clear. Many tasks in the PV system are affected, so some important tasks are presented, and an approach to describe two possible scenarios is given.

Pharmacovigilance is a complex and comprehensive topic. Therefore, the following chapters discuss only urgent questions.

6.3.1 Good pharmacovigilance modules

Good pharmacovigilance practices are a set of guidelines for the conduct of pharmacovigilance in the EU and apply to all medicinal products authorised in the EU, regardless of whether they are centrally or nationally authorised [28]. The question arises if the UK will adopt GVP modules in its current versions or if it will develop its own legal provisions for PV in the long term. Such specific PV regulations would require careful assessment of the minor differences.

Good pharmacovigilance practice modules are updated on a regular basis. A practical example is presented regarding risk management measurements for the CP as described in GVP Module V and Module XVI, which were both updated in March 2017. Planning and implementing risk minimisation measures and assessing their effectiveness are key elements of risk management. To fulfil this requirement, a risk management plan must be submitted to EMA. For CPs, the EMA specifies the RMP and additional risk minimisation measures are published in the European public assessment report (EPAR) [81, 82]. After Brexit, it will be possible that RMMs diverge with regard to different decisions by the national authorities and different requirements of the authorities. On the other hand, if the MHRA recognises EPARs of the EMA in the future, this problem would be less obvious for centralised approvals.

6.3.2 Pharmacovigilance databases

In pharmacovigilance, global collaboration of data is desired because possibilities for early identification of signals increase considerably when safety data from all sources

are merged. A problem specific to the potential ‘hard Brexit’ scenario concerns data access. The EudraVigilance database, the system for managing and analysing information on suspected adverse reactions to medicines which have been authorised in the EEA, is co-ordinated and managed by the EMA on behalf of European countries, and therefore also for the UK. An improved version of the EudraVigilance system will launch on 22 November 2017; with the publication of this new system, MAHs will no longer have to provide suspected unexpected serious adverse reaction (SUSAR) reports to NCAs. A simplified SUSAR reporting method will reduce duplication of efforts with a direct report to the new EudraVigilance system [83]. To register the EudraVigilance database, a residence in the community is demanded [84]. Should the UK fully leave the EU, it would subsequently have access to a smaller range of data sets.

The UK could opt to establish its own separate system for PV, which would likely require sponsors and MAHs to submit copies of all safety data submitted to EU and probably to the US FDA as well, thus involving some duplication of effort. Alternatively, the UK could agree with the EU to operate in a manner analogous to Norway, whereby the UK continues to submit adverse events/drug reactions to EudraVigilance. Another possibility for the UK is to resort to reporting adverse drug reactions on systems such as VigiBase, the World Health Organization (WHO) Global Individual Case Safety Report database. Due to the enhanced collaboration between the EMA and the WHO, which is a legal requirement under Article 27 of Regulation (EC) No 726/2004, the VigiBase will include EudraVigilance data [85]. Those data could also be used for monitoring and signal detection in the future.

6.3.3 Qualified person for pharmacovigilance

Another problem for pharmacovigilance is the uncertainty surrounding the status of UK-based QPPVs. According to Article 8(3)(ia) of Directive 2001/83/EC, to sell into the EEA, a QPPV residing in a member state of the union is mandatory for each MAH. The QPPV is responsible for ensuring the safety of the company’s products and compliance with its pharmacovigilance obligations [21]. Furthermore, this person must be permanently and continuously at the disposal of the MAH and experienced in all aspects of pharmacovigilance. Detailed information on the role and responsibilities of the QPPV and guidance for an MAH on supporting the QPPV adequately are specified in GVP module I, Pharmacovigilance systems and their quality systems) [86].

The EMA and CMDh have furthermore stated explicitly in their question-and-answer paper regarding Brexit that some pharmacovigilance activities must be conducted from within the EEA [42, 66]. This indicates that MAHs should begin making arrangements as early as possible to ensure compliance with this requirement post-Brexit. On this basis, companies who have a QPPV based in the UK will need to relocate or identify a new QPPV, identify a local QPPV for the UK and update the PSMF at a minimum. This will impact several QPPVs based in the UK and possibly hinder their futures, not to mention their support teams in their QPPV offices. The duplication of QPPVs is an immense task and is cost intensive. Marketing authorisation holders may not be able to recruit new

QPPVs and associated personnel to replace all those QPPVs currently working in the UK.

6.3.4 Pharmacovigilance system master file

Market authorisation holders are required to maintain a PSMF, which describes the company's pharmacovigilance system. As stated in the EMA and CMDh question-and-answer paper regarding Brexit and according to Commission Implementing Regulation (EU) No 520/2012, the PSMF must be located within the union (EEA) [42 ,66]. Additionally, Implementing Regulation (EU) No 520/2012 Article 7 (1) dictates that the PSMF should be located at the site where the EEA-QPPV is based or where the company conducts the bulk of its EU pharmacovigilance activities [28]. Thus, concerned companies need to revise the PSMF.

It is generally an electronic document, so relocation from the UK is unlikely to be a concern for most MAHs. Nevertheless, MAHs with a PSMF located in the UK will therefore need to change the location of the PSMF and QPPV to a member state, with regard to centralised authorisations, within the union (EEA). This is achieved by updating the Article 57 database without the need for a variation [66]. In case the marketing authorisation for a nationally authorised medicinal product has to be transferred to a new legal entity, a new summary of the pharmacovigilance system must be submitted via variation procedure C.I.8.a as type IAIN variation [42].

According to pre-authorisation procedural advice for users of the CP, it is sufficient that the data stored electronically is directly available at the site of the PSMF [87]. Nevertheless, although it is validated, operational and accessible at all times for EU markets and EU QPPV, there is a need to clarify if the server of the PSMF can be physically located and administered outside the EU. The supervisory authority for pharmacovigilance is the CA of the member state in which the PSMF is located; this question should be appointed to the NCA if this a relevant case.

If pharmacovigilance activities must move from the UK to the EU, a solution for the MAH could be a subcontract of certain activities of the pharmacovigilance system to third parties. It shall nevertheless retain full responsibility for the completeness and accuracy of the PSMF, and the MAH retains ultimate responsibility for the pharmacovigilance system [87]. Hopefully, the UK will continue to accept the EU PSMF template and not force companies to develop a UK-specific document.

6.3.5 Work sharing in PV

In his article, an EEA-QPPV and head of pharmacovigilance states, '*Over the last few years there has been a concerted effort through safety referrals (for example Article 31 referrals) and work-sharing assessment of Periodic Safety Update Reports (PSURs) to reduce duplication of activities relating to assessment of emerging safety concerns and changes to benefit/risk profiles of established medicines over the last few years'* [88].

He furthermore reflects on previous activities whereby each NCA assessed PSURs, providing an evaluation of the benefit-risk balance of a medicine, which were submitted

to them by MAHs, and that work-sharing assessment changed this procedure and led to a single assessment of PSURs. He describes how this procedure resulted in *'harmonized assessment and harmonized recommendations for labelling changes or other safety actions'.* In 2016, work-sharing assessment further streamlined and simplified this procedure following the introduction of the PSUR repository [88].'

There is much uncertainty about how these PSUR single assessment procedures will be conducted post-Brexit. It is not the EMA that conducts the assessment, but rather the NCAs represented in PRAC rapporteur. Following Brexit, the PRAC will no longer include UK representation. On the basis of a statistic evaluation from the EMA accessed 29 March 2017, the MHRA is rapporteur in 16% of the procedures [52], significantly more than any other CA (see Figure 15).

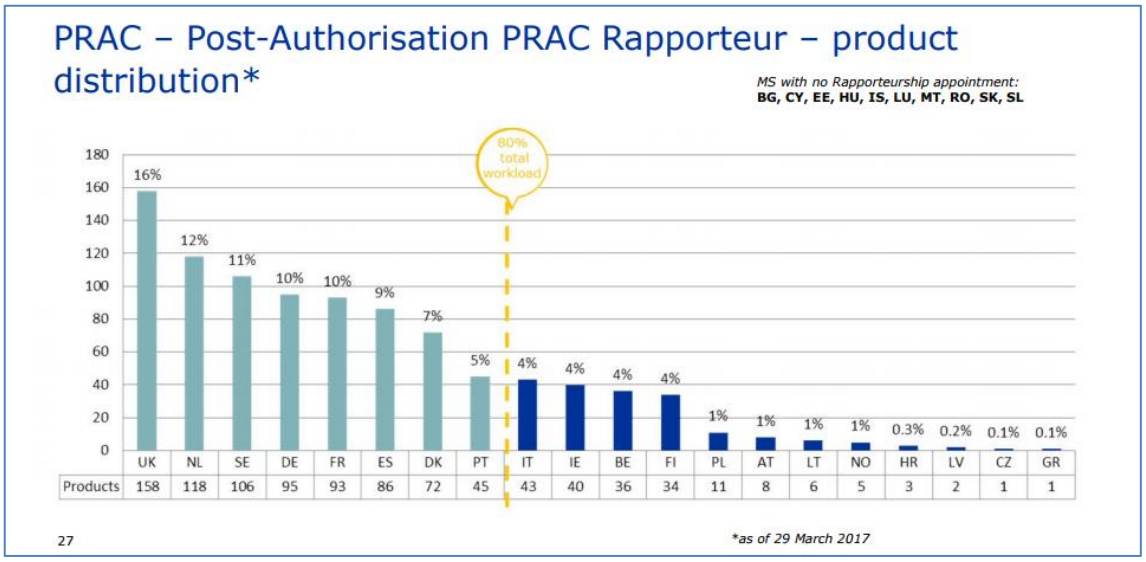

Figure 15: EMA statistics on the role of the PRAC in pharmacovigilance procedures

This implies that the work must be reallocated from the MHRA to the other member states. This will lead to a challenge, as the resources to perform this function must be expended in other MS. This could impact fees for pharmacovigilance services.

6.3.6 Future scenario regarding PV

Considering the UK outside of the EU, a potential regulatory framework with respect to PV in the UK from April 2019 shall be presented as a proposal for an MRA regarding pharmacovigilance in order to maintain a high degree of harmonisation and minimise additional costs and administrative burdens relating to pharmacovigilance activities in the UK and EU post-Brexit. The UK further operates in alignment with the current and future EU pharmacovigilance regulations, which implies the following:

- Continued use of the EMA's GVP
- Development of a work-sharing process with the MHRA regarding referrals and PSURs
- Further access to EudraVigilance databases

7 Manufacturing and import/export

If the UK gains 'third country' status with a hard border between the UK and the EU, rules around free movement of products will cease to apply, which will have a significant impact on the manufacturing and import/export of finished products, active substances and investigational medicinal products in the UK and the EU. According to guidelines issued jointly by the EMA/EC and CMDh, Brexit poses significant repercussions relative to manufacturing facilities, batch release sites and QPs currently located in the UK [42,66].

A research analysis in the union database (EudraGMDP) referenced in Article 111(6) of Directive 2001/83/EC and Article 80(6) of Directive 2001/82/EC, which is maintained and operated by the EMA, notes the quantity of certificates, including certificates for veterinary medicines and investigational medicinal products, that are currently valid in the UK (Publication Date: 10 July 2017) [89].

Table 1: Overview of the amount of licences registered in the UK in EudraGMDP database

Type of license	**Number registered licences in UK**
Manufacturing and import authorisations	594
API registrations	201
Wholesale dealer licences	2154

This analysis clearly reveals the huge amount of licences concerned, which necessitates the discussion of possible models for a future solution.

The next chapters discuss the consequences of viewing the UK as a third country in the environment of manufacturing, importing and distribution. Since Brexit would have several impacts for not only manufacturing companies but also the companies supplying or importing their active substances or finished products from the EU to the UK and vice versa, it is important to discuss possibilities for an agreement to help solve the concerns and need for action regarding this field due to Brexit.

7.1 The future of EU GMP certificates and GMP Inspections

Regarding European Community Directives 2001/83/EC and 2003/94/EC, manufacturers and importers located in the EEA must hold an authorisation issued by the NCA of the member state where they carry out these activities [21]. This has been implemented into national law in the UK, demanding an authorisation issued by the MHRA for manufacturers and importers. With respect to imports from third countries, this manufacturing authorisation is a 'manufacturer's licence' (MIA), which is a requirement under Regulation 17 of the Human Medicines Regulations 2012.

In the EU, manufacturers must additionally comply with EU good manufacturing practices (GMP) in order to obtain a manufacturing or import authorisation. These GMP are defined as *'that part of Quality Management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and*

as required by the Marketing Authorisation, Clinical Trial Authorisation or product specification' [90]. The principles of GMP and the detailed guidelines are applicable to all operations which require the authorisations referenced in Article 40 of Directive 2001/83/EC. The transition of the GMP directives to UK law can be found in Regulations 37- 41 of the Human Medicines Regulations 2012 [91].

The MHRA itself regularly releases the Orange Guide, an essential reference work for all those involved in the manufacture and distribution of medicines in Europe [92]. Both this compilation by the MHRA and the number of GMP inspections the agency conducts evidences the strong role of the UK authority in developing rules and guidance in the field of GMP (see Table 2) [92].

Table 2: MHRA statistics of GMP inspections conduced in 2016 by the MHRA, compared to 2015

	2016	2015
Total number of inspection	324	303
UK inspections	242	224
Overseas inspections	82	79

The UK is not expected to abandon its current GMP standard. Nevertheless, dependent on the outcome and legal construction established after two years, GMP rules and regulations in the UK may start to develop independently from EU GMP. Therefore, although the UK is accepting EU directives through the withdrawal bill, UK and EU must reach GMP agreements to ensure recognition between UK and EU GMP certification in the future. Without such an MRA, frameworks could diverge over time. Manufacturers in the UK would be monitored by EU GMP inspections, and manufacturers in the EU would be monitored by UK GMP inspections. It is not in the will of authorities that GMP inspections would be doubled in the future.

A solution is a mutual recognition agreement between EU 27 and the UK with the reciprocal obligations to apply at least the EU GMP rules and to recognise mutual inspections. The EU already has experience with mutual recognition agreements (MRAs) regarding GMP. Mutual recognition agreements for the recognition of GMP inspections already exist for several other countries, including Australia, New Zealand, Canada, Japan and Switzerland. The aim is to allow EU authorities and their counterparts to rely on each other's GMP inspections, waive batch testing of products on entry into their territories and share information on inspections and quality defects. Japan and Switzerland already share Information on GMP compliance through EudraGMDP. Just this year, regulators in the EU and United States have agreed to recognise inspections of manufacturing sites for human medicines conducted in their respective territories on both sides of the Atlantic. This enters into force on 1 November 2017, but will be in a transitional phase until July 2019 [93]. A mutual recognition program should also include the UK in the 'joint audit programme' for EEA GMP inspectorates. This would maintain the verification of

equivalence and consistency in practically applying GMP standards, and it would also preserve confidence in the equivalence of EEA GMP systems to all member states and all other EU MRA partner countries [94].

If the UK and the EU do not reach an agreement, the UK could follow the WHO-published GMP guidelines for medicinal products and drug substances and the ICH guideline question-and-answer for active pharmaceutical ingredients (APIs). Additionally, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) is relevant to GMP on an international level. The PIC/S is an organisation of various countries which aims to harmonise and enhance GMP standards [95]. As the EU and the UK are members of the PIC/S [96] and the PIC/S GMP guidelines are nearly identical to EU GMPs, strong alignment of rules and regulations could continue after Brexit irrespective of the outcome and legal construction. However, contrary to the EU, international GMP guidelines are only non-binding recommendations.

7.2 Manufacturing site & import of the active substance

A question-and-answer paper from the EMA and CMDh states that as of the date of the withdrawal of the UK from the union*, 'active substances manufactured in the UK will be considered imported active substances'* [42,66]. Imports of active substances from third countries into the EU result in different legal obligations compared to EU active substance producers. Directive 2001/83/EC dictates that '*manufacturing authorisation holders are obliged to use, as starting materials, only active substances that have been manufactured in accordance with the detailed guidelines on GMP for starting materials'* [87]. Chapter 2 has already discussed aspects of the future of GMP, but nevertheless, as of 2 July 2013, Article 46b(2) of Directive 2001/83/EC, establishes strict rules for the import of active ingredients in the EU. Each import from countries outside of the EU must be accompanied by a written confirmation of compliance to GMP by the CA of the exporting country [21]. This written confirmation is always part of the delivery documents [97]. This means that the MHRA will have to provide written confirmation to the EEA competent authorities after Brexit.

The process of a written confirmation is independent of the existence of MRAs, but the commission publishes a list of countries which, following their request, have been assessed and are considered to have equivalent rules for GMP to those in the EU. Active substances manufactured in these countries do not require a written confirmation. At the moment, this list contains Switzerland, Israel, Australia, Brazil, Japan and the United States [98]. This is a possible solution for the UK, but the MHRA must apply for the listing that the commission can conduct the equivalence assessment foreseen in Article 111b(1) of Directive 2011/62/EU [33]. It can be expected that the MHRA would experience no challenges in applying which would lead to reduced work, costs and time.

Article 46b(4) of Directive 2011/62/EU presents a further exemption for a written confirmation for manufacturing sites in non-EU countries that possess a certificate of GMP following a successful full inspection by a European authority [33]. In this case, the exemption only applies for a period not exceeding the validity of the certificate of GMP.

Afterwards, the written confirmation is once again required [33]. Because UK companies have been inspected regarding GMP when the MHRA was a national authority of an EU country, this could be sufficient – especially as it concerns the prevention of supply shortages – until the moment of a re-inspection expiry of GMP certificate. From this moment on, the UK company would again need to be inspected by a European authority, which raises the question of whether this is a plausible a long-term solution in view of lacking human resources of authorities. This matter again highlights the need for an MRA regarding GMP.

Moreover, as a result of the implementation of the directive, some countries request import authorisation for a special type of active substances produced in a third country. An example is the German *'import authorisation pursuant to section 72 of the Medicinal Products Act [German drug law "Arzneimittelgesetz"]',* which is mandatory for not only for importing medicinal products but also '*for active substances, which are of human, animal or microbial origin or are manufactured using genetic engineering, or other substances of human origin intended for the manufacture of medicinal products*'. This import authorisation must be requested from the CA of the importing country, and the holder of the import authorisation is responsible for GMP compliance. Regarding this special type of active substances, the importer requires a certificate in accordance with Section §72a AMG in order to prove GMP-compliant production in the third country. A waiver for the §72a certificate occurs if the country of the manufacturing site is mentioned in the list in 111b(1) of Directive 2001/83/EC [99].

Another aspect to consider is that registration requirements for companies involved in the sourcing and supply of active substances from or to the UK may change. Whether active substances have been procured inside or outside the EEA impacts the licensing process. For example, a distribution licence is sufficient in the UK if the active substance is procured inside the EEA, but after Brexit, an import licence will be required. This must be reported to the CA [100].

Marketing authorisations which contain a certificate (CEP) to prove that the relevant monographs of the European Pharmacopoeia suitably control the quality of the active substance shall continue to be valid since this certificate is issued by the European Directorate for the Quality of Medicines (EDQM). The EDQM is a directorate of the Council of Europe and is distinct from the European Union. The UK is therefore protected through membership in the Convention on the Elaboration of a European Pharmacopoeia [101].

Pharmaceutical companies which source their active substances from the UK or transport them to the UK will not have much time to prepare for the new situation - especially concerning the prevention of supply shortages - since the import rules will be valid as soon as the UK leaves Europe if there is no special agreement. To address this, the followings steps must be taken from manufacturer importers and exporters of active substances in the UK and in the EEA who are importing from or exporting to the UK:

- Determine the appropriate registration required
- Check national provisions regarding special requirements due to import/export of active substance

- ‘From the date of Brexit, apply for written confirmation (if there is no exemption for the UK)

7.3 Manufacturing site and import/export of the finished product

The same conditions apply to finished medicinal products as to active substances. As of the Brexit date, *‘medicinal products manufactured in the UK will be considered imported medicinal products’* [42,66]. Since it is significant if a product will be transferred within or outside the EEA, the effect of this requirement is that such an activity can only be carried out by a person who is authorised to manufacture medicinal products in the scope of import from third countries with a final destination in the EEA, or vice versa in the UK. A distributor in this case will no longer be able to import medicinal products from third countries [100].

Product-specific import authorisations are issued from the competent authorities of the EEA, which ensures that the import of medicinal products into their territory is subject to an authorisation in accordance with Article 40(3) of Directive 2001/83/EC and Article 44(3) of Directive 2001/82/EC. The authorisation is granted upon fulfilment of a number of conditions which are defined in Articles 41 and 42 of Directive 2001/83/EC and Articles 45 and 46 of Directive 2001/82/EC (e.g. availability of a QP within the union, GMP inspection). The same applies for import and export of investigational medicinal products for use in trial sites located in the EU, and vice versa [21]. Again, the same applies for finished products as for active substances with regard to import authorisation, pursuant to Section 72 of the Medicinal Products Act (AMG) [99]. With respect to the marketing authorisation, the MAH will need to specify an authorised importer established in the union (EEA) to fulfil the above criteria and submit the corresponding variation (see Variation Guideline B.II.b.2) [42,66]. The next chapter discusses further requirements regarding batch release of the finished product.

7.4 Batch release / role of QP / re-testing

The EMA and CMDh have clearly communicated the expectation that batch certification will be required within the EU. In accordance with Article 51(1) of Directive 2001/83/EC, the QP of the manufacturing and import authorisation holder *‘is responsible to certify that each batch of medicinal product intended to be placed on the EEA market was manufactured in accordance with EU GMP requirements and the marketing authorisation’*. This suggests that the MAH will need to transfer its current UK-based site of batch release to a location established in the union (EEA) and submit the corresponding variation, considering Variation Guideline B.II.b.2 [42,66].

Thus, in practice, either the QP of the batch release site in the UK must change residence or a new QP in the EEA must be appointed. For the batch release for the UK market, the MHRA/UK legislation requires a QP to live in the UK. Consequently, two QPs for the batch release with seats in the relevant legal areas would be required. Without a bilateral agreement, it may not be possible for UK QPs to work in Europe, and vice-versa.

In Annex 16 of GMP Guidelines Chapter 1.4, a QP can rely on the certification of a batch from another QP if the product is manufactured within the EU. However, regarding products imported from a third country, it is clarified that the QP certifying the import from third county can rely on neither any confirmation of GMP nor regulatory compliance from a QP established in a third country, as this process is not part of Chapter 1.5 concerning batch release of products outside the EU.

Furthermore, Annex 16 of GMP Guidelines Chapter 1.5.4 requires that a QP performs additional re-testing of products manufactured in a third country after import: '*The QP certifying the finished product is responsible for ensuring that each finished medicinal product batch has been manufactured in accordance with GMP and the MA. Unless an MRA or similar agreement is in place between the EU and the exporting country, the QP is also responsible for ensuring that the finished medicinal product batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products is in accordance with the requirements of the MA'* [102]. The second sentence is an exemption from the obligation to carry out an EU re-test for countries for which MRAs are in force.

Without such an MRA between the UK and the EU, the required re-testing will generate significant additional work between the UK and the EU. However, actual MRAs still require the EU GMP to perform a certification of the products after import. Dependent on the outcome and legal construction established after Brexit, possibilities to accept EU and UK QP certification – and thereby avoid unnecessary additional work – may need re-assessment. It will be a challenge to develop models for how imports from the UK to the EU and vice versa may be exempt from re-certification and re-release procedures while maintaining the safety of the products.

8 Further aspects

In addition to regulatory aspects, there are other relevant topics that should be reflected within the discussion of Brexit. These include parallel import and parallel distribution, falsified medicines directive, implications for Intellectual Property rights, regulatory data protection and supplementary protection certificates, the legal status 'Limited' and handling of investment.

8.1 Parallel import / parallel distribution

This chapter focuses on the consequences of Brexit on parallel import, a significant and relevant field for the pharmaceutical market in particular. The following figure offers information about the main parallel-import markets. The total market in 2016 was worth €5.5 billion and the UK is the second-largest net-import country, with a share of 20% by value [103].

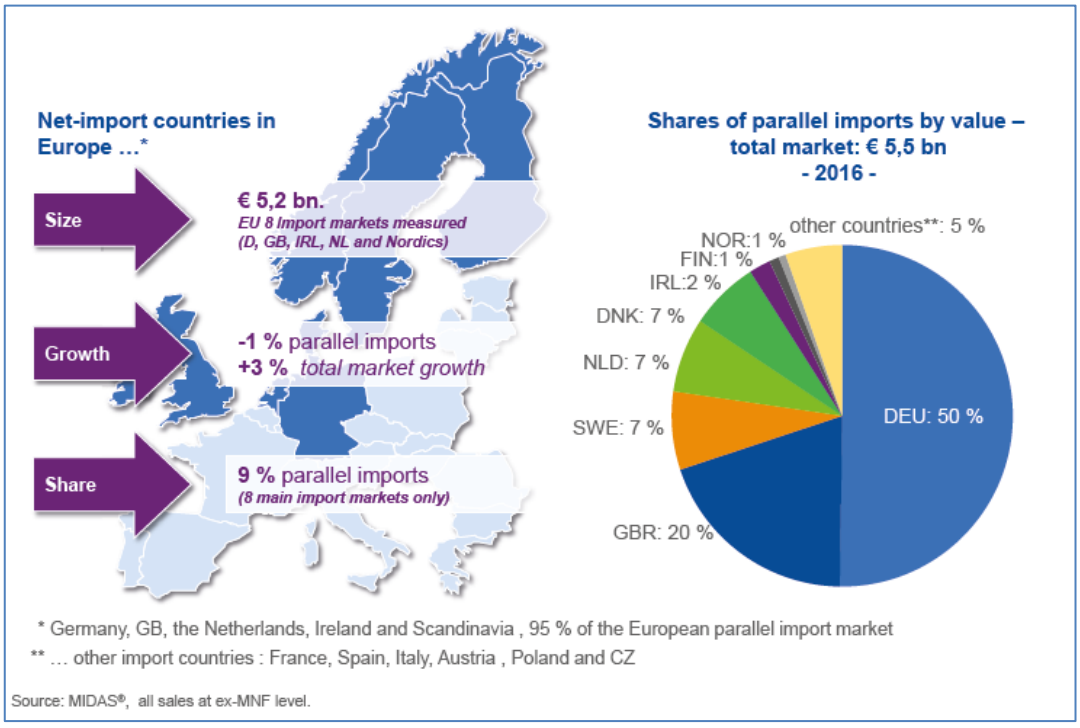

Figure 16: Destination for parallel trade

Independent of any trade issues in the context of Brexit, two perspectives affect this field of business: the regulatory view and the trademark perspective.

Parallel import of pharmaceuticals stems from price differentials between different national markets within the EEA that are due to non-harmonised health systems. Further drivers of parallel trade with pharmaceuticals in Europe are legal framework (e.g. in Germany, parallel import trade is supported by national import quota), exchange rate fluctuations and socio-cultural factors. [103]. Parallel import companies buy products marketed by the original manufacturer at a lower price in one EEA country, then re-package or re-label the products and sell them at a higher price in another EEA country. Repackaging or re-labelling requires pharmaceutical manufacturing authorisation issued by

the CA in the country of destination. Furthermore, re-packaging companies are obliged to follow GMP under the supervision of an EU QP and are subject to periodic inspections by the CA.

Basically, parallel-imported medicinal products are under the protection of applicable laws (trademark protection) since the owners have the right to prevent others from using them and from placing their protected products on the market. Importing such products would consequently infringe on the trademark rights of those products. The principle of free movement of goods within the common European market with regard to Article 28 of the EC TFEU would be hindered, but the legal principle of 'exhaustion' that is provided for in Article 13 (1) of the Council Regulation No 207/2009/EC states the following: '*A Community trademark shall not entitle the proprietor to prohibit its use in relation to goods which have been put on the market in the Community under that trade mark by the proprietor or with his consent'* [104]. In summary, once trademark owners sell a product labelled with a trademark within the EEA or consent to such a sale, the trademark right becomes 'exhausted' and they can no longer enforce it. However, the effect of the exhaustion of trademark rights is limited to goods that were first distributed to the market within the EEA. Therefore, any imports from outside the EEA that lack the consent of the trademark holder of the involved medicines immediately constitute a trademark infringement. In the late 1990s and early 2000s, the ECJ issued a series of decisions in which the court stated that Article 7(1) of the former Trademark Directive 89/104/EEC had to be interpreted as establishing a general principle in the community trademark jurisdiction; an example is the judgement Case C-187/80, Merck vs. Stephar [105].

Given that restriction, it is becoming clear that parallel import is a business model that is strictly limited to trades within the EEA. Only a scenario of the 'Norwegian trade model', meaning a membership in the European Economic Area, would provide the UK with the advantage of full accessibility to the European Single Market and therefore to the parallel imports. However, in the event of a 'hard Brexit' departure from the European single market, the existing rules on exhaustion of trademark rights will cease to apply for parallel imports both into and out of the UK.

However, irrespective of whether the UK leaves the European single market, it must be noted that parallel imports are enshrined in the pharmaceutical legislation. They must be subject to a second regulatory assessment before their parallel distribution. In the EEA, there is no harmonised approach for the assessment of a parallel import product in 'a simplified procedure'. In the judgement 'De Peijper', the court states that *'it is for the member states, within the limits imposed by the Treaty, to decide what degree of protection they intend to assure and in particular how strict the checks to be carried out are to be'* [106]. For example, in Germany, no parallel imported medicinal product may be imported or placed on the German market unless the company has received a corresponding licence by the NCA for human medicinal products. Evaluation criteria are made which could include the stipulation that a parallel product must be interchangeable with the national reference medicinal product. Furthermore, any variation must be reported, e.g. a new import country. On its webpage, BfArM clearly states that parallel import *'is not possible if the medicinal product is authorised and marketed outside the EU or EEA*'.

Therefore, the UK as an import country is out of scope [107]. Whether this affects all existing approvals with the UK as the import country must be clarified and the authorities would have to officially withdraw the country from the licence.

This national authorisation procedure does not apply to medicinal products with central marketing authorisations. In this context, the parallel import of nationally authorised medicinal products should be distinguished from the parallel distribution of centrally authorised medicinal products. The EMA checks parallel-distributed medicinal products based on centrally authorised medicinal products for compliance with the conditions specified in community legislation for medicinal products and in the marketing authorisation of the product. Since the entry into force of Regulation (EC) No 726/2004 on 20 May 2004, Article 57 (o), notifications of parallel distribution of centrally authorised medicinal products have become mandatory throughout the EU [22]. The EMA has therefore developed a particular procedure. An initial notification must be sent to the agency to inform it of the intent to source, re-package and distribute a centrally authorised medicinal product from one or more member states to one or more member states. The agency checks if the particulars of this notification comply with the marketing authorisation and EU legislation on medicinal products and issues and, if so, issues a parallel distribution notice to confirm. If this is not the case, a letter of non-compliance is issued for the product [108]. In consequence, after Brexit, the EMA must therefore state, in a non-compliance letter, the withdrawal of the UK as a member state of destination.

To emphasise the importance of the UK as a member state of destination in parallel distribution, an analysis was conducted of active initial notices in the parallel distribution register of the EMA. This register includes 19,396 active notices (accessed 25 July 2017) [109]. Figure 17 only displays countries with a volume above 1%.

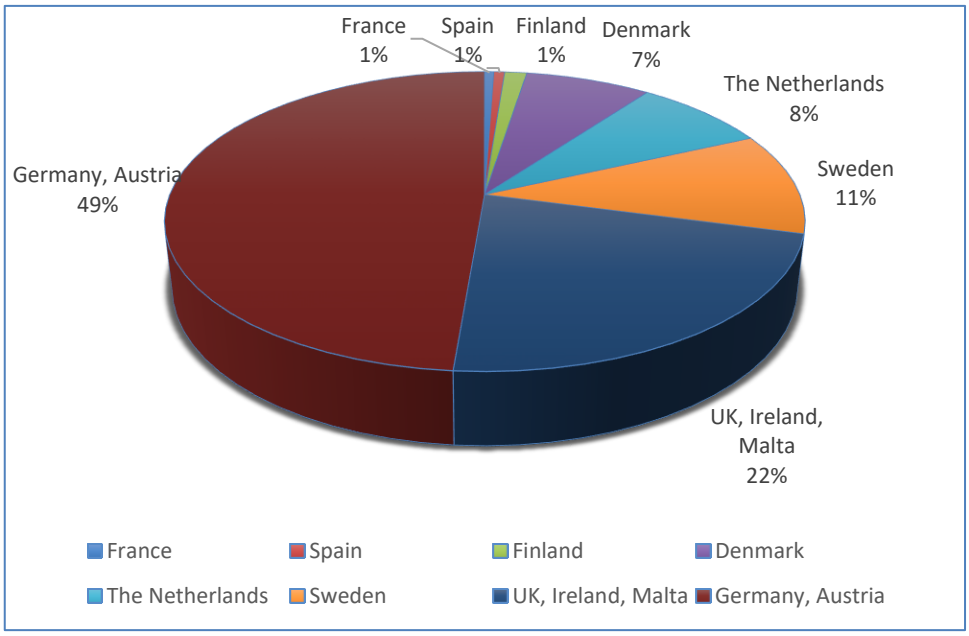

Figure 17: Percentage of active initial notices per country in the parallel distribution register of the EMA

The figure illustrates that Germany in particular is a strong import country, but that UK companies reported 22% of the parallel distribution products in the database. For countries with many parallel import approvals, such as Germany, it is of course particularly difficult to waive the UK as an import country.

Finally, as Chapter 7 has noted, many wholesale distributors in the EU are specialised in trading pharmaceuticals within the EEA and possess a simple wholesale distribution licence and GDP certificate. For export to a country outside the EEA, such a wholesale dealers licence will no longer be sufficient after Brexit; see Chapter 7 for a more detailed explanation. These scenarios highlight how the parallel import business between the UK and the EU will undergo major changes, and Brexit may mark the end of any legal parallel import practices between the EU and the UK.

8.2 Falsified medicines directive

To counter the threat of falsified medicines entering the legal supply chain, the European Parliament and Council have released the Falsified Medicines Directive (FMD) [33]. The EU Commission has published additional technical details for the further design of safety features with the Delegated Regulation (EU) 2016/161 in the Official Journal of the EU. Starting from 9 February 2019, only prescription medicines which bear the new safety features may enter circulation. This aims to improve patient safety by mandating MAHs and manufacturers to install a system that prevents falsified medicines from entering the legal supply chain [110]. To accomplish this, MAHs must connect with the European Medicines Verification System to upload the unique identifiers via the European Hub and with the National Medicines Verification Systems to verify the medicines.

Since the FMD comes into force on 9 February 2019, before the UK leaves the EU, any changes to the UK's Human Medicines Regulations 2012 to implement the FMD would remain in place until the UK government at that time decides to change them. Switzerland is also participating voluntary in the FMD, which implies that being an EEA country is not a strict requirement for participation. Given the global nature of falsified medicines, it is likely that the UK will to adopt pack serialisation to maintain its reputation as a safe part of the medicines supply chain. To sustain additional costs for producing different packs for the UK in the long run, it is also in the interest of the manufacturers to participate in the FMD. A non-profit organisation which will manage the UK Medicines Verification System under the supervision of the UK NCAs has already been founded and is currently constructing the national verification system.

8.3 Implications for Intellectual Property (IP) rights, regulatory data protection (RDP) and supplementary protection certificates (SPC)

Intellectual Property in the pharmaceutical industry is extremely important. IP relates to someone's idea, invention, creation, e.g., that can be protected by law from being copied by someone else. Regarding Article 52 (1) of the European Patent Convention, European patents are one form of IP, as they *'shall be granted for any inventions, in all fields of*

technology, provided that they are new, involve an inventive step and are susceptible of industrial application' [111]. However, in addition to patents, MAHs in Europe can benefit from a range of EU incentives, such as supplementary protection certificates (SPCs) and RDP, which are closely linked to the EU regulatory framework for medicinal products. This applies to cases such as an SPC relating to a medicinal product for children for which data has been submitted according to a Paediatric Investigation Plan with respect to Regulation (EC) No 1901/2006 [30]. Furthermore, the proposed Unified Patent Court (UPC) system and the corresponding unitary patent shall offer companies the opportunities to obtain a single patent valid in 25 participating EU member states and to enforce their patent rights on a pan-European basis [112].

This chapter examines key aspects of EU patents as well as SPCs, data protection and the impact on the proposed unitary patent. In addition, it considers which changes may occur when the UK leaves the EU.

8.3.1 European patents

In principle, there will be no legal implications for European patents. They are assessed and managed uniformly through the European Patent Convention (EPC) and the European Patent Office (EPO), but are validated in each member state and protected under national law in each of the countries designated in the application. The European Patent Convention (EPC) is an international agreement among 38 states and is independent from the EU [113]. In this respect, the UK can remain a contract state of the European Patent Convention (EPC), so European patents can continue to include the UK.

The only task which will need to be amended is a change in the 'United Kingdom Patents Act', which currently references EU Directives 2001/83/EC and 2001/82/EC regarding the rules for the 'Bolar exemption'. These rules allow the use of a patented medicine both for the purpose of obtaining regulatory approval in the UK or elsewhere and to enable a public body to assess if a medicine should be used in healthcare, without infringement [114].

8.3.2 Supplementary protection certificate

Supplementary protection certificates are a form of patent term restoration to compensate for regulatory delays in the approval of medicinal products and are covered in the EU through EU Regulation (EC) No 469/2009. They have a maximum term of five years, and the holder of the patent and related SPCs on a pharmaceutical product can enjoy an overall maximum of a 15-year patent plus SPC protection from the date that the product first obtained marketing authorisation in the EEA [115]. It is extended to 5.5-year patent and 15.5-year patent, if the product is awarded a paediatric extension under Regulation EC No 1901/ 2006 [30].

Whilst SPC applications are examined and granted nationally by the patent offices of individual EU member states, it is anticipated that Brexit will not affect pending and existing SPCs. Due to the EU Withdrawal Bill, SPCs will be converted directly into UK law post-Brexit; however, the UK can decide to put in place an alternative legal basis for an

equivalent UK SPC system. For example, further modifications may be drafted, such as UK SPCs being calculated based on the date of the 1st marketing authorisation in UK, instead of the 1st marketing authorisation in the EEA. It is also possible that the UK may enact SPC rights after its exit that are more favourable to innovator companies, for example to allow UK SPCs with a longer term or which are extending their scope to include other products, such as medical devices.

8.3.3 Regulatory data protection

Regulation (EC) No. 726/2004 [22] and Directive 2001/83/EC [21] provide for data protection for pharmaceuticals, which must be considered separately from a product's patent position. The RDP period in Europe is commonly referred to as '8+2+1', which represents the following:

- Article 10.1 2001/83/EC - a period of eight years of true data exclusivity, beginning with the first marketing approval in the EU, during which the EMA may not progress an abridged marketing application which references an originator's preclinical and clinical trial data, Article 10 (1)
- A further period of two years of market exclusivity, during which a generic product cannot be placed on the market, Article 10 (1]
- A further one-year marketing exclusivity period may be obtained whereby the originator is granted a further marketing authorisation for a significant new indication, within the original 10-year exclusivity period, Article 10 (5] [21]

It is expected that the UK will continue to provide RDP at the existing level after Brexit. Still, as Chapter 8.3.2 has noted, a major consideration will be whether RDP commences from the date of the first marketing authorisation in the EEA or the first marketing authorisation in the UK. There may be the potential to enhance RDP protection in a separate UK system, for example in relation to the criteria for obtaining additional RDP for a new indication or the duration of the protection. How closely these rights will continue in their present form in the UK is likely to depend on whether and to what extent the UK regulatory framework remains connected to or aligned with the EU system.

8.3.4 The unitary patent and UPC

Under the current European patent system, an applicant for patent protection has the option to file applications in individual European countries. However, most applicants choose to file and prosecute a single European patent application through the EPO. Once granted, a single European patent may be entered into multiple contracting states and immediately receive patent protection in each state. However, even a patent obtained through the EPO must be individually enforced in each European country. Although the EPO system greatly streamlines the process for gaining patent protection in Europe, enforcement is still performed within the national court systems of each individual state, often requiring multiple simultaneous or overlapping litigations to effectively pursue infringers [116].

The proposed UPC system and the corresponding unitary patent will offer companies the opportunities to obtain a single patent valid in 25 participating EU member states and to enforce their patent rights on a pan-European basis. The UPC Agreement (OJ EPO 2013, 287) was signed on 19 February 2013 by all EU member states except Croatia, Poland and Spain. Companies will no longer need to validate a patent in each MS. There is much discussion of the advantages and disadvantages of the unitary patent. On the first hand, it is expected to be a simpler, more efficient and cost-effective mechanism for obtaining, exploiting and protecting patent rights across Europe, for example since it only requires one infringement procedure, not many national court proceedings [117]. Nevertheless, disadvantages and weaknesses are discussed, e.g. that at a single patent decision regarding patent infringement is enforceable in all member states [118].

An essential obstacle for participation of the UK in the UPC system after Brexit is CJEU Opinion 1/09, which rejected the initial draft agreement for the creation of a European patent judiciary as being incompatible with union law. Political operators understood Opinion 1/09 as excluding UPC participation for countries that are not EU member states. After the Brexit vote, this opinion was doubted from several views, e.g. the Gordon/Pascoe Opinion. The UK's participation in the Unitary Patent Scheme is therefore still in question [119]. If the UK will no longer be part of the UPC system, then a decrease in attractiveness after Brexit due to the need for a national UK patent cannot be ruled out. Nevertheless, the UK announced on 28 November 2016 that it will ratify the UPC Agreement.

The entire system can only come into force if ratified by the three member states in which the highest number of European patents had effect in 2012, namely France, Germany and the UK. Of those three countries, the system still lacks ratification from the UK and Germany [120]. Under the present UPC agreement, all other member states cannot proceed without the UK and Germany – at least for as long as the UK remains an EU member state. If the UK no longer agrees after Brexit, it would be necessary to create a new agreement which could be adopted without the consent of the UK. This would cause a delay in the implementation of the UPC.

8.4 Legal status: ‘Limited’

Many entrepreneurs in Germany have organised their businesses in the legal form or with the participation of an English ‘private company limited by shares’ (Limited or Ltd.), as this has advantages such as establishment within a few days and no minimum capital despite full limitation of liability [72]. After the Brexit referendum, the question has arisen as to the consequences of the withdrawal of the UK from the EU for this legal form.

Due to the recognised jurisprudence of the ECJ, known as ‘Überseering case’, case C-208/00 of 5 November 2002, the freedom of establishment of an English company such as a Limited company is guaranteed in Europe. A branch of a Limited company with the administrative seat and place of management in another EU country is therefore possible, but must have a registered office in the UK [121]. In the commercial register of

the country, the ‘Limited’ company cannot be registered as such; it is instead registered on ‘the Companies House’ in the UK.

Since the freedom of establishment is only guaranteed in Europe, the lack of an agreement after Brexit will cause such entrepreneurs to lose that freedom. They might no longer be recognised as such in the rest of the EU, with the result being that the limitation of liability could be invalidated. If then only the national company law of the administrative seat is applied after Brexit, all companies which do not comply with the requirements for a capital company will be re-qualified as partnerships. This classification has serious consequences for the liability: shareholders of a Limited company are directly liable without restriction. This results in the exact situation that companies want to avoid by establishing a foreign corporation.

The future of British ‘Limited’ companies outside of the UK depends on whether the EU and the UK agree in the exit negotiations. On the assumption of a ‘hard Brexit’, making a transformation of the company law should be considered; otherwise, the limitation will remain a foreign entity in German law. Companies that still want to wait must stay informed about the individual effects of Brexit at an early stage. Nevertheless, it is important to have a plan for each scenario. In the worst case, this must be implemented quickly, and above all in a timely manner. The other possibility is to switch to the national legal forms already available in Germany, e.g. to a GmbH, an AG or - if the minimum capital worries the entrepreneur - a UG (limited liability). The German ‘Industrie und Handelskammer’ already published a guideline providing service to affected companies [122]. As the prospects for the UK are far from foreseeable, the change to a new company form to form recognised in the respective country would represent the safest approach.

8.5 Handling of investment, especially from funding

The Journal of Oncological Sciences describes in its perspective article about ‘Cancer funding and Brexit’ success in research as *‘a product of the effective funding schemes set up by the Union*”, and as well “*as the opportunity presented to many scientists to collaborate with others in their field across the continent*’ [123].

According to calculations by the Royal Society, between 2007 and 2013, the UK received €8.8 billion in R&D funding from the EU. It also participates in the Horizon 2020 programme, which distributes billions of Euros in scientific research grants across the single market [124]. Access to collaborative programmes is also possible from outside the EU. The conditions of participation in Horizon 2020 are specified in the participation rules in Regulation (EU) No 1290/2013 and defines participant criteria and minimum conditions [125], e.g. Switzerland collaborates as an external participant [126]. According to this model, the UK could become an associated country or a third country to Horizon 2020 in order to maintain eligibility for funding. However, broad compliance with EU principles is necessary to gain access to funding and collaboration, meeting the minimum conditions of Regulation No 1290/2013 [125]. Although the Switzerland is external participant at present, Switzerland is one example which demonstrates that a loss of access to the

Horizon programme is possible. In 2014, a Swiss referendum resulted in a vote to limit mass immigration. Since this result infringed on a free movement accord with new EU member state Croatia, Switzerland immediately lost access to the Horizon 2020 programme, forcing a desperate Swiss emergency measure to temporarily regain access [127]. Even so, the loss of confidence in Swiss participation has seriously hampered the country's contribution to joint research projects; according to a statistic of 2015, the country has participated in just 328 projects since the outset of Horizon 2020, compared to the UK's 2,431 projects [128].

In summary, it is difficult to calculate the impact of Brexit on Horizon 2020 funding. There are diverging views in the literature regarding the impact since so many factors are involved. One assurance is that larger UK pharmaceutical companies would be less impacted if the UK was separated from Horizon 2020. Their presence in other EU countries will still make them eligible for EU research funding in the future. However, smaller companies might not have this opportunity and may need to seek other funding sources if the UK is no longer part of EU research funding.

The general uncertainty associated with Brexit is expected to also have a negative impact on external funding for pharmaceutical R&D from banks and bond markets. An analysis by a consultant company has revealed that in the first quarter of 2016, UK-based companies received 37% of the $3.5 billion in venture capital invested across Europe, and that a losing access to venture capital must be seen as critical with respect to new inventions, and especially regarding small companies and start-ups [129]. If the flow of venture capital into the UK decreases, other European countries will try to attract funding that was previously destined for the UK.

9 European Medicines Agency, consequences of relocation and future role of the MHRA

Currently based in London, the EMA and its approximately 900-member staff will have to relocate to another EU member state post-Brexit. The EMA is a decentralised EU agency. Its core responsibility is the protection and promotion of public health through four missions: facilitating development and access to medicines, evaluating applications for marketing authorisation, monitoring safety of medicines across their lifecycle and providing information to healthcare professionals and patients [130]. This task is fulfilled by a regulatory network of around 3,700 European experts who primarily originate from the NCAs of the member states [131]. They are part of the assessment teams, working parties and consultant groups of the EMA or engage with one of the seven scientific committees [130]. In 2016, the EMA recommended 81 medicines for approval, including 27 new active substances [132].

The location of the agency after Brexit was unknown at the time of finishing this master thesis, but criteria were already maintained [131] and 19 applications were submitted [133]. The European Council will determine the agency's new location by common agreement in the margins of the General Affairs Council meeting on 14 and 15 November 2017. The procedure for relocating EU agencies that are currently located in the UK was published by the European Council on 22 June 2017 in a document that sets out the criteria and process for deciding the new EMA location [131]. The following picture illustrates the main procedure for the determination [135].

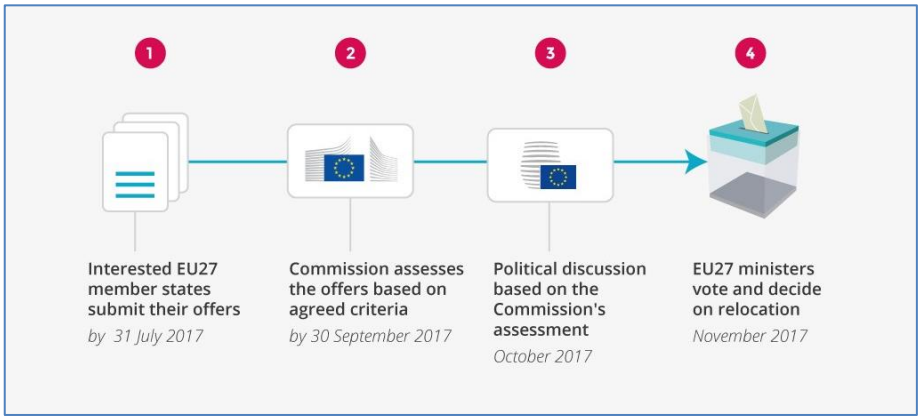

Figure 18: Four-step procedure to decide on the new location of the EMA

In the selection process, experts from the EU Commission will initially evaluate all the applicant sites according to six criteria. These criteria are based on the joint declaration of the EP of the council of 19 June 2012 but take into account that the matter of concern is a transfer of an existing agency as well as that maintenance of their operations is of the utmost importance [131]. The following unweighted criteria are mentioned:

1. *'The assurance that the agency can be set up on site and take up its functions at the date of the United Kingdom's withdrawal from the Union*
2. *The accessibility of the location*

3. *The existence of adequate education facilities for the children of agency staff*
4. *Appropriate access to the labour market, social security and medical care for both children and spouses*
5. *Business continuity*
6. *Geographical spread'* [132]

Further objective criteria are focusing on the tasks of the EMA and the regulatory environment result from Annex I of the procedure, e.g. the co-ordination of seven scientific committees supported by 34 working parties and advisory groups that meet regularly. The agency will be consulted regarding their specific requirements during the negotiation phase [131], so those criteria will also factor into the relocation decision process.

Apart from those objective criteria, the joint statement also refers to the objective to prioritise acceding states in the distribution of the seats of future agencies [131]. Although this procedure concerns relocation rather than the establishment of new agencies, the spirit of that leader's agreement is considered as well.

If further criteria will play a role which were e.g. published by a joint letter of pharmaceutical industries associations, such as the importance of the biopharmaceutical sector and in particular the number of pharmaceutical companies present in the country in question, the size of the medical research community, providing local availability of experts in different scientific fields and the involvement of national regulatory agencies [135], is not predictable. However, the high number of 19 applicants indicates that there is immense political interest in the location of this authority. Although the union's institutions are strictly neutral and their work is closely managed by the EU organs and governments of the member states, they hope to benefit from the short connection to the agency for the domestic pharmaceutical sector as well as for a higher influence of their national public health authorities. The first institutional shift is a primary indicator of future positioning in the negotiation procedure in upcoming distribution and ranking tasks according to Brexit [136]. Hopefully, from a regulatory perspective, the process also includes criteria of 'regulatory intelligence'.

The move from the UK to a country within the EU raises many questions, however, so the agency is preparing for the burdens associated with the relocation of the site. The following consequences are anticipated:

- Delays in the timetables of EMA procedures
- Delays in the EMA roadmap for outstanding projects (e.g. clinical trial database)
- Loss of staff and of experienced and qualified experts
- Decrease of influence for domestic companies in the area of London (proximity to the EMA location)

Therefore, the EMA has already presented a business continuity plan which prioritises its tasks and classifies them into three priority levels. The most important area of concern is activities that are directly related to the assessment and safety monitoring of medicines or vital to maintaining the infrastructure of the European medicines regulatory networks, and therefore to the safety of patients, which must still be ensured even under the more severe conditions that Brexit can pose [53].

In order to ensure continuity in core areas, the EMA is temporarily suspending its activities relating to the following:

- *Development of the European Medicines Web Portal, a publicly accessible Internet platform to contain information on all medicines marketed in the EU;*
- *Collaboration in the eSubmission project, which aims for the secure and effective electronic exchange of documents between authorities and applicants for human and veterinary medicinal products;*
- *Development of a 'transparency roadmap' of the EMA;*
- *Participation in the Heads of Medicines Agencies benchmarking activities (from 2018).*

In addition, the EMA has already reduced the number of audits, restricted the participation of EMA employees in external meetings and conferences and reduced the number of meetings and workshops. Forty-three EMA employees who previously worked for the lowest-priority activities are now focusing on preparations for the UK's withdrawal [53].

There will be secondary effects regarding Brexit on the MHRA. The MHRA will certainly need to take over certain duties currently handled by the EMA and other member state health agencies. The MHRA will also need to make changes in both high-level processes and duties and day-to-day operations. Unless MHRA and NCAs or EMA negotiate some level of continuity and use of directives, regulations, guidelines, databases, marketing authorisation approvals and so on, much of this will have to return to the MHRA. The MHRA mentioned the following top-three priorities in its business plan for 2017 and 2018 [137]:

1. To develop consensus around a proposed model for future regulation of medicines and medical devices in the UK, post Brexit which protects public health, facilitates innovation, and minimises burden on industry in order to influence and support HMG negotiations and make the UK an attractive global regulator.

2. To develop an international strategy and enhanced national strategy for collaboration and engagement with key partners and stakeholders to facilitate better regulation, innovation, and delivery of our strategic priorities.

3. To develop the next five-year corporate plan for the Agency which builds on our unique capabilities and drives a competitive global edge that works for industry and the Agency, so we can flourish as an influential and respected regulator within the UK and internationally.

To prepare for the move, it is important to retain as many staff as possible and to carry out strict impact assessment to clarify the relocation process for the EMA and work. However, whilst the fear remains that the negotiations will lie in the hands of politicians, the hope is that they will appoint negotiators from within the EMA who understand the heavy issues associated with the relocation.

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10 Possible model for future regulatory relationship

In addition to the results that this thesis has detected and discussed, certain points were identified with room for improvement. In order to propose possible solutions – at least regarding a transitional phase – this chapter presents a past regulatory collaboration model and its potential as template for future co-operation of regulatory bodies with the MHRA. In a further step, it examines the model regarding practical aspects and possibilities for use in similar or 'reversed' ways. This informs a proposal for a guideline described as the 'BREXIT procedure' for the recognition process of marketing authorisations. This proposal is presented as a basis for further consideration by experts in regulatory authorities.

10.1 CADREAC – A reversal?

In the context of the EU enlargement, nearly all old dossiers of the candidate countries had to be upgraded to meet current EU standards and requirements, and commission decisions on certain medicinal products had to be 'phased-in' to apply commission decisions on mutually recognised, referrals and centrally authorised products to the corresponding products in the concerned countries.

The Collaboration Agreement between Drug Regulatory Authorities in EU Associated Countries (CADREAC) was a key player in facilitating the EU enlargement with regard to medicinal products and regulatory affairs activities. All CADREAC procedures were perceived as successful, widely used and well accepted [138]. The mission of CADREAC, which started in 1997 with 12 countries, was the facilitation of a smooth transition of regulatory conditions in EU-associated countries in order to achieve regulatory standards required by the 'Acquis Communautaire' [139].

The main goals were described as the following:

- *'To facilitate the implementation of the European standards and requirements;*
- *To create an appropriate atmosphere which could facilitate EU in the process of the accession of the Central and East European (EE) countries;*
- *To facilitate the process of implementing new procedures that are mutual recognition;*
- *To create a forum for discussing the strategy of joining the European Union (by avoiding the duplication of the activities);*
- *To prepare meetings of the regulatory bodies participating in the agreement among themselves and with the European Union;*
- *To participate in the European network for regulatory medicinal information.'* [140]

An active co-operation started between the EMA and the Central and EE countries via CADREAC and took place on three levels:

- *'The implementation of a commonly accepted simplified procedure of the medicines registered in the EU under the CP;*

- *Exchange of information on the safety of these medicines;*
- *Participation of CADREAC observers in the working groups of the Committee for Proprietary Medicinal products and EMA.'* [140]

To prepare the adhesion of countries, the CADREAC countries developed certain guidelines and procedures in preparation for their EU accession. Several procedures and agreed upon documents had been published; the most important ones describing the regulatory process are the following:

- Common procedure on the granting of MAs by CADREAC Drug Regulatory Authorities for MPs authorised in the EU by CP and the post-authorisation activities – variations, renewals and handling of pharmacovigilance information
- Common CADREAC Procedure for retrospective inclusion of centrally authorised MPs for human use in the Common CADREAC Simplified System
- Common procedure on the granting of MAs by CADREAC Drug Regulatory Authorities for MPs authorised in the EU by MRP, including the retrospective inclusion of MPs for human use

The outcome of their discussions had a considerable influence on the fate of marketing authorisations in concerned countries. In particular, the CADREAC simplified procedures were used to achieve harmonisation with corresponding EU products as early as the pre-accession phase [141].

With a view to the objectives of this procedure, similar goals for the future use of UK approvals can be derived from the CADREAC procedure. The following table presents CADREAC goals and proposes the main goals of a BREXIT procedure.

Table 3: A comparison of the CADREAC procedure goals and goals derived from the CADREAC procedure for a proposed BREXIT procedure.

No.	CADREAC Goals	Brexit Goals
1	Implementation of regulatory standards	Maintenance of the European regulatory standards in the UK
2	Implementing new procedures of mutual recognition	Implementing a standardised process for the mutual recognition of CP and for DCP/MRP
3	Forum for discussing the strategy of joining the EU	Forum for discussing the strategy of the withdrawal
4	Preparation of meetings	Preparation of meetings with the MHRA with NCAs and the EMA
5	Participation of CADREAC observers in the working groups of the Committee for Proprietary Medicinal products and the EMA.	Participation of the MHRA in the working groups of the CHMP and the EMA

To prepare for the withdrawal of the UK, the proposal is to develop BREXIT guidelines based on the CADREAC guidelines to describe a frame for an authorisation procedure,

which the MHRA can then use for granting a marketing authorisation of a medicinal product which has been authorised. Although it is not considered mandatory for the applicant either, it would help to reduce duplication of work. In general, the idea is based on the following simple information principle illustrated in Figure 19.

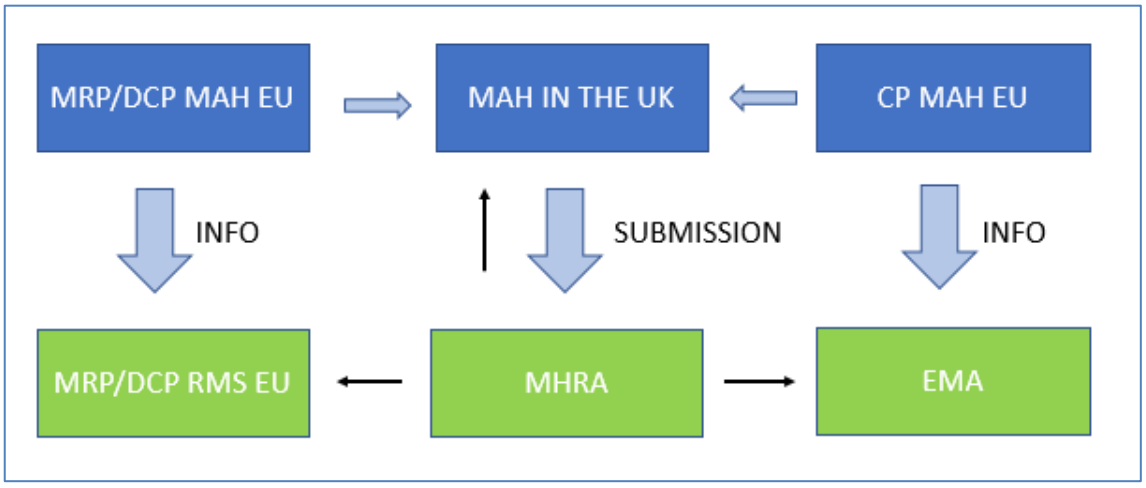

Figure 19: Recognition procedure after the withdrawal and flow of information

Tables 4 and 5 depict two guideline frame proposals regarding the following:

- Recognition of authorisations approved via CPs by the UK (MHRA) and recognition of post-authorisation activities plus handling of pharmacovigilance information
- Recognition of authorisations approved via MRP and DCP procedures by the UK (MHRA) and recognition of post-authorisation activities plus handling of pharmacovigilance information

Table 4: Proposal for a guideline frame for the recognition of central marketing authorisations by the UK (MHRA) & recognition of post-authorisation activities based on the CADREAC procedure

Guideline 1: Recognition of central marketing authorisations by the UK (MHRA) & recognition of post-authorisation activities
Purpose: Guideline which describes an authorisation procedure which can be used by the MHRA for granting a marketing authorisation of a medicinal product which has been authorised in the EU following the centralised procedure, including the subsequent variations and renewals of such marketing authorisations.
Conditions: Recognition of EC decision and of CHMP opinions by the MHRA, acceptance of the EU Summary of Product Characteristics (SmPC), patient information leaflet (PIL) and labelling, recognition of 'good practices' (e.g. GMP, GCP, GLP)
Requirements: Involvement of the MHRA in the procedure (mechanisms for appropriate exchange of information between EU authorities and the UK), the MHRA will inform the EMA of all relevant post-marketing experience and all regulatory actions taken with respect to each product authorised according to the described procedure, and vice versa. Access to the required databases. Publication of the MHRA outcome/recognition with the UK approval date on an MHRA approval register. The

MHRA will keep the products authorised following this procedure harmonised as much as possible with the products authorised in EU. The difference between these products and products centrally authorised in the EU, if any, should be in pre-defined parameters.

Benefits: Harmonisation of SmPC, PIL, labelling and documentation, avoidance of duplication of work, medicinal products could be made available to patients in the UK area without unnecessary delay, less resource intensive, provision of enhanced regulatory process.

Initiation of the procedure: By EU MAH (optional procedure)

Submission: The EU MAH informs the EMA that an application will be submitted in the UK, and should agree that the EMA may make available to the MHRA concerned any information on the quality, safety and efficacy of the concerned product. The applicant (UK MAH) submits the application to the MHRA, and the UK MAH certifies that the application is identical to the application accepted in the EU.

Time of submission: The procedure can be finished only after the applicant submits the final commission decision. The required timing of submission and the period of time expected by the MHRA concerned for the issue of a decision is no longer than the period of time from the CHMP opinion to the commission decision (67 days).

Documents to be submitted by the applicant: A duplicate of the EMA dossier with a written confirmation that documents comply with the dossier submitted to the EMA

Variations

Procedure: A similar procedure as for marketing authorisation will be used for processing such applications.

Timing: An application is submitted within two months of the acceptance of a change in the EU, i.e. type IA, type IB variation, type II variation or notification of the minor changes in labelling or PIL not connected with the SmPC (Article 61.3 Notification) was approved.

Handling of Pharmacovigilance information:

Requirements: The PRAC notifies the MHRA of urgent pharmacovigilance or other safety information and referral procedures (withdrawal, suspension, amendment of product information). In the case that an urgent action is necessary because of a safety issue (Article 107i procedure), the PRAC will immediately inform the MHRA of the outcome of the procedure. Once a commission decision is available, the UK MAH will notify the MHRA concerned without delay about the changes accompanying these safety actions. Vice versa, in the case of urgent pharmacovigilance or other safety information occurring on the territory of the UK having an impact on the benefit/risk ratio of the medicinal product, the MHRA will immediately inform the PRAC. Participation in rapid alert procedure.

Renewals: Same procedure as for the approval process.

Table 5: Proposal for a guideline frame for the recognition of DCR and MRP marketing authorisations by the UK (MHRA) and recognition of post-authorisation activities based on the CA-DREAC procedure

Guideline 2: Recognition of DCP & MRP marketing authorisations by the UK (MHRA) & recognition of post-authorisation activities

Purpose: Guideline which describes an authorisation procedure which the MHRA can use for granting a marketing authorisation of a medicinal product which has been authorised following DCP and MRP procedure, including the recognition of post-authorisation activities.

Conditions: Recognition of the RMS opinion (after RMS closes the procedure) by the MHRA and recognition of CMDh opinions and the CHMP with referral opinions, acceptance of the harmonised SmPC, PIL and labelling, recognition of 'good practices' (e.g. GMP, GCP, GLP)

Requirements: Involvement of the MHRA in the procedure (mechanisms for appropriate exchange of information between the RMS and the UK), the MHRA will inform the RMS of all relevant post-marketing experience and all regulatory actions taken with respect to each product authorised according to the described procedure, and vice versa. Access to the required databases. Publication of the MHRA outcome/recognition with the UK approval date on an MHRA approval register. The MHRA will keep the products authorised following this procedure harmonised as much as possible with the products authorised in the EU. The difference between these products and products authorised in the EU, if any, should be in pre-defined parameters

Benefits: Harmonisation of SmPC, PIL, labelling and documentation, avoidance of duplication of work, medicinal products could be made available to patients in UK area without unnecessary delay, less resource intensive, provision of enhanced regulatory process.

Initiation of the procedure: By EU MAH (optional procedure)

Submission: Applicant informs the RMS that an application will be submitted in the UK and should agree that the RMS may make available to the MHRA concerned any information on the quality, safety and efficacy of the concerned product (assessment report). The applicant (UK MAH) submits the application with high quality national translations of SmPC, PIL and labelling to the MHRA. Furthermore, the UK MAH certifies that the application is identical to the application accepted by the RMS.

Time of submission: The procedure can be finished only after the RMS closes the procedure and after approval in one of the RMS or CMS. The required timing of the submission and the period of time expected by the MHRA concerned for the issue of a decision is no longer than the period of time for granting of national marketing authorisations in the CMS (30 days).

Documents to be submitted by the applicant: A duplicate of the dossier with a written confirmation that documents comply with the dossier submitted to the RMS.

Variations

Procedure: A similar procedure as for marketing authorisation will be used for processing such applications (submitting and implementing identical variations). A letter of acceptance of the variation in question, sent by the RMS to the MAH and to the MHRA.

Timing: An application is submitted to the MHRA within two months of the acceptance of a change in the EU, i.e. type IA, type IB variation, type II variation or notification of the minor changes in labelling or PIL not connected with the SmPC (Article 61.3 Notification) was approved.

Handling of Pharmacovigilance information:

Requirements: The RMS notifies the MHRA of urgent pharmacovigilance or other safety information and referral procedures (withdrawal, suspension, amendment of product information). In the case that an urgent action is necessary because of a safety issue (Article 107i procedure), the RMS will inform the MHRA without delay of the outcome of the procedure. Once a commission decision regarding referral outcome is available, the UK MAH will promptly notify the MHRA concerned about the changes accompanied with these safety actions. Vice versa, in the case of urgent pharmacovigilance or other safety information occurring on the territory of the UK and having an impact on the benefit/risk ratio of the medicinal product, the MHRA will immediately inform the RMS. Participation in rapid alert procedure.

Renewals: Same procedure as for the approval process

10.2 Pan European Regulatory Forum on Pharmaceuticals initiative and IPA assistance program

In the past, various assistance programmes in the context of EU enlargement were established to provide practical advice for implementing European pharmaceutical legislation and their interpretation in the concerned states. For example, the first working group, the ‘Pan European Regulatory Forum on Pharmaceuticals’, agreed on the principle that *‘there are no minimum requirements for the Acquis below the standard set out in the hard law’* [143].

The later-established assistance program IPA was set out for preparatory measures for the participation of candidate countries, e.g. Croatia, which were already part of the EU, as well as for the potential candidate countries, namely Albania, Bosnia and Herzegovina, Montenegro, Serbia and Kosovo. The aim of this program was to build contacts and relationships between the EMA (former EMEA) and potential candidate countries mentioned above for future collaboration in the authority’s activities and its relationships with member states.

This project has the following purposes:

• *to prepare the NCAs in the candidate and potential candidate countries who are active in the field of medicinal products relating to the work of the EMEA for their future participation in EMEA networks*

• *to contribute to the creation of communication and information exchange systems to enable the future participation of candidate and potential candidate countries in EMEA networks* [141]

The program supported the organisation of conferences to prepare the countries for integration into the European regulatory network for medicines. These activities helped to identify areas that might need additional action to ensure the smooth transposition of the EU ‘aquis communautaire’ into the national legislation of these future EU member states.

In the context of Brexit, those assistance programs are a good basis to cultivate a similar working group for regular knowledge sharing to maintain synergies with the participation of scientific experts of the MHRA. Furthermore, the implementation of a process for the recognition of MA, referrals and variations after Brexit should be tasked by such a working group. Instead of phasing in the products, the BREXIT working group should set up and advise a recognition process and its rules to provide guidance for all stakeholders. The MHRA could only be an observer in scientific committees such as the CHMP and PRAC; an active membership is excluded because the right to vote does not even have EEA states.

11 Limitations

Taking into account the complexity of the topic, where not only regulatory aspects play a role but also the political and the economic ones, the present master thesis was focused on how from a regulatory affairs point of view, a good approach should be established in order to ensure the access of medicinal products to the patient.

Nevertheless, the research was conducted in a time of uncertainty factors. Statements from politicians and experts were considered with caution as they are often only a representation of interests. The present analysis therefore has its limitations due to the lack of literature and lack of scientifically meaningful data. In addition, it is unavoidable that in the discussion, certain degree of subjectivity can be found. In fact, it would have been more objective if the proposals would be accompanied by a survey result. However, it is adequate to provide the information which is needed to conduct gap analysis and decision analysis for the individual case scenario.

It was impossible to demonstrate a possible delay in drug approvals through figures and to refer to already existing models for similar approaches, since there are none. This was the challenge of this thesis, trying to discuss a proposal and make an approach to a situation without precedent in the history of the Union.

A comprehensive survey would have enabled more in-depth comparisons between the different requirements of all stakeholders and such a survey could reflect if the Brexit implications are already detectable. Current statistics of e.g. timelines for marketing approvals at EMA could for example illustrate how the Brexit discussion and the fact of relocation influences timelines and quality of assessments already now.

Therefore, this master-thesis only presents hypotheses on the effect of Brexit. Legal uncertainty limits the generalizability and interpretability of findings but future research would benefit from a further developed process. A follow up study could be an approach to a further analysis for the findings of this thesis. Further research could therefore improve on this thesis by utilising comprehensive survey so that the opinions of different kind of stakeholders could be evaluated more efficiently. Also, a survey would permit the use of more sophisticated data analysis and the analysis of within hypotheses regarding the effect of Brexit on subjective basis.

Furthermore, although this analysis demonstrated a good structure and can help to find a decision for a special topic, the findings cannot be generalised to all companies because of their different orientations. To be able to decide on the strategy, the company's position must be clearly defined. For a future survey, the companies structure should be requested to cluster the different strategies.

12 Conclusion and outlook

There has been an active debate in the media regarding the political and economic impacts of the UK's withdrawal from the EU and their related consequences. A series of reports has also discussed the position of the pharmaceutical industry. Although some academic papers and events have considered the pros and cons of Brexit for particular parts of the pharmaceutical industry, no report has focused mainly on the regulatory aspects rather than on trade issues. This thesis therefore consciously avoids connections to future trade models and concentrates on the regulatory facts in the worst-case scenario of a 'hard Brexit'. The mission is always to remain as objective as possible and to consider the perspectives of the authorities and the industry. Since the basis of scientifically established literature is weak, the challenge is to avoid speculation in a field of huge political interest.

The intention of this thesis has been to analyse the different areas in the lifecycle of a human medicinal product in the context of Brexit. It has offered an up-to-date overview of the current status by addressing the relevant issues concerning human regulatory aspects. As a result, the analysis of the various fields demonstrates a lack of regulatory guidance. Brexit guidance currently available from the EMA and CMDh needs urgent expansion for greater clarity. So far, these only provide guidance on the 'musts' and give no recommendations for the 'uncertain' space or the future role of the UK in the approval process. Regulatory initiatives in the EU are urgently needed to overcome the issue of a lack of adequate information to guide Brexit.

One important development that is achieved in this master thesis is the identification of approaches and presentation of proposals for a future system in the regulatory environment after Brexit. The approach creating a guideline close the CADREAC procedure reflects the experiences that have been made in this voluntary procedure with respect to EU enlargement. It is a suggestion, and should be seen as a basis and incentive for further discussion. In this context, and due to the urgency of further regulatory guidance, pragmatism is generally in order. A European approach for a guideline should hence minimise the complexity of the process. A solution presented for many further aspects of regulation might be a series of MRAs in relation to human medicinal products. Similarly, authorities can refer to existing mechanisms in place for non-EU countries, including MRAs involving the United States, Canada, Australia, Switzerland and Japan. Guidelines and agreements must now also be negotiated in order to create legal certainty for pharmaceutical enterprises. In summary, further efforts should be taken to maintain the harmonisation status of authorisations in the UK and Europe. In view of the legal uncertainty, both the regulatory community and the industry have deemed a prospective regulatory harmonisation and convergence to be paramount. A timely availability of safe and effective procedures can only be achieved through the co-ordination of regulatory co-operation between authorities and the industry and by promoting the development of common regulatory recognition approaches capable of confronting the legally uncertain environment.

With a view to the tasks of MAHs, the outcome is that they will need to carefully consider how to manage their products. Particular emphasis must be placed on changes regarding the marketing authorisation in order to ensure its continuous validity and exploitation once the UK has left the union. Failure to do so will result in an interruption to supply and a potentially lengthy delay in getting products back into the market. This is of special importance for MAHs, as there may be substantial decisions to make in terms of transferring contract services to other EU counties while finding a solution for maintaining the licence in the UK. It is important to screen dossiers and to conduct a gap and a decision analysis to take necessary steps as soon as possible. Companies with headquarters in the UK will be affected by Brexit as well as companies with a current location outside the UK. The interests can differ for each company and will always require a case-by-case assessment. It should be acknowledged that all decisions regarding Brexit shall be accompanied by internal – and if necessary, external – experts, as it requires specific and strong regulatory knowledge. Nevertheless, the number of experts is assumed to be limited because of the urgent need of guidance, which necessitates independent expert panels that both industry and authority systems may approach to set up a system of regulatory ‘Brexit’ intelligence.

The primary goals in the uncertain environment of Brexit are to avoid a delay in approvals and to minimise bureaucratic hurdles for future processes as much as possible. The processes of the European authorities should not be hindered, with the aim of ensuring rapid access to new medicines. A strict business plan is the only feasible option to avoid delays in drug approval. Statistics reflecting the UK’s position in the pharmaceutical regulatory environment have confirmed and raised awareness of the strong role of the MHRA in all of the described fields of the regulatory system. In conclusion, the present thesis can support a regulatory affairs manager in answering upcoming questions, and it furthermore offers advice for developing a Brexit strategy that takes into account companies’ interests. This can enable regulatory affairs departments in Europe to provide adequate evaluations that are necessary for the strategic decisions of a company.

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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