MASTER THESIS

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“The legal, logistical and financial Implications of the BREXIT concerning Marketing Authorizations of Medicinal Products”

verfasst von / submitted by

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1 Introduction

The European Union, an economic and political community of states, has continuously grown by admission of new member states. Numerous countries have made efforts to join the EU in order to liberalize trade with neighboring countries. For the first time in its history one member state, the United Kingdom, has decided to leave the community. On 25 March 1957 the Treaty on the Functioning of the European Union (TFEU; also referred to as the Treaty of Rome) was signed by Belgium, France, Italy, Luxembourg, the Netherlands and West Germany and intiated the creation of the European Economic Community (EEC). (European Union, 2019) This treaty was valid on January 1 1958. (European Union, 2019) The main goal was to establish a customs union and in addition to create a single market for goods, labor, services, and capital across the EEC's member states. Only in the 1960s did the UK plan to join the community. President of France, Charles de Gaulle, rejected the first applications in 1963 and 1967. In 1969, UK made a third application that was finally successful. The United Kingdom's membership of the EEC came into effect on 1 January 1973. Since 1975 EU skepticism in the UK was always an issue. The first referendum covering the topic whether the UK should remain within the EU was held in 1975. 67.2% of the voters were in favor of staying in. A graphic concerning the opinions within the UK population regarding staying within the EU is presented below (Mortimore, 2016). There were clearly waves of in favor of staying and in favor of leaving. Under Cameron’s premiership, the polls have swung first against EU membership then more recently in its favor. In 2015 and first half of 2016 all of the MORI polls showed a majority wanting to stay in the EU. Then, a MORI poll in the beginning of June had “leave” back in the lead. “But as the history of British attitudes to Europe tells us, such swings are by no means unprecedented, and there is no guarantee the lines may not cross back again.” (Mortimore, 2016)

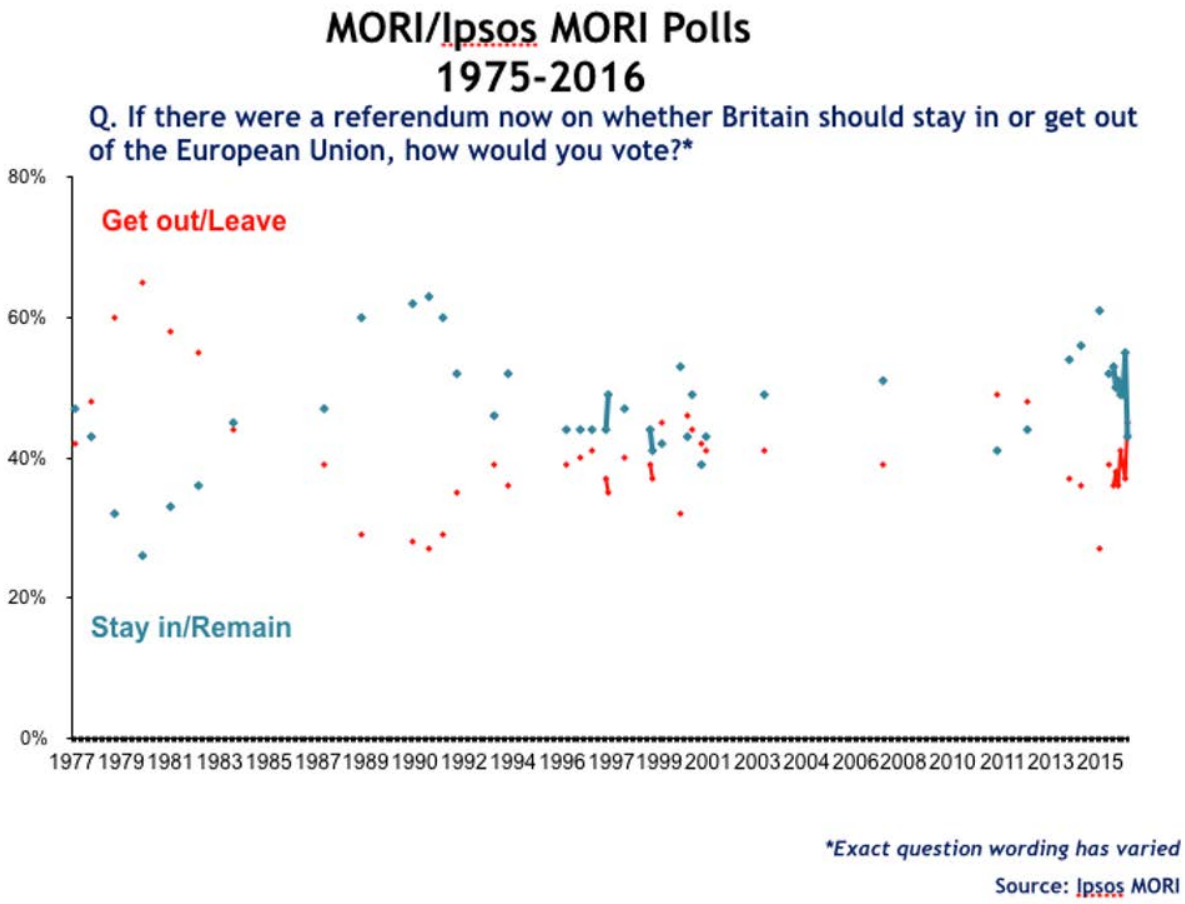


Figure 1: Changing views on the prospect of a Brexit. Ipsos Mori (Mortimore, 2016)

The result of the nationwide referendum in the UK on 23rd June 2016 is that the UK will exit the EU on 29. March 2019. (EMA, 2018c) This so-called “BREXIT” means that the EU legislation will no longer be valid in the UK. (EMA, 2018c) Probably neither supporters of the EU nor the skeptics would have considered the complexity of such an exit from the EU would bring.

1.1 Problem formulation

At this stage, the UK and the EU are only negotiating the big outlines of their future cooperation and still there seems to be no common path. One can only assume when detailed adjustments of current common legislation will be on the negotiation agenda. Nevertheless, there are economically significant consequences related to these details. Pharmaceutical companies currently operating in both territories will need to prepare the necessary actions to maintain their marketing authorizations and sustain their batch

release and pharmacovigilance responsibilities. (Pisani, Kirby and Qin, 2018) Therefore, it is necessary to consider all possible scenarios and to weigh their probability. It is also necessary to budget essential adaptions related to the different scenarios. Currently, status 01. January 2019, the EU and the MHRA, the national competent authority for medicinal products in the UK, did not agree on their exact post BREXIT relationship. Additionally the MHRA has not ratified any post BREXIT regulations concerning UK legislation.

This master thesis will cover the necessary considerations marketing authorization holders will need to take into account concerning regulatory affairs, pharmacovigilance and quality assurance.

It will focus on the legal, logistical and financial implications of the BREXIT concerning Marketing Authorizations of Medicinal Products. Pharmaceutical companies will benefit from a concise overview of the impact, that is to be expected and the financial, logistical and legal implications the BREXIT will have on their business.

After analyzing all the parameters that affect the obligations and requirements for the stakeholders, we will be able to display a trend and the risks and chances related to these changes. Based on that, strategic decisions could be facilitated and necessary investments planned.

A data lock point for this thesis has been set to be the 01. January 2019 and will portray the situation at that date.

1.2 Research question

What are the most probable implications in terms of regulatory affairs, pharmacovigilance and quality assurance?

What chances and risks emerge for the industry?

2 Method

For this master thesis the scenario planning method is used which was originally developed by the US army, but is commonly used in trend research. The plausible

scenarios concerning the future relation of UK towards the EU and their implications are portrayed using the scenario planning method.

This master thesis will start with a description of the current situation. Literature search tools are used to analyse the expected legislative situation, which will analyse the most recent (after 2016) publications concerning European medicinal products law and expected developments due to BREXIT.

In the end a description and analysis of the potential development of the core, topics (financial, legal and logistical implications in regards to batch release, pharmacovigilance and marketing authorizations) will follow including an analysis of which driving forces and critical uncertainties could have an impact on the development. These different possibilities of development will be put in relationship to another and will be weighted in order to position them in a scenario filter to discuss the possible trends.

3 Brexit Process

3.1 United Kingdom's (UK) withdrawal from the European Union (EU)

"On 29 March 2017, the United Kingdom notified the European Council of its intention to withdraw from the European Union" (EMA, 2018c) and a completely new situation arose. The withdrawal process according to Article 50 of the Treaty on European Union, is set to 2 years. (EMA, 2018c) This process has been since known as Brexit. There is no precedent for this situation, since no Member State has previously decided to leave the EU, which makes this situation very interesting.

The exit of the UK from the EU requires both parties to settle their future relationship. (Velthuijsen and PricewaterhouseCoopers B.V., 2016) Several scenarios are possible once the UK is no longer a member of the EU for example the UK becomes an EEA member also referred to as the "Norwegian option", or a Free Trade Agreement "FTA" can be agreed on, or also a Bilateral Agreement similar to the "Swiss option" maybe possible or a "No access agreement". (Velthuijsen and PricewaterhouseCoopers B.V., 2016) The negotiators on each side must settle the situation for all areas and find a solution for all open issues, which will be accepted by the stakeholders. UK and the EU

and all involved stakeholders will suffer from an unsettled relationship also referred to as a “no deal” or “hard brexit” scenario if an agreement is not reached before 29th March 2019 on how the future relationship will look. (Velthuijsen and PricewaterhouseCoopers B.V., 2016)

The negotiations are proceeding and in the following table the key Brexit dates (Kwon and Ritchie, 2018) are presented.

June 23, 2016	“Britain votes to leave the European Union by 51.9 percent to 48.1 percent.”(Kwon and Ritchie, 2018)
March 29, 2017	“Prime Minister Theresa May invokes Article 50, officially triggering the process of the UK exiting the EU.”(Kwon and Ritchie, 2018)
June 9, 2017	“After calling a snap general election, the Conservative party, of which Prime Minister May is a member, loses its majority in the British Parliament.”(Kwon and Ritchie, 2018)
June 19, 2017	“UK and EU politicians begin formal negotiations regarding a potential Brexit agreement.”(Kwon and Ritchie, 2018)
March 19, 2018	“The UK and EU agree on a 21-month transitional period after Brexit to soften the blow to businesses—provided a withdrawal deal is agreed upon before the UK’s departure.”(Kwon and Ritchie, 2018)
August 23, 2018	“The British government publishes a detailed set of documents outlining how its citizens and businesses should prepare for a “no-deal” Brexit.”(Kwon and Ritchie, 2018)
September 13, 2018	“The government releases more “no-deal” documents, including guidance on regulating medicines and medical equipment.”(Kwon and Ritchie, 2018)
October 18, 2018	“Prime Minister May scheduled to meet with EU leaders in what may be the last chance to agree on a Brexit deal.”(Kwon and Ritchie, 2018)
November 14, 2018	“Draft Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community agreed at negotiators' level.”(Kwon and Ritchie, 2018)
November 25, 2018	EU27 leaders met to endorse the draft Brexit withdrawal agreement and to approve the draft political declaration on future EU-UK relations
January 15, 2019	The UK House of Commons voted to reject a Brexit deal

Before March 29, 2019	"The European parliament must ratify the withdrawal agreement."(Kwon and Ritchie, 2018) (Unlikely, since it was not approved by the UK house of commons).
March 29, 2019	"Britain will exit the EU."(Kwon and Ritchie, 2018)
December 31, 2020	"Brexit transition period to end; the new economic and political rules will officially begin."(Kwon and Ritchie, 2018)

Table 1: Key Brexit Dates (Kwon and Ritchie, 2018) and own representation

3.2 Current Situation

"On 19 March 2018, EU and UK negotiators announced that significant progress had been achieved regarding the draft withdrawal agreement: more than 75 % of the legal text had been settled, based on previous commitments undertaken by both sides in a joint report in December 2017. In particular, in the draft withdrawal agreement negotiators settled two of the priority issues in their entirety – citizens' rights and the financial settlement; and importantly also approved the proposed transitional arrangements – to cover a 21-month period following the UK's date of withdrawal from the EU until 31 December 2020." (Cîrlig C., 2018) However, less than 3 months to Brexit, the post EU exit relationship regarding the regulations for medicinal products have not yet not been settled. A positive milestone was reached on 15th November 2018 when the negotiators published an agreed Withdrawal Agreement to outline of the political declaration together with an accompanying joint statement. (HM Government, 2018) This outline is a milestone for the advancement; still it is necessary that the negotiations concerning the details of the political declaration continue. (HM Government, 2018).

The draft of the withdrawal agreement between the EU and the UK is an attempt to settle the relationship after Brexit. (HM Government, 2018) This "…585-page draft withdrawal agreement is long and complex and contains several controversial clauses." (George, 2018). The remaining EU 27 accepted the withdrawal agreement in November 2018 and approved the draft political declaration on future EU-UK relations. (Kwon and Ritchie, 2018) The UK House of Commons needs to approve the withdrawal agreement before the European Commission can ratify it. The vote was schedule for December 11, 2018; it was then postponed to January 15, 2019 and was then rejected.

The withdrawal agreement defines an implementation phase or also called transition period to last approximately for two years after 29 March 2019 before defined arrangements according to the agreement for UK-EU relations come into force. On August 6 2018, the MHRA has published a guidance document discussing the implications of the implementation or transition period also for medicinal products and these details will be discussed further on. (MHRA and VMD, 2018)

The draft agreement states that, the UK will stay inside the single market and remain subject to EU laws and regulations until the end of December 2020. (HM Government, 2018) During this period, all existing "…EU regulatory, budgetary, supervisory, judiciary and enforcement instruments and structures will continue to apply within the UK". (George, 2018) The transition period can be extended, by mutual agreement before July 1, 2020, for an unspecified period. (George, 2018) The transition period will only be possible if the withdrawal agreement is ratified on time. "During the transition period it is essential that the EU and the UK settle their post Brexit relationship. The European Federation of Pharmaceutical Industries and Associations (EFPIA) Director General Nathalie Moll said the agreement's failure to contain an explicit reference to the importance of securing long-term, extensive cooperation around the regulation of medicines is not in the best interest of patients." (EFPIA, 2019)

4 Status quo situation in the EU

The EU is built on the four pillars of freedom; free movement of goods, capital, services and labor. (European Commission, 2019) Medicinal products for human use in the EU are regulated by a legal framework harmonizing regulations and requirements. (European Commission, 2019) Every medicinal product, before being sold, requires a valid marketing authorization, issued by the respective competent authority. (European Commission, 2019) The quality, safety and efficacy of authorized medicines is assured by define standards in order to protect public health. (European Commission, 2019) Requirements and procedures for marketing authorization, including the rules for post marketing surveillance of authorized products and also rules concerning manufacture, wholesale and advertising can be found in Directive 2001/83/EC and in Regulation (EC) No 726/2004. (European Commission, 2019) Rules for medicinal products for human use is covered in Volume 1

of "The Rules Governing Medicinal Products in the European Union." (European Commission, 2019)

"In addition, numerous guidelines of regulatory and scientific nature have been adopted to facilitate the interpretation of the legislation and its uniform application across the EU (Notice to Applicants Volume 2: marketing authorization procedures and other regulatory guidance)." (European Commission, 2019)

Several stakeholders are involved in the processes defined for marketing authorizations. These stakeholders are described in detail below.

4.1 Identification of the stakeholders

Competent Authorities:

The European Medicines Agency (EMA)

"The European Medicines Agency (EMA) is responsible for the evaluation and supervision of medicines, for the benefit of public and animal health in the European Union (EU). The European Medicines Agency (EMA) is a decentralized agency of the EU, located in London. It began operating in 1995. The Agency is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU."(EMA, 2018c)

"EMA protects public and animal health in 28 EU Member States, as well as the countries of the European Economic Area (EEA), by ensuring that all medicines available on the EU market are safe, effective and of high quality."(EMA, 2018c)

"EMA serves a market of over 500 million people living in the EU." (EMA, 2018c) Currently the EMA is located in London, but due to the Brexit, the EMA was forced to relocate. In November 2017, it was announced that the EMA would build up its new headquarters in Amsterdam. (EMA, 2018c) It is planned, that immediately following the exit of the UK from the EU, EMA will operate in Amsterdam. (EMA, 2018c)

"EMA is working on the scenario that the UK will become a third country as of 30 March 2019. As a consequence, the UK will no longer be able to engage as (co)-rapporteur for new marketing authorization applications for which the centralized procedure would finish

after 30 March 2019. This is without prejudice to the outcome of the withdrawal negotiations." (EMA, 2018c)

"Preparations by the European Medicines Agency (EMA) have been initiated to ensure that the EMA can continue to deliver to protect public and animal health even after the UK leaves the EU on 30 March 2019."(European Medicines Agency, 2018)

During a meeting between EMA and EU trade associations in September 2018 coordinated by the EMA, stakeholders were updated on EMA's Brexit Business continuity plan before the EU exit of the UK. (European Medicines Agency, 2018)

A tracking tool showing the main milestones and deliverables for the Agency's move to Amsterdam has been published and is presented below:

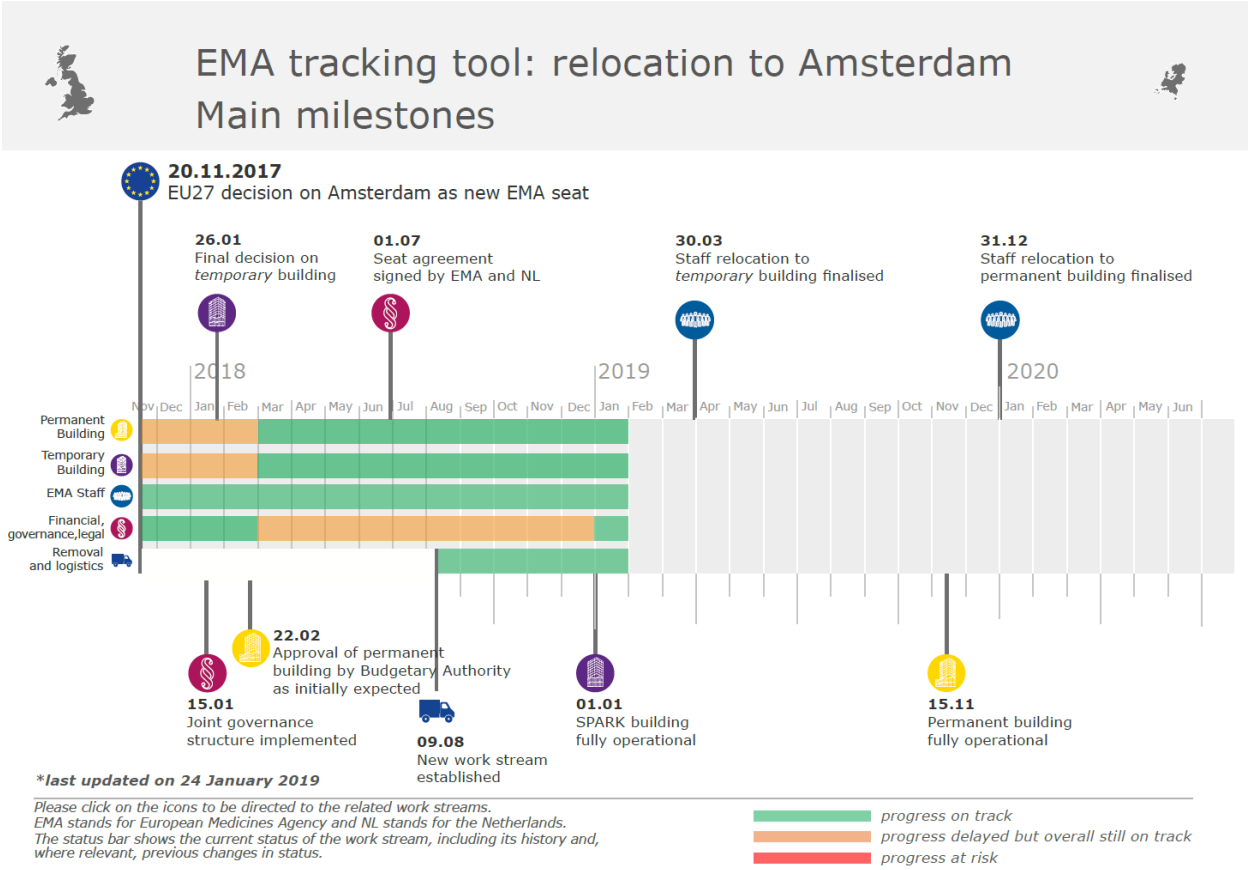


Figure 2: EMA tracking tool: relocation to Amsterdam Main milestones (EMA, 2019)

According to the Brexit preparedness business continuity plan (BCP) (Phase 3 commenced on 1 October 2018) "the temporary suspension or reduction of some additional activities, including the scaling back of guideline development and revision, and

the temporary putting on hold of non-product-related working parties have been laid down." (EMA, 2018a)

The National Competent Authorities (NCA)

The national competent authorities are mainly in charge of the authorization of medicines for the EU, that are not authorized via the centralized procedure. (European Medicines Agency, 2016)

They also "…supply thousands of European experts who serve as members of the Agency's scientific committees, working parties or in assessment teams supporting their members."(European Medicines Agency, 2019a) Previously the majority of the experts were supplied by UK. Following the Brexit the remaining national competent authorities will need to take over the work, and this can result in a deceleration of the processes and procedures and consequently a delay in market access for medicinal products under assessment.

The Medicines & Healthcare products Regulatory Agency (MHRA)

"The Medicines and Healthcare products Regulatory Agency (MHRA) is the national regulator for human medicines (as well as medical devices, clinical trials and blood products) in the UK." (UK Government, 2019b). "It is the intention of the UK government and hence the MHRA to retain a close working partnership in respect of medicines regulation after the UK leaves the EU, in the interests of public health and safety. In July 2017, a statement was published in the Financial Times, by the Secretary of State for Health and Secretary of State for Business, Energy and Industrial Strategy. In this statement, the following principles, regarding a post-Brexit regulatory system for medicines, were presented: patients should not be disadvantaged; innovators should be able to access the UK market as quickly and simply as possible; and UK will continue to play a leading role in both Europe and the world in promoting public health." (Clark, 2018) Following the current development, it is questionable whether these principles will be fulfilled. And since a 'no deal' scenario is possible, the UK has drafted various guidelines to guarantee that as of 30 March 2019 the MHRA will be prepared for all possible situations. (UK Government, 2018c)

UK government has published notices for involved parties (ie. businesses and citizens) for them to be prepared and plan accordingly. (UK Government, 2018c) In any case, these guidelines must also be ratified by the UK government in order to become valid legislation. The most important guidelines for marketing authorization holders are:

1. “Submitting regulatory information on medical products if there’s no Brexit deal” (UK Government, 2018c)
2. “How medicines, medical devices and clinical trials would be regulated if there’s no Brexit deal” (UK Government, 2018b)
   Updated January 2019 (UK Government, 2019c)
3. “Batch testing medicines if there’s no Brexit deal” (UK Government, 2018a)
4. “Technical information on what the implementation period means for the life science sector” (MHRA and VMD, 2018)
5. “Further guidance note on the regulation of medicines, medical devices and clinical trials if there’s no Brexit deal” (UK Government, 2019b)

The details of these guidance documents will be presented further on.

Independent electronic systems (portals) will need to be constructed by MHRA (similar to the portals used within the EU) for the MAHs to submit regulatory information concerning:(UK Government, 2018b)

- “marketing authorization (MA) applications” (UK Government, 2018b)
- “periodic safety update reports (PSURs)” (UK Government, 2018b)
- “pediatric investigation plans (PIPs)” (UK Government, 2018b)
- “clinical trial applications” (UK Government, 2018b)
- “qualified person for pharmacovigilance (QPPV)” (UK Government, 2018b)
- “pharmacovigilance system master file (PSMF)” (UK Government, 2018b)
- “notifications individual case safety reports (ICSRs)” (UK Government, 2018b)
- “transmission of anonymized single patient reports (ASPRs)” (UK Government, 2018b)

Although the MHRA is optimistic and has promised that, these systems will be running by 29th March 2019 (UK Government, 2018b), delays are to be expected. Delays may be due to technical implementation issues, validation process, registration process and usability training for authority and MAHs.

EU medicines regulatory network (EMRN)

“The EMRN manages some aspects of regulation including EU licensing procedures, pharmacovigilance and legal presence requirements.” (UK Government, 2019c) According to the EMA, “The European medicines regulatory network is the cornerstone of EMA's work and success. The interactions of over fifty national competent authorities for both human and veterinary medicines are coordinated by the network, with the aim to find the best expertise for medicines evaluation, regardless of where experts are based by multinational assessment teams.” (European Medicines Agency, 2019a) The two main advantages of the network are the pooling of expertise and of information. “In addition, resource optimization by referring across the regulatory network and encourage cross-border fertilization of scientific expertise. Important information on medicines, including suspected side effects reported with medicines; the oversight of clinical trials; inspections to check compliance with good practice in the clinical development, manufacturing and distribution, and safety monitoring of medicines can be shared between European countries and analyzed together. The EMRN definitely reduces unnecessary duplication and supports efficient and effective regulation of medicines across the EU.” (European Medicines Agency, 2019a)

Benefits of EMRN for EU citizens (European Medicines Agency, 2019a)

1. “Member States pool resources and coordinate work to regulate medicines efficiently and effectively”. (European Medicines Agency, 2019a)
2. “Certainty for patients, healthcare professionals, industry and governments by ensuring consistent standards and use of best available expertise.” (European Medicines Agency, 2019a)
3. “Reduction of administrative burden through the centralized authorization procedure, helping medicines to reach patients faster.” (European Medicines Agency, 2019a)
4. “Acceleration of exchange of information on important issues, such as the safety of medicines.” (European Medicines Agency, 2019a)

Other Stakeholders:

Marketing Authorization Holders (MAHs)

The legal responsible of a registered medicine is the marketing authorization holder (MAH). (European Comission, 2015) The current EC Guide to Good manufacturing practice (GMP) and the related legislation defines the responsibilities of the MAHs. The EC Guide to GMP Annex 16 states that, "…the ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy, lies with the marketing authorization holder (MAH)" (European Comission, 2015).

Marketing authorization holders need to guarantee compliant manufacturing as well as maintaining MAs in line with current scientific standards is set down in Article 23 of Directive 2001/83/EC and Article 27 Directive 2001/82/EC. (European Comission, 2015) In addition as laid out in Article 81 of Directive 2001/83/EC, MAHs need to ensure continued and appropriate availability of medicines. (EMA, 2016)

Regulations define, that MAHs of a medicinal product authorized within the EU, must be established within the EU. (EMA, 2016) In addition, the MAH has further responsibilities defined by EU legislation in order to secure the safety of patients and the quality of the medicinal products. Firstly, the MAH must ensure that the batch release of his product is performed within the EU.(EMA, 2016) Secondly, every MAH must establish a precise pharmacovigilance system and have an EU Qualified Person for Pharmacovigilance at their service. (European Medicines Agency, 2017) MAHs must also keep their marketing authorizations up to date and submit any necessary changes concerning manufacture, safety, product information etc., as a variation application to the responsible competent authority without delay.(EMA, 2016)

In general marketing authorization management requires a lot of effort and planning. Usually pharmaceutical companies have a dedicated regulatory affairs department, which is responsible for obtaining and maintaining marketing authorizations and which is in close collaboration with the departments responsible for pharmacovigilance and quality assurance.

4.2 Core topics

Batch release

Although according to Annex 16 of the EU GMP guideline, "…the ultimate responsibility for the performance of a medicinal product lies with the marketing authorization holder" (European Comission, 2015), the Qualified Person is an essential position with an undoubted responsibility. (European Comission, 2015) "The QP is responsible for ensuring that each individual batch has been manufactured and checked in compliance with laws in force in the Member State, where certification takes place, in accordance with the requirements of the marketing authorization (MA) and with Good Manufacturing Practice (GMP)."(European Comission, 2015)

Hence, it is obligatory that every MAH ensures batch control testing according to the approved specifications for the medicinal product within the EU and batch release by a QP in the EU. (UK Government, 2018a)

The guidance published by the UK government in September 2018, "Batch testing medicines if there's no Brexit deal" (UK Government, 2018a), summarizes the situation concerning batch testing and release before Brexit in the following way:

"Manufacturers can batch test medicines anywhere in the EU, EEA or other third countries with whom the EU has a 'Mutual Recognition Agreement' (MRA) under Article 51(2) of Directive 2001/83/EC." (UK Government, 2018a)

"For human medicines manufactured in the UK, a UK-based Qualified Person must certify the batch testing and ensure compliance with the MA and Good Manufacturing Practice (GMP) guidelines. These medicines can then be sold or supplied anywhere in the EU or EEA, including the UK, without further certification." (UK Government, 2018a)

"For human medicines manufactured in the EU/EEA, the batch testing and certification or release by an EU or EEA based QP allows a batch of human medicines to be sold in any other EU or EEA country (subject to the requirements of the country), including the UK, without the need for any further certification."(UK Government, 2018a)

"For human medicines manufactured in a third country outside the UK, EU or EEA and imported into the UK through the EU or EEA, batch testing is required within the UK, EU

or EEA, unless the medicine has been manufactured in a third country with which the EU has an MRA."(UK Government, 2018a)

"A human medicine manufactured in a third country requires a QP based in the UK, EU or EEA to certify that it meets all the required standards and specifications of the Marketing Authorization, before it can be sold or supplied in the EU or EEA (including the UK)."(UK Government, 2018a)

Marketing Authorization Holders Responsibilities including Pharmacovigilance

According to the guidance's published by the UK government in January 2019, "How medicines, medical devices and clinical trials would be regulated if there's no Brexit deal" and "Further guidance note on the regulation of medicines, medical devices and clinical trials if there's no Brexit deal", the situation before Brexit is the following (UK Government, 2019b) (UK Government, 2019a):

"The EU legal framework for human medicines sets standards to protect public health and ensure medicines are safe and effective. The rules for marketing authorization and monitoring authorized products are primarily laid down in Directive 2001/83/EC and in Regulation (EC) No 726/2004." (The Secretary of State and the Minister for Health, 2012)

In the UK the authorization of products, including their manufacture, import, distribution, sale and supply, as well as labelling, advertising and pharmacovigilance is handled by the Human Medicines Regulations 2012. (The Secretary of State and the Minister for Health, 2012) The MAH is responsible a medicinal product, specifically in regards to the products safety, quality and efficacy. (European Comission, 2015) "The designated QP is responsible for the quality of the product and its release to the market only if it complies with the authorized product specifications. A MAH in the EU has one legal prerequisite that is that he must be established in the EU." (The Secretary of State and the Minister for Health, 2012)

After a medicinal product has been authorized numerous standardized pharmacovigilance processes need to be conveyed to. (European Medicines Agency, 2019b Monitoring the safety of a medicine, once it is on the market is the cornerstone of pharmacovigilance. Extensive guidance has been published to enable all stakeholders to meet their legal pharmacovigilance obligations. "Good pharmacovigilance practices

(GVP) are a set of measures drawn up to facilitate the performance of pharmacovigilance in the European Union (EU). GVP apply to marketing authorization holders, the European Medicines Agency (EMA) and medicines regulatory authorities in EU Member States. They cover medicines authorized centrally via the Agency as well as medicines authorized at national level."(European Medicines Agency, 2019b) An essential responsibility of a MAH, in regard to PV, according to "Guideline on good pharmacovigilance practices (GVP) Module I – Pharmacovigilance systems and their quality systems" (European Medicines Agency, 2012) is to "…permanently and continuously have at its disposal an appropriately qualified person responsible for pharmacovigilance in the EU..". (European Medicines Agency, 2012). The pharmacovigilance system master file (PSMF) must define the pharmacovigilance processes of every MAH. "The PSMF definition is provided in Article 1(28e) of Directive 2001/83/EC and the minimum requirements for its content and maintenance are set out in the Commission-Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC. The detailed requirements provided by the Commission Implementing Regulation are further supported by the guidance in GVP Module II. The PSMF shall be located within the EU, either at the site where the main pharmacovigilance activities are performed or at the site where the qualified person responsible for pharmacovigilance operates. Following European Economic Area (EEA) agreements, the PSMF may also be located in Norway, Iceland or Liechtenstein." (European Medicines Agency, 2017).

4.3 The critical uncertainties

"The draft agreement establishes a single customs territory between the EU and UK during the transition period. The draft agreement also specifies under Annex V, which EU regulations related to medicinal products, medical devices and substances of human origin would apply to the UK during the transition period. Articles 44, 45 and 46 of the agreement also clarify that the EU and UK will continue to make information related to past and ongoing procedures for medicines and conformity assessments for devices available to one another." (Cîrlig C., 2018)

Although the Draft Agreement defines the aspects of medicinal products and responsibilities of MAHs during the transition period there is no information about the situation after the transition period is over. Only if both parties accept the draft agreement then will negotiations be able to start to set up the regulations for medicinal products on a long term.

The responsibilities of a MAH within the EU are clearly laid out in the EU legislation and it easy for MAHs to plan any necessary legal, logistical and financial steps if necessary changes are to come up. After the Brexit the situation for the MAHs is not clear. This is why it is necessary that MAHs (and all other stakeholders) need to know as soon as possible how the following scenarios will be settled once the UK has exited the EU:

Batch release

Will it be possible that batch release/batch control for a product for the EU market is performed in UK (and vice versa)?

Pharmacovigilance

Will it be possible that the Qualified Person for Pharmacovigilance of the MAH for a medicinal product authorized in the EU is placed in the UK (and vice versa)?

Will it be possible that the Pharmacovigilance System Master File of the MAH for a medicinal product authorized in the EU is located in the UK (and vice versa)?

Marketing Authorizations

What is the impact for a marketing authorization holder for an authorization of a medicinal product, which is authorized by UK as RMS?
What is necessary if the marketing authorization holder is based in the UK and holds marketing authorizations in the EU (and vice versa)?

5 Post Brexit Regulations

"Subject to any transitional arrangement that may be contained in a possible withdrawal agreement, as of the withdrawal date, EU rules in the field of medicinal products for

human and veterinary use no longer apply to the United Kingdom." (CMDh, 2018a). Two critical aspects concerning the future situations for MAHs are that:

- EU marketing authorization holders must be established in the EU (or EEA) (CMDh, 2018a)
- key activities like pharmacovigilance and batch release must be performed in the EU (or EEA) (CMDh, 2018a)

5.1 Options for MAHs concerning batch release/batch control

5.1.1 The batch release/batch control for a product for the EU market is performed in UK

The situation for MAHs that perform batch release and batch control in the UK for a product for the EU market will be the following: Since the UK is considered a third country after 29 March 2019, the batch release and batch control can no longer be performed in the UK for a product intended for the EU. The result is that MAHs are obliged to transfer their QP, their site of batch release and batch control somewhere within the EU.

The following actions will be necessary, in order be compliant:

- Transfer of QP and batch release site to EU
- Transfer of batch control testing site to EU
- Transfer of analytical methods to new facility in EU (including qualification and validation of site)
- Submission of variation application to change site of batch control and batch release
- Inform competent authorities about new location of QP or new QP

The actual transfer activities are mainly dependent on the participating parties (i.e. MAH; manufacturing sites). The political decisions and negotiations could also influence these activities depending on the development of the regulatory landscape within the EU.

The financial aspects to be considered are:

- Financial investigation for transfer of analytical methods
- Financial investigation for qualification and validation of new batch control site

- Fees for variation application (dependent on number of Marketing Authorizations involved.)

Any investments in direct relation to the new facilities and transfer between sites are not subject to legal development but more on the private parties involved. Concerning the fees for variation applications there could be several different trends. In the worst case, the MAH will be obliged to pay a variation fee for every single product effected in every country that it has been approved in. However, it is also possible that the EU will allow the MAH to submit one variation for all its products concerned for one collective fee. Then the MAH investment concerning regulatory fees would be less. In any case, the investment for the regulatory work will increase, since all necessary documents within the registration dossier and product information of every single product must be updated. But according to the CMDh practical guidance ,"Brexit-related variations can be grouped, where the grouping does not delay implementation of changes which need to be in place by the time of UK's withdrawal from the EU." (CMDh, 2018b)

Logistically the MAH must consider the following:

- Relocation of QP including requalification with new responsible national competent authority
- Possibly necessity to delegate new QP

Whether the QP decides to move within the EU is a personal decision and may be influenced by the political landscape under discussion, but it is hard to judge in advance.

Each EU member state individually defines the necessary qualifications to be able to act as a QP. Therefore it may be easier to be qualified as a QP in some member states and more difficult (meaning more requirements necessary) in other member states. Depending on where in the EU the QP will reside after Brexit, it may take longer or shorter for him to be qualified. This difference will determine the time needed until compliant batch release and batch control can be performed.

The worst-case scenario would be that the UK will be considered a third country and all of the above measures have to be implemented by day one of the Brexit (29. March 2019). This would mean an immense financial burden for the MAH due to

variation fees and even more the necessary analytical method transfer that must be performed very fast.

Critical is whether the UK and EU will agree on the withdrawal agreement and then a 2 year transition period would give all stakeholders additional time to implement the necessary changes. A positive trend could be if the EU and the UK can agree on a Mutual Recognition Agreement (MRA) and the two parties would then accept batch release and batch control testing within one of the two territories. If this agreement can be reached before the transition period has ended, it would mean that MAHs with batch release in the UK for products intended for the EU must not transfer their batch release and batch control sites to the EU (and vice versa).

5.1.2 The batch release/batch control for a product for the UK market is performed in EU

The guidance published by the UK government in September 2018, “Batch testing medicines if there’s no Brexit deal” (UK Government, 2018a), summarizes the situation concerning batch testing:

“In order to ensure continuity of supply in medicines however, the UK will continue to accept batch testing of human medicines carried out in countries named on a list set out by the MHRA. On exit day, this list would include EU countries, other EEA countries and those third countries with which the EU has an MRA.” (UK Government, 2018a)

“For human medicines manufactured in a country on the MHRA’s QP list, which have the relevant QP certification, the MHRA will continue to recognize certification, release and assurance of compliance with the MA and with GMP guidelines, if conducted by a QP based in the listed country, without the need for any further certification.” (UK Government, 2018a)

The uncertainties concerning batch release in the EU for products intended for the UK market are less in comparison to the scenario described under 5.1.1. Since the UK can decide independently which countries, it will accept on its “white list”. The best scenario would be a MRA agreed under consensus between the EU and UK.

Considering the above, for MAHs that perform batch release and batch control testing within the EU for UK products, no action is necessary now. Possible changes of this set up, are not expected, unless the UK recalls this approach. Then the possible implications described in 5.1.1 should be considered by these MAHs.

5.2 Implications for the Qualified Person for Pharmacovigilance and Pharmacovigilance System Master File

5.2.1 QPPV and PSMF placed in the UK responsible for products in the EU

After Brexit it will not be possible for the QPPV and PSMF to reside in the UK for a product intended for the EU. (UK Government, 2018b) The result is that MAHs are obliged to transfer their QPPV and their PSMF site somewhere within the EU.

Consequently, a series of individual processes is necessaryto remain compliant:

- Transfer of QPPV and PSMF site to EU
- Update of Article 57 database
- Type IA IN variation submission for new PSMF

According to the “Practical guidance for procedures related to Brexit for medicinal products for human use approved via MRP/DCP” by CMDh (CMDh, 2018b):

“A variation to submit the summary of the pharmacovigilance system will not be necessary in cases where the MA is transferred within companies belonging to the same parent company and the same PSMF will continue to be used. Upon a change in the QPPV or location of the PMSF, the Article 57 database should be updated by the MAH immediately to allow continuous supervision by the Competent Authorities.” (CMDh, 2018b)

The following financial aspects need to be considered:

- Financial investigation for transfer of PSMF location
- Fees for variation application (dependent whether MAH will be transferred and on number of Marketing Authorizations involved.)

Logistically the MAH must consider the following:

- Relocation of QPPV including requalification with new responsible national competent authority
- Possibly necessity to delegate new QPPV
- Increase of regulatory work (update of necessary documents)

5.2.2 QPPV and PSMF placed in the EU responsible for products in the UK

According to the guidance published in September 2018, “How medicines, medical devices and clinical trials would be regulated if there’s no Brexit deal” (UK Government, 2018b) after 29. March 2019:

“The Qualified Person for Pharmacovigilance (QPPV) should be established in the UK on day one, although those without a current UK presence will have until the end of 2020 at the latest to do so, but would nevertheless be required to make arrangements for providing the MHRA with access to the relevant safety data related to UK Marketing Authorizations at any time. Companies may choose to have the EU QPPV take on responsibility for UK MAs until the UK QPPV can be established. A variation should be submitted to the MHRA to change QPPV.” (UK Government, 2018b):

Consequently, a series of individual processes will be necessary, to stay compliant:

- Establishing a UK PSMF
- Delegating a UK QPPV
- Submission of variation to MHRA to change QPPV and UK PSMF

The following financial aspects need to be considered:

- Financial investigation for establishing UK PSMF
- Financial investigation for delegating UK QPPV
- Fees for variation application
- Fee for service providers offering service for UK QPPV and UK PSMF

Logistically the MAH must consider the following:

- Establishing UK QPPV and UK PSMF
- Possibly necessity to negotiate agreement with service providers
- Increase of regulatory work (update of necessary documents)

5.3 Implications for Marketing Authorizations

5.3.1 UK Marketing Authorizations

The most important aspects concerning MA after Brexit are laid out in the Guidance "How medicines, medical devices and clinical trials would be regulated if there's no Brexit deal" (UK Government, 2018b):

Legal presence requirements

"A MAH needs to be established in the UK by the end of 2020. Until then, the MHRA will require a contact in the UK. A Change of Ownership will need to be submitted to MHRA to change from an EU MAH to a UK MAH for UK MAs." (UK Government, 2018b)

"At present, the MHRA requires a named individual who can be contacted in the event of a safety issue, and has the ability to require independent re-testing of medicines and also the ability to withdraw a product from the market. This will continue if there is no deal." (UK Government, 2018b)

If it is necessary to assign a service provider with MAH, QPPV and QP services the fees will need to be considered. It can be estimated that the full service palette (MAH, QPPV and QP) in the UK will cost the EU MAH approximately 20 000 Euros per year (not including any additional local services by the hour).

Centrally authorized products

Centrally Authorized Products (CAPS) are authorized by a procedure overseen by the EMA and are authorized in all EU member states. "All CAP MAs will automatically be converted into UK MAs on 29 March 2019 to ensure such medicines will continue to be recognized for use in the UK." (MHRA, 2019). This process is also refrred to as so called "grandfathering". MHRA informed all CAP Marketing Authorization Holders (MAHs) on 02 January 2019 with details "...of the conversion process and to provide them with the opportunity to opt out of receiving a UK MA. MAHs can opt-out of the grandfathering process for all or some of their CAPs by notifying the MHRA in writing by 22nd April 2019.

If an MAH chooses to opt-out, after 22 April 2019 their product(s) will no longer be licensed in the UK. This will mean they can no longer be placed on the market in the UK. MAHs will need to submit baseline data dossier to the MHRA within a defined period from exit day and also agency will not accept variation notifications until it receives baseline data."(MHRA, 2019)

Several trade groups "..want MHRA to eliminate the requirement for MAHs to file baseline data and urged the agency to look into getting the information from the European Medicines Agency (EMA) instead." (Taylor, 2018)

"The compiling of baselines is a time-consuming and labor-intensive: impacts MAHs' staff administrative cost challenging, if not impossible, for companies to complete for all concerned products in the time available. The high volume of baseline submissions required around Exit day will also likely place a strain on MHRA systems and resources," the trade groups write.(Taylor, 2018) In order to submit variation notifications on time MAHs must submit baseline data immediately and this adds to the burden on MAHs resources.

Legally this has several effects on the MAH:

- Establishing a MAH in the UK
- MAH is required to follow defined conversion process

The following financial aspects also need to be considered:

- Costs for establishing MAH in UK
- Costs for conversion process
- Costs for compiling and submitting baseline dossier
- Costs for possible necessary renewal (since UK MA will be initial and not yet renewed)
- The compiling of baselines: impacts MAHs' staff administrative cost

Logistically the MAH must consider the following:

- 2 registrations for one medicinal product authorized in the EU and UK could result in a product with different specifications and commitments
- Registering for national UK databases for submission
- Increase of regulatory work (baseline submission, further renewal submission)

Initial Marketing Authorization applications

“After EU Exit, an initial MA application will need to be submitted to the MHRA and will go through a national assessment.” (UK Government, 2018b) The UK national marketing authorization approval process should place “..no greater burden on industry.” (UK Government, 2018b). In particular, since the MHRA wants “to ensure that patients can access new and innovative medicines at the same time as EU patients.” (UK Government, 2018b)

Legally this has several effects on the MAH:

- Establishing a MAH in the UK

The following financial aspects also need to be considered:

- Costs for establishing MAH in UK
- Registration costs

Logistically the MAH must consider the following:

- 2 parallel registration procedures will result in a medicinal product authorized in the EU and UK with different specifications and commitments
- Registering with national UK databases for submission
- Increase of regulatory work (2 separate registration processes)

Medicines licensed via Mutual Recognition and Decentralized Procedures

“Medicinal products authorized via a DC or MR procedure in the UK prior to 29 March 2019 will be not need to undergo any deliberate conversion process after Brexit as they already hold a national UK MA.” (UK Government, 2018b) These products already hold a national marketing authorization. However, after a while the dossier of the product in the UK may develop differently depending on different authority demands and requests.

EU Procedures in progress at Brexit

“If there’s ‘no deal’, the outcome of EU procedures (including mutual recognition, decentralized and centralized procedures) that have not reached the decision phase at

the time that the UK exits the EU, will not be valid in the UK."(UK Government, 2018b) In any case, the MHRA proposes to consider EU decisions where possible.

For centralized procedures: "The application, as submitted to the EMA, will need to be submitted to the MHRA. If the Committee for Medicinal Products for Human Use (CHMP) has issued an opinion by exit day, MHRA will make its decision taking into account the CHMP opinion. If not yet at the opinion phase, the MHRA will continue to assess the application as a national procedure. MHRA will take into account any CHMP assessment that had already taken place." (UK Government, 2018b)

For mutual recognition or decentralized procedures: "At time of EU Exit, it is proposed that a transitional provision will be made for MR and DC procedures in progress immediately before Exit day. These procedures currently already result in a national MA. MHRA will complete the assessment (the transitional process for this will depend on how far the procedure has got immediately before Exit day) but if successful, they will be approved as a national (UK) MA." (UK Government, 2018b)

Logistical implications if MAH has ongoing registration procedures:

- Re-Submission of applications to the MHRA
- Communication with MHRA has to be established (registration plan readapted)

<u>Medicinal products authorized via MRP or DCP with UK as RMS</u>

If a marketing authorization holder holds authorizations of medicinal products which were authorized via a decentralized procedure (DCP) or mutual recognition procedure (MRP) with UK as reference member state (RMS) a transfer to a new RMS needs to be performed (RMS switch). This is the case for 409 human and 291 veterinary medicinal products (Platzer, 2018). Most of the remaining EU competent authorities have increased their capacity and are eager to accept new RMS roles. MAHs need to contact the future and current RMS before initiating any actions since it needs to be ensured that both reference member states (current and future) accept the transfer. (CMDh, 2018b)

For the application the MAH needs to complete the CMDh request form and include the the reason for changing the RMS, the confirmation that the current RMS has agreed to the RMS change, information if all procedures have been recognized and a list of the Concerned Member States (CMS). (CMDh, 2018b)

According to CMDh “Practical guidance for procedures related to Brexit for medicinal products for human use approved via MRP/DCP” (CMDh, 2018b): “The switch can be applied for at any point in time after the End of Procedure in a new MAA. However, for the implementation of the switch all other pending regulatory procedures, e.g. variations, renewals, etc., have to be closed. MAHs should preferably discuss the availability and timing beforehand with the proposed new RMS.” (CMDh, 2018b)

“If UK remains RMS for an ongoing procedure which has not been finalized before 29 March 2019 then the procedure will be stopped. According to the Withdrawal Agreement (European Commission, 2018) Article 123, paragraph 6 United Kingdom shall not act as leading authority for risk assessments, examinations, approvals and authorizations at the level of the Union or of Member States acting jointly.” (UK Government, 2018b) At a symposium of the middle European association of regulatory affairs in November 2018, it has been communicated that should one CMS consider the medicinal product critical for public health, then the procedure may go on. This provision has not been officially communicated and may still be subject of discussion.

‘Generic’ reference products

Any MA in accordance with Articles 10 and 10a of Directive 2001/83/EC or Articles 13 and 13a of Directive 2001/82/EC referring to an European reference product will remain valid. (MHRA, 2018)

EU reference medicinal products can be used as generic originators during the transition phase also. This is also clearly stated in Article 45 of the “Draft Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union” (European Commission, 2018). The applicants in the UK or the EU, therefore can refer to a product authorized within the EU or in the UK until December 2020, the proposed end of the implementation phase. (European Commission, 2018) After the transition period, the situation will probably change. Then products that were authorized while the UK was still part of the EU or during the transition period can still be considered EU reference medicinal products. Medicinal products authorized after December 2020 in the UK cannot be a reference medicinal product for an EU procedure ccording to Articles 10 and 10a of Directive 2001/83/EC or Articles 13 and 13a of Directive

2001/82/EC. (European Commission, 2018). Vice versa a product authorized in the EU after December 2020 cannot be taken as reference medicinal product for a marketing authorization procedure submitted in the UK. After Brexit MHRA will no longer be able to access data of EU medicinal products, hence new applications for generic MA in the UK need to refer to reference medicinal products authorized in the UK. (UK Government, 2018b)

This means that after 2020 the generic landscape of products authorized in the UK and in the EU could be very different. Since MAHs will need to evaluate whether the reference product is available in UK and the EU and initiate adequate applications. If the reference medicinal product is available in only one of the two territories, the generic product can also only be authorized there.

The financial implications of the expected change of possible reference medicinal products cannot be defined by any additional fees or increase of workload but more in a reduction of possible marketing authorizations reduction of possible market access and therefor a lower revenue.

5.3.2 EU Marketing Authorizations

Legal presence requirements

MAHs based in the UK, holding marketing authorizations in the EU must transfer their MA to a legal entity based in the EU before the end of the transition period. (UK Government, 2018b) This can be either a company subsidiary or if necessary a service provider taking over the tasks as MAH. In addition, the transfer of the MAH to a different legal entity requires several administrative preparations and the submission of a number of documents to the concerned member state.

Change of MAH or of batch release need to be submitted according to the dedicated procedures (MA transfer application or variation application) in a timely manner, while simpler adaptions can be submitted as part of future regulatory submissions. “An update of the package leaflet to delete the name of the product in the UK can be included as part of a future regulatory procedure (e.g. variation, renewal) affecting the package leaflet. The earliest opportunity after 29 March 2019 should be used. Changes to the local

representative mentioned in the product information are dealt with at a national level." (UK Government, 2018b)

EU Procedures in progress at time of Brexit

"For marketing authorization procedures (MAAs) that are expected to be closed after 29 March 2019, the future MAH, QPPV, batch release sites, batch control sites, intended Official Medicines Control Laboratory (OMCL), if applicable, and nominated local representatives for Member States other than UK must be located in the Union (EEA). Where it has not been possible to amend the application in this regard prior to the submission of the MAA, such change will need to be made during the decentralized procedure."(UK Government, 2018b) Day 106 or Day 160 responses should include the updated product information accompanied by an updated Summary of the Pharmacovigilance System. (UK Government, 2018b)

"The applicants are encouraged to request the changes as early as possible, in particular concerning manufacturing sites, as the acceptability of the proposed changes will need to be assessed. For MRP, necessary updates should be made via the appropriate variation procedure in advance of submitting the application to the CMS. During an ongoing MRP any necessary update of the application should be made with the Day 40 responses and is limited to issues not covered by the variation regulation like the future MAH." (CMDh, 2018b) The following documents should be submitted:

- "A letter requesting the change of applicant and signed by both the previous and the new applicant." (CMDh, 2018b)
- "A confirmation (as part of the cover letter) that complete and up-to-date file concerning the medicinal product or a copy of this file has been made available to or has been transferred to the new applicant." (CMDh, 2018b)
- "Updated application form and affected annexes (includes proof of establishment of the new applicant within the Union (EEA) issued in accordance with national provisions and which should be no older than 6 months and the power of attorney for a person communicating on behalf of the new applicant)." (CMDh, 2018b)
- "Updated summary of the pharmacovigilance system." (CMDh, 2018b)

- “Any other documents of the marketing authorization dossier affected by the change of applicant, as relevant (e.g. an updated Letter of Access for an application that includes an Active Substance Master File).” (CMDh, 2018b)

“The applicants are encouraged to request the changes as early as possible as the acceptability of the proposed changes will need to be assessed.” (CMDh, 2018b)

The marketing authorization holder will be forced to consider several legal and logistical implications:

- Logistical: How complicated will it be to set up new MAH entity
- Legal: How fast new agreements settled (MRA).
- Financial: delays in market access due to slower processes
- Regulatory fees to NCA
- Preparation of documents
- Costs for service providers

6 Analysis

The scenario technique establishes a trend analysis of a likely scenario to come into force. For this first of all the positive and negative extremes are described.

The possible scenarios:

For a MAH the positive would be a simplification of the regulations (legal), cost reduction (financial) and a reduction of work load (logistical).

The negative extreme for MAHs would be a complication of the regulations, cost explosion and an increase of work load.

The trend line would result in no change of the scenario and would probably be equivalent to the situation during the transition phase.

In which direction the trend will develop, is dependent on several influencing factors and the driving forces involved. The main stakeholders, as discussed above in detail, are the MHRA, the EMA as well as the MAHs. These stakeholders are dependent on the decisions reached by the European Commission and United Kingdom Government. According to the consensus reached, the stakeholders will be able to pursue their

individual goals and, most importantly, maintain public health standards. Several influencing areas will be impacted and hence will determine the impact of the development for the MAHs:

1. Process of the negotiations (including time for UK needed to act as independent NCA)
2. Political situation
3. Development Regulatory landscape

Process of negotiations

The ongoing negotiations since the UKs decision to exit the EU have resulted in a draft withdrawal agreement, which was accepted by the EC end of November 2018. This withdrawal agreement defines a transition period of approximately 2 years after 29 March 2019 in which the 2 parties (EU and UK) can define their future relationship. But, this draft withdrawal agreement will only come into effect if it is approved by UK parliament and afterwards ratified by the EC. If a consensus concerning the post Brexit relationship can be reached quickly then MAHs will be able to adjust their strategies and actions accordingly without a long delay. Nevertheless, if it will take longer for the parties to settle the details of the future relationship, then MAHs will be left drifting in insecurity. This will have significant impact on legal, logistical and financial aspects and an impairment in public health in particular to shortage and unavailability of medicinal products.

Due to the number of unsettled issues i.e. the Ireland border for which it very difficult to find a solution that will suit all parties, the negotiations concerning the post Brexit regulations will probably take the maximum possible time until the end of 2020. The transition period could be extended and hence the MAHs would be without definite scenarios for even longer.

Political relation

There are several options for the future political future relation of UK towards the EU: EEA member “Norwegian option”, Free Trade Agreement “FTA”, Bilateral Agreement “Swiss option” and “No access agreement”. (Velthuijsen and PricewaterhouseCoopers B.V.,

2016). The option, which would mean the least necessary adaptions for MAHs, would be that UK in the future would become an EEA, as Norway or Liechtenstein are currently. EEA members are equivalent to EU members in regards to regulatory processes for marketing authorization applications and variations, responsible roles like QPPV and QP and batch release regulations. After that, a Bilateral Agreement comparable to the status Switzerland currently has to the EU would have the least impact for MAHs. While Switzerland has an independent registration process and individual requirements, many other issues are harmonized in particular due to the Mutual Recognition Agreement (MRA) EU GMP status is recognized by Switzerland. A Free Trade Agreement would mean further necessary adaptions for MAHs and a “No access agreement” would be equivalent to a “Rest of World” status and MAHs would be probably need to cope with a number of completely new requirements.

Development Regulatory landscape

Currently the regulatory requirements concerning medicinal products are harmonized and managed by the European medicines regulatory network (EMRN). “The system for regulating medicines in Europe is unique in the world. It is based on a closely-coordinated regulatory network of national competent authorities in the Member States of the European Economic Area (EEA) working together with the European Medicines Agency (EMA) and the European Commission.” (European Medicines Agency, 2019a). The EMRN consists of regulatory authorities from the EEA countries, the European Commission. The EMRN is responsible for establishing professional competence and harmonized standards for the regulation of medicines in the EU. (European Medicines Agency, 2016).

The trend line would result in no change regarding regulatory regulations in the EU and UK equivalent to the current (pre Brexit) situation.

Scenario Planning

The positive extreme would be that regulatory regulations in the UK would be simplified and MAHs would have less requirements. This scenario is rather unlikely since the MHRA has ever since been known as a very strict and rigorous authority. Also an authority who

acts as role model and scientific lead concerning the development of new prerequisites and guidelines.

All harmonized rules between Member States will expire in the UK after Brexit, according to Art. 50 §. 3 TFEU (Treaty of the Functioning of the European Union). (CMDh, 2018a) Meaning after the exit from the EU the complete EU Acquis commun- autaire will no longer be valid in the UK. (CMDh, 2018a) In addition, any regulations concerning the regulation of medicinal products (i.e. for central authorization procedures and variations, orphan drug and pediatric development), decisions from EU organizations for example the UK will not accept approval notifications for CAP or also decisions by the European Court of Justice will no. (European Union, 2012) It should be considered, that the nationally British implemented community law according to EC 2001/83 will remain applicable also in the UK. In order to avoid a disruption to business the UK government is transferring the complete European Medicinal Product Regulations into national law. The aspects of the European human medicinal products legislation will need to be integrated into national UK law, Human Medicines (Amendment etc.) (EU Exit) Regulations 2019, to maintain quality supply of medicines.
“The amendments to the 2012 Regulations address the fact that the UK will no longer be part of the harmonized EU medicines network…” and “…make appropriate changes to reflect the fact that the Medicines and Healthcare products Regulatory Agency is acting as a standalone regulator outside the EU network.” (UK Government, 2019a)

If MAHs are currently, (preBrexit) present in the EU and also supply the UK market and plan to maintain this situation post Brexit several aspects need to be considered. The most probable implications in terms of regulatory affairs, pharmacovigilance and quality assurance are summarized in the table below.

Descriptor	Projection	Expected Option	Metric
GMP recognition	Option A: EU and UK will accept GMP certificates of each other due to settled MRA's	EU and UK will accept GMP certificates of each other	Number of countries with MRA with UK
	Option B: EU and UK will not accept GMP certificates of each other		
Requirements to obtain qualification and accreditation as Qualified Person and QPPV	Option A: Requirements reduced, otherwise shortage of qualified persons that can be recruited for these positions expected	Requirements reduced	Requirements for UK QP and QPPV vs. EU requirements
	Option B: Requirements increased		
Business critical roles (i.e. General Manager) and residency requirements	Option A: Requirements reduced		Requirements for UK critical roles vs. EU requirements
	Option B: Requirements increased since UK has different regulations after Brexit	Requirements increased	
Customer and supplier contracts.	Option A: Contract scope reduced		Contract scope for UK vs. EU scope
	Option B: Contract scope increased since UK has different regulations after Brexit contract will need to cover ROW scenario	Contract scope increased	
Considerations for workforce Continuity planning	Option A: Workforce reduced		Share of Workforce UK vs total workforce
	Option B: Workforce increased since UK is no longer part of union and hence duplication of procedures	Requirements for Employees increased	
Staffing investments in order to adhere to requirements	Option A: Investments for Employee reduced		Share of staffing investments UK vs. EU
	Option B: Investments for Employee increased since UK is no longer part of union and	Investments for Employee increased	
Shipping costs	Option A: Shipping costs decrease		Share of shipping on total costs
	Option B: Shipping costs increase because of higher customs	Shipping costs increase	
Authority fees	Option A: Authority fees could minimally decrease since UK wants to stay attractive for companies. Additional workload for MHRA, which is no longer covered by EMA, increases MHRA costs.	Authority fees decrease	Share of authority fees on total costs
	Option B. Authority fees increase		

Descriptor	Projection	Expected Option	Metric
MAH Resources	Option A: MAH resources decrease		Share of MAH resources for UK MA vs. MAH resources in total
	Option B: MAH resources increase due to duplicated structure for EU/UK (personnel and financial)	MAH resources increase	
MHRA independence	Option A: MHRA will use EU systems and portals		Share of portals, databases, system for UK vs. s EU
	Option B: MHRA will act as act independent NCA and set up own of database, portals, systems	MHRA will act as act independent NCA	
Batch Release efforts	Option A: Batch release efforts will decrease		Share of efforts Necessary for batch release in UK vs. batch release in total
	Option B: Batch release efforts will increase due to 2 (EU/UK)necessary material and production lines and necessary replacement of central documents by individual files (SMF, SOPs) and creation of new functions	Batch release efforts will increase	
Pharmacovigilance efforts	Option A: PV efforts will decrease		Share of efforts necessary for pharmacovigilance in UK vs. batch release in total
	Option B: PV efforts will increase since it will become difficult to acquire QPPV, there will be additional reporting lines and additional necessary IT support (additional electronic interfaces) and also different expedite reporting processes	PV efforts will increase	

Table 2: Key descriptors and possible options

Considering the ongoing debates and negotiations concerning the future relationship it is not very plausible that UK will become an EEA member or accept a bilateral agreement and therefor a status of either a free trade agreement or ROW status will be more likely. However, it should be taken into account that negotiations arranging mutual recognition agreements covering i.e. GMP qualifications will most likely be settled.

Since many of the substantial topics (i.e. pharmacovigilance processes) were predominantly shaped and established by the MHRA, the processes will firstly remain according to the EU processes (Bundesverband der Arzneimittelhersteller, 2016). It can be expected that, the UK will develop their own submission scheme for PSURs (differing from the EU harmonized birth date list) and independent referrals (risk assessment procedures) could be triggered in the UK. This means that additional or modified pharmacovigilance and regulatory provisions will be in place in the UK resulting in

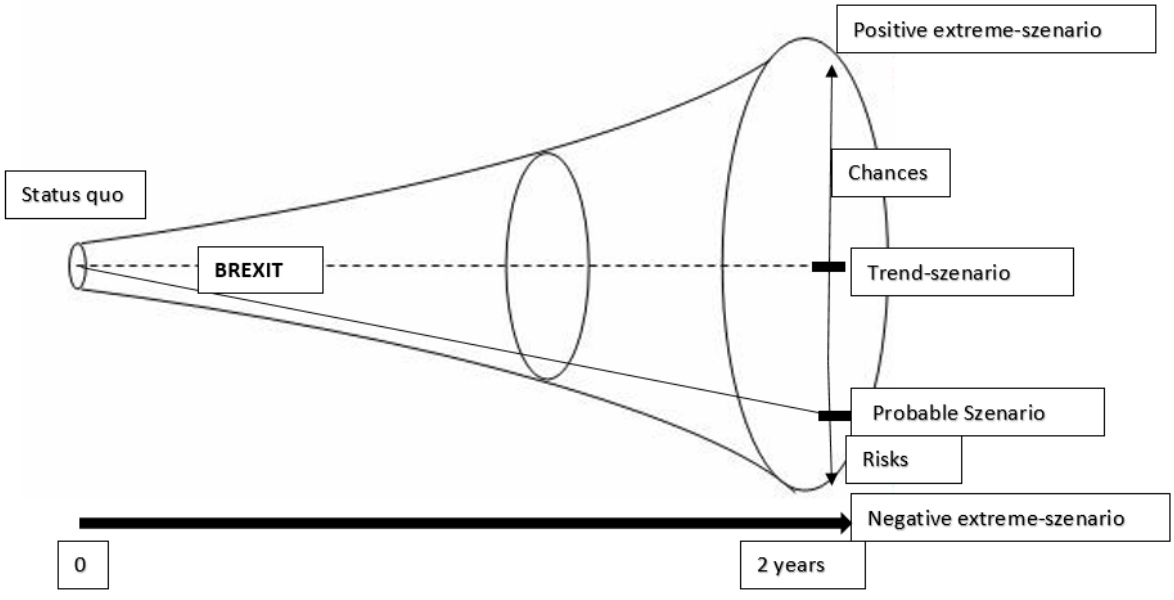
different wordings in SMPC and PIL of the products in the EU and UK. (Bundesverband der Arzneimittelhersteller, 2016) In addition, risk management plans only valid for the UK could evolve including additional studies (PASS/PAES) and restrictions for the marketing authorizations. (Bundesverband der Arzneimittelhersteller, 2016)

Eventually the UK legislative landscape in respect to medicinal products will inevitably develop differently than EU legislation.

The negative impact for MAHs is a complication of the regulations and diverting requirements in the EU and the UK. (Bundesverband der Arzneimittelhersteller, 2016) This will make the situation rather difficult for the MAH and it would be necessary to consider UK as a completely different authorization with a ROW regulatory landscape.

Taking into consideration, the most likely scenario development a scenario funnel was established. The funnel demonstrates that a majority of the descriptors will develop towards the negative extreme scenario. The regulations and requirements will probably increase, hence increasing necessary efforts for MAHs to adhere to quality, regulatory affairs and pharmacovigilance legislation. MAHs can measure the impact of the proposed trend by using the metrics described in table 2. It is crucial that MAHs evaluate the necessary actions to uphold their status in the UK in relation to the expected turn over and whether the necessary investments remain feasible.

Figure 3: Scenario Funnel



Chances and Risks

The probable scenario could be improved towards the positive extreme scenario if EMA and UK are able to develop legislation for medicinal products in close collaboration. A parallel development of the regulatory landscape would be possible if the two regions cooperate and a consensus is reached regarding the requirements for MAHs in the EU and in the UK.

MAHs could face risks if the UK regulations develop in an even more regulated direction and an even larger gap in reference to EU legislation. In this case, it can be assumed that the majority of MAHs will not maintain their MA in the UK. This of course will have a negative impact on patients in the UK.

7 Resumée

The situation post Brexit concerning batch release, marketing authorization holders responsibilities including pharmacovigilance is essential to maintain authorizations of medicinal products and ensure safe and effective treatment for patients.

Batch release/batch control recognition between the two territories will only be possible if the EU and the UK can settle a mutual recognition agreement to accept QPs and batch release sites in both territories. (Cîrlig C., 2018)

Qualified Person for Pharmacovigilance of the MAH for a medicinal product authorized in the EU needs to be placed in the EU while the QPPV for a product in the UK needs to be placed in the UK. The Pharmacovigilance System Master File of the MAH must also be placed in the territory where the medicinal product is authorized, EU or UK. However, transitional periods are possible. (UK Government, 2018b)

Marketing authorization holders will face tremendous legal, logistical and financial implications due to Brexit. MAHs will need to consider whether maintaining all MA is worthwhile and economically feasible. A reduction of MA for medicinal products means a deterioration concerning supply of treatment for the patients. The process of the negotiations (including time for UK needed to act as independent NCA), the agreed political relationship and the development of the regulatory landscape will influence the impact of the development for the MAHs.

Marketing authorization holders face complex considerations since this new situation requires concise planning in order to comply with all regulations. Because of the very high financial investments that are necessary, it is crucial that all pharmaceutical companies are well prepared. MAHs will need to measure the impact of the proposed trend by using the descriptors identified: GMP recognition, requirements to obtain qualification and accreditation as Qualified Person and QPPV, business critical roles, customer and supplier contracts, workforce continuity planning, staffing investments in order to adhere to requirements, shipping costs, authority fees, MAH resources, MHRA independence, efforts for batch release and pharmacovigilance efforts.

The most crucial point is that, if the pharmaceutical companies cannot adapt their regulatory, safety and quality systems according to the new regulations on time, this will lead to a possible shortage of supply of medicinal products effecting patients and public health.

In addition and of perhaps even greater impact Brexit will bring disadvantages for EU and UK citizens. Medicines will no longer be regulated effectively since the UK will not be part of EMRN and the pool of resources. (European Medicines Agency, 2019a) The advantage of referring to a pool of experts and resources will be abolished. That means that patients, healthcare professionals, industry and hence governments cannot rely on consistent standards. (European Medicines Agency, 2019a) Innovative medicines will be approved with a delay due to the increase of the increase of workload caused by the individual regulatory authorization procedures. In addition, a delayed exchange of information on important issues, (ie. safety of medicines) is probable since the oversight of clinical trials; inspections to check compliance with good practice in the clinical development, manufacturing and distribution, and safety monitoring of medicines is no longer centralized with the EMRN, but dealt with in the UK and EU individually. (European Medicines Agency, 2019a) The additional or modified pharmacovigilance and regulatory provisions that will be in place in the UK, will result in different wordings in SmPC and PIL of the products in the EU and UK. In addition, risk management plans only valid for the UK could evolve including additional studies (PASS/PAES) and restrictions for the marketing authorizations. All of these aspects will definitely not improve the situation for the patients and possibly mean a decrease in compliance and hence therapeutic effectiveness. In addition, the employment situation in the effected countries are

negatively impacted due to necessary reorganization measurements of the businesses because of lost sales.

8 Abstract

The United Kingdom (UK) announced to the European Council its intention to withdraw from the European Union (EU) on March 29th 2017 and initated a completely new situation. The timeframe provided in Article 50 of the Treaty on European Union for such processes is 2 years. This process has been since known as Brexit. There is no precedent for this situation, since no Member State has previously decided to leave the EU.

There are a number of financial, logistical and legal implications for marketing authorizations in particular concerning batch release, pharmacovigilance and marketing authorization holder ship.

After Brexit, the MAHs Qualified Person responsible for a medicinal product authorized in the EU needs to be placed in the EU and may not remain in the UK. Similar rules will apply to other key functions like the QPPV. The Pharmacovigilance System Master File of the MAH must also be placed in the territory where the medicinal product is authorized. Currently an implementation period has been laid out to last until December 2020.

The scenario planning technique, a procedure used for trend research, was used to analyze the possible developments. Descriptors, that could affect these developments, were used to define a positive and a negative extreme scenario. Within the rage of the scenarios the most likely scenario was projected that shows that the majority of the descriptors will develop towards the negative extreme scenario. It is expected that regulations and requirements will increase hence increasing necessary efforts for MAHs to adhere to quality, regulatory affairs and pharmacovigilance legislation. MAHs will need to measure the impact of the proposed trend by using the following: GMP recognition, requirements to obtain qualification and accreditation as Qualified Person and QPPV, business critical roles, customer and supplier contracts, workforce continuity planning, staffing investments in order to adhere to requirements, shipping costs, authority fees, MAH resources, MHRA independence, Batch Release efforts and Pharmacovigilance efforts.

MAHs need to evaluate the necessary actions to uphold their status in the UK in relation to the expected turn over and whether the necessary investments remain feasible. It is

difficult to predict the chances and particularly the risks that emerge for the industry from the BREXIT. MAHs could face risks if the UK regulations develop in an even more regulated direction and an even larger gap in reference to EU legislation. In this case, it can be assumed that the majority of MAHs will not maintain their MA in the UK. This of course will have a negative impact on patients in the UK.

Because of the very high financial investments that are necessary, it is essential that the all pharmaceutical companies are well prepared. The most crucial point is that if the pharmaceutical companies cannot adapt their regulatory, safety and quality systems according to the new regulations on time, this will lead to a possible shortage of supply of medicinal products effecting patients and public health. In addition, the employment situation in the effected countries will be negatively impacted due to necessary reorganization measurements of the businesses as a result of lost sales.

9 Zusammenfassung

Am 29 März 2017, entstand eine komplett neue Situation, als das Vereinigte Königreich vor der Europäischen Kommission das Vorhaben eines Austrittes aus der Europäischen Union bekannt gab. Der Zeitrahmen für diesen Austritt, der seitdem als Brexit bezeichnet wird, ist gemäß Artikel 50 des Vertrages der Europäischen Union, maximal 2 Jahre. Das ist ein Präzedenzfall, denn kein Mitgliedsstaat hatte zuvor vor die Europäische Union verlassen.

Es gibt zahlreiche finanzielle, logistische und rechtliche Konsequenzen für Zulassungsinhaber, insbesondere bezüglich Chargenfreigabe, Pharmakovigilanz und Zulassungshaltung. Eine Herausforderung stellt auch die Tatsache dar, dass von EU Zulassungsinhabern bestellte sachkundige Personen sich auch innerhalb der EU befinden müssen und daher nach dem Brexit nicht mehr im Vereingten Königreich ansässig sein dürfen. Zusätzlich muss sich auch der Pharmakovigilanz System Master File in dem Territorium befinden, in dem sich der Zulassungsinhaber befindet. Gegenwärtig wurde eine Implementierungsphase bis Dezember 2020 festgesetzt.

In dieser Masterarbeit wurden mittels der Szenariotechnik, welches ein Verfahren der Trendforschung ist, die möglichen Entwicklungsoptionen berücksichtigt, Anhand von Deskriptoren, die diese Entwicklungen beeinflussen, wurden ein positives und negatives Extremszenario definiert. In der Brandbreite dieser beiden Extremszenarien wurde ein mögliches Entwicklung Szenario projiziert, welches demonstriert, dass sich die meisten Deskriptoren in Richtung des negativen extremen Szenarios entwickeln werden. Es kann erwartet werden, dass Regularien und Vorrausetzungen zunehmen und deshalb werden sich die Bestrebungen der Zulassungsinhaber erhöhen müssen um der Gesetzgebung bezüglich Qualität, Pharmakovigilanz und Zulassung zu entsprechen.

Zulassungsinhaber müssen die Konsequenzen dieses Trends abwägen, insbesondere in Bezug auf die GMP Anrechnung, die Vorrausetzungen um als Sachkundige Person und QPPV tätig zu werden und die Unabhängigkeit der MHRA. Die personellen Investitionen um dem zusätzlichem Aufwand gerecht zu werden und der finanzielle Aufwand für Versandkosten, Gebühren der Behörden müssen berücksichtigt werden ebenso wie die Ressourcen des Zulassungsinhabers in Bezug auf Chargenfreigabe und Pharmakovigilanz.

Zulassungsinhaber müssen die notwendigen Aktionen evaluieren um ihren Status innerhalb des Vereinigten Königreiches beizubehalten und diese in Bezug setzen zum erwarteten Umsatz und dann abwägen ob die Investitionen plausibel sind.

Es ist schwierig die möglichen Chancen und auch die Risiken welche für die Industrie durch den Brexit entstehen vorauszusagen. Das Risiko der Zulassungsinhaber besteht darin, dass möglicherweise die Regularien des Vereinigten Königreiches noch strikter werden und es entsteht dadurch ein immer größerer Unterschied zur EU Gesetzgebung. In so einem Fall, kann man davon ausgehen, dass ein Großteil der EU Zulassungsinhaber ihre Zulassungen im Vereinigten Königreich nicht beibehalten werden.

Aufgrund der notwendigen sehr hohen finanziellen Investitionen, ist es essentiell, dass alle pharmazeutischen Unternehmen gut vorbereitet sind. Kritisch ist sicherlich, dass wenn pharmazeutische Unternehmen nicht rechtzeitig ihre Zulassungs-, Pharmakovigilanz- und Qualitätssysteme den neuen Vorgaben anpassen, wird das zu einer Einschränkung von verfügbaren Arzneimitteln kommen und auch eine negative Auswirkung auf die öffentliche Gesundheit haben, sowie auf die Beschäftigungslage der betroffenen Länder aufgrund von Sanierungsmaßnahmen der Unternehmen durch entgangene Umsätze.

10 Abbreviations

BCP	Business continuity plan
BREXIT	Br(itain) Exit
CA	Competent Authority
CAPs	Centrally Authorized Products (CAPs).
CMDh	Coordination Groups for Mutual Recognition and Decentralized Procedures - human
CMS	Concerned Member State
CPP	Certificate of Pharmaceutical Product
DCP	Decentralized Procedure
EEA	European Economic Area
EEC	European Economic Community
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EMRN	European medicines regulatory network
EU	European Union
GMP	Good manufacturing practice
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MHRA	Medicines & Healthcare products Regulatory Agency
MRA	Mutual Recognition Agreement
MRP	Mutual recognition procedure
NCA	National Competent Authority
OMCL	Official Medicines Control Laboratory

QP	Qualified Person
QPPV	Qualified Person for Pharmacovigilance
PAES	Post authorization efficacy studies
PASS	Post authorization safety studies
PIL	Product Information Leaflet
PSMF	Pharmacovigilance System Master File
RMS	Reference Member State
SmPC	Summary of Product Characteristics
UK	United Kingdom
ROW	Rest of World
TFEU	Treaty of the Functioning of the European Union

11 References

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11.2 Tables and Figures