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Brexit and Impact on Pharmaceutical Industry

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ABSTRACT
The continuing uncertainty around Brexit has caused concern in the pharmaceutical industry and among health care professionals and patients. The exact consequences of Brexit on the pharmaceutical supply chain in the United Kingdom will depend on whether a deal is reached and what it entails, but it is likely to be affected by the withdrawal of the United Kingdom from the European Union. Regulatory issues and delays in supply have the potential to negatively affect the ability of UK residents to receive an adequate and timely supply of necessary medicine. Brexit will mean changes to the established relationships between the UK and the EU covering the development, authorisation and supervision of medicines, as well as trade between the UK and other EU member states. Such changes are likely to have a significant impact on public health in both the UK and the remaining 27 countries of the EU and the non-EU members of the European Economic Area (EU27/EEA). Pharmaceutical companies will have to comply with the new legal requirements associated with the withdrawal, which will not be without cost[1].
KEYWORDS – United Kingdom, Brexit and European Economic Area

I. INTRODUCTION

On 29 March 2017, the United Kingdom (UK) submitted the notification of its intention to withdraw from the European Union (EU). This means that unless a ratified withdrawal agreement establishes another date, all EU primary and secondary law ceases to apply to the United Kingdom from 30 March 2019 at 00:00h (CET) and the UK becomes a 'third country'. Subject to any transitional arrangement in a possible withdrawal agreement, as of this date, the EU rules in the field of medicinal products for human and veterinary use no longer apply to the United Kingdom. [2]

This has, in particular, the following consequences in the different areas of EU law on medicinal products:

• EU law requires that marketing authorisation holders are established in the EU (or European Economic Area (EEA));

• Some activities must be performed in the EU (or EEA), related for example to pharmacovigilance, batch release, quality control etc. As a consequence, marketing authorisation holders may be required to adapt processes and consider changes to the terms of the marketing authorisations of their medicines in order to ensure that they remain valid once the UK leaves the EU

Preparing for the withdrawal is therefore not just a matter for EU and national authorities, but also for private parties. In view of the considerable uncertainties, in particular concerning the content of a possible withdrawal agreement, marketing authorisation holders of centrally authorised medicinal products for human and veterinary use are reminded of legal repercussions, which need to be considered when the United Kingdom becomes a third country.

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Marketing authorisation holders may be required to adapt processes and to consider changes to the terms of the marketing authorisation in order to ensure its continuous validity and exploitation, once the United Kingdom has left the Union. Marketing authorisation holders will need to act sufficiently in advance to avoid

any impact on the continuous supply of medicines for human and veterinary use within the European Union. In particular, the Commission and the European Medicines Agency expect marketing authorisation holders to prepare and proactively screen authorisations they hold for the need for any changes. The necessary transfer or variation requests will need to be submitted in due time, considering the procedural timelines foreseen in the regulatory framework.

II. OVERVIEW

The pharmaceutical supply chain is likely to be affected by Brexit at numerous stages. The United Kingdom is currently a member of the European Medicines Agency (EMA), which facilitates the single market for medicines in the EU. If the United Kingdom leaves with a deal, there will be an important transition period that should prevent large disruptions of medicine supplies. If there is no deal, the United Kingdom will immediately not be subject to EU law or EMA regulations, which could affect supply. The extent of United Kingdom involvement in EU pharmaceutical activities will affect drug production, authorization, regulation, trade, health and safety monitoring, and research.[2]

Depending on the post-Brexit UK-EU relationship, pharmaceutical companies might need separate centres in the United Kingdom and EU to test and release medicines, which could incentivize moving their headquarters from the United Kingdom to the EU, as the EMA already did. The EMA currently approves marketing authorizations for the entire EU, but if the UK Medicines and Health products Regulatory Agency (MHRA) is unwilling to accept EMA decisions, drugs will need to undergo an additional authorization process to reach UK markets. This will likely mean increased costs and delays in medicines becoming available in the United Kingdom and could deter companies from selling their medicines in the UK market altogether. Additionally, if the United Kingdom is unwilling to accept regulatory requirements from other agencies, such as the EMA or the Food and Drugs Administration (FDA) of the United States, a new regulatory system will need to be developed .[3]

Public health Implications

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

• Possible delays in marketing authorisation for medicines;
• The effects on supervision activities and pharmacovigilance, specifically signal detection and the conduct of Post Authorisation Safety Studies (PASS);
• Incident and crisis management;
• Public health threats (such as pandemic influenza);
• Possible medicines shortages;
• The supply of medicines as a result of changes to trade and supply chains. We sought to consider the effects of each of these consequences for the EU27/EEA as well as the UK.

Regulatory Impacts

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

Centrally authorised products

For the products that are currently authorised in the EU (those that received a marketing authorisation via the centralised procedure between 1995 and July 2017): • The effect for the UK is that a transposition into UK law will have to be performed for 978 medicinal products which received a marketing authorisation via the centralised procedure between 1995 and July 2017. • The effect on the EU27/EEA is that the marketing authorisation holder will have to be transferred from a UK holder to a EU27/EEA-based holder for over one third of these products (361; 37%). For the products which will be authorised after the withdrawal of the UK, Scenario 2 could lead to a lack of submissions and delays in submissions of marketing authorisation applications compared to Scenario 1: • The median lag of submission could be 2-3 months (based on existing submission delays in third countries for centrally authorised products containing a new active substance – see Figure 3). Note that this is shorter than other estimates reported in the literature (Campbell 2017; Fahy and Hervey 2017; Gulland 2017a; Gulland 2017b; Hatswell 2017; Tryl 2016); • 5-15% of applications could be submitted more

than a year after the EU27/EEA submission; • Some products might never be authorised in the UK because of lack of any marketing authorisation submission (45% of applications had not been submitted to all three reference countries following submission to the EMA at the time of our analysis7); • The MHRA would face a sudden increase in workload in procedures involving human medicinal products, this increased workload could subsequently increase the assessment timelines

The relocation of EMA to Amsterdam

There have already been doubts about the speed of implementation of some key pieces of approved EU legislation. Now there could be further delays to the enforcement of new laws because of the possible disruption of the transfer of EMA's headquarters. In addition, the agency, which handles the centralized approval of new drugs and variations to their authorizations while also coordinating the regulatory activities of the EU's 28 member states, is also drawing up new guidelines for existing legislation.

Brexit is due to take place at the end of March 2019. But its regulatory effects will start to hit companies from early 2018, particularly those based in the UK or with subsidiaries in the country. After Brexit, the UK will become a non-EU state classified as a "third country" in EU legislation with a legal position in relation to Union rules much the same as other countries outside Europe. The country is likely to assume this new legal status only after the end of a transition period of at least two years starting in April 2019. The availability of a transition period is considered by the industry to be particularly important. "[We and other industry] organizations are of the opinion that the agreement of transitional arrangements after March 2019 will be critical in ensuring there is minimal disruption to patients receiving medicines after the UK leaves the EU," a spokesperson for the European Federation of Pharmaceutical Industries and Associations (EFPIA) told *Pharmaceutical Technology Europe.* [3]

Public health and economic consequences

The extent of Brexit's repercussions on the pharmaceutical and related industries, both in the UK and the remaining EU member states, will depend on the final deal reached in the current UK–EU negotiations on withdrawal and whether a free trade agreement (FTA) is included. A deal is due to be achieved by October 2018 to give the European Parliament and the 27 members states time to approve it. One outcome could be that the UK and its licensing agency, the Medicines and Healthcare products Regulatory Authority (MHRA), will continue to be involved in the EU's medicine approval and other public health activities in much the same way at present.

Under this scenario, Brexit's public health and economic consequences would be "minimal" for both the EU and the UK, according to a report (1) on the public health implications of Brexit, completed in November 2017 by the London-based Office of Health Economics (OHE), a consultancy partly funded by the pharmaceutical industry.

Two other scenarios described by OHE would involve the UK introducing a standalone regulatory system within the context of a UK–EU free trade agreement. In the absence of a free trade agreement, trading between the two would be conducted under the rules of the World Trade Organization (WTO). With both outcomes, there would be mutual recognition agreements (MRA) on good manufacturing practice (GMP) and other regulatory inspections but not of batch release processes.

In the OHE's worst-case scenario, the UK–EU negotiations would breakdown without a deal on public health cooperation or MRAs. Trade between the two would be controlled entirely by WTO rules.

Amidst a lack of legal certitude, UK-based companies and business are having to plan for the possible transfer of market authorizations to legal entities in the EU's remaining 27 member states or for the application for new authorizations, which would be among a number of additional burdens on EMA before and after Brexit.

In order to identify and measure the economic consequences of Brexit from the perspective of pharmaceutical companies we considered costs associated with: • Changes to the supply chain, such as:

- batch testing for products imported into the EU from third countries;
- batch release of products to be distributed and used in the EU;
- new import and export procedures between the EU27/EEA and the UK.

• Post-authorisation procedures and pharmacovigilance, such as:

- the need for a Qualified Person for Pharmacovigilance (QPPV) in both the UK and the EU27/EEA1 ;
- reporting requirements for adverse reactions in the UK and signal detection activities;
- resources for post-authorisation activities and procedures.[4]

Facts about UK's Import and Export

The UK exports an average €65 billion worth of chemical and related products annually, of which 53% go to the EU27/EEA;

• In 2016, the UK exported €15,816 million of pharmaceutical products and imported €7,768 million;

• The UK imports around 54% of its pharmaceuticals from Germany, the Netherlands and Belgium;
• The UK exports 48% of its medicines to three EU countries: Germany, the Netherlands and France;
• The UK has the highest number of sites certified to import pharmaceuticals from third countries (357), ahead of Germany (262);
• The UK is specialised in the manufacturing, importation and batch certification of advanced therapy medicinal products (gene and cell therapies);
• 37% of the active substances processed in the UK are included in the World Health Organization's list of essential medicines

What Does Brexit Mean for EU and UK Regulatory Submissions?

The withdrawal of the United Kingdom from the European Union had many concerns. One of them being Regulatory Submissions. To smoothen the submissions process, the EU and the UK have set up a clear set of rules. Many of them are related to the existing and new marketing authorisation applications (MAAs) for CAPs, DCP and MRP, Batch testing, QP Certification, etc. Let us have a look at what Brexit means for the EU and the UK Regulatory Submissions. Here is a clear-cut Brexit impact summary that has recently been published by a consulting firm.[5]

EU	UK
New Marketing Authorization Applications for Centrally Authorized Products (CAPs)	
• MAH must be present in the EU	• MAH must apply for a separate authorization
New Marketing Authorizations for Mutual Recognition Procedure (MRP)/Decentralized Procedure (DCP)	
• The same process applies to the EU	• MAH must have a separate application
Existing Marketing Authorizations	
• MAH must be located in the EU/EEA • CAPs must have an MAH in the EU • UK (Co-)rapporteurs must be assigned to other EU/EEA member states • In case of MRP/DCP, RMS/CMS cannot be in the UK. If UK is the RMS, it must be transferred to RMS in the EU	• MAH must be located in the UK by the end of 2022 • CAPs are automatically granted authorization for one (01) year to share the baseline data with MHRA • Contact is needed in the UK from Feb 1, 2021
Batch Testing and QP Certification	
• Batch testing must be within the EU/EEA or with a mutual recognition agreement (MRA) country. • QP certification must be within the EU/EEA. From 1 Jan 2022, products exported to Northern Ireland must have re-testing and QP certification in Northern Ireland.	• Batch testing must be within the EU/EEA/MRA country. • QP certification is not if certified by a QP in the EU/EEA • Wholesalers importing from EU/EEA must name an RPi on WDA by 1 Jan 2023.
Batch Testing for Products Manufactured in the EU/EEA	
• Batch testing must be performed within the EU/EEA	• No additional batch testing is required for imports until 1 Jan 2023
Batch Testing for Products Manufactured in a Third Country with no MRA with the EU	
• Batch testing must be performed within the EU/EEA	• Batch testing must be performed within the EU/EEA or the UK • No additional batch testing is required for imports until 1 Jan 2023
Access to Eudravigilance	
• EU can continue reporting to Eudravigilance	• UK will no longer have access to

	Eudravigilance. With UK's new systems, ADRs must be reported to MHRA
GMP and GDP	
• EU's GMP and GDP guidance applies	• The UK will follow EU's GDP and GMP guidance until 1 Jan 2023

III. CONCLUSION

The withdrawal of the UK from the EU will induce legal and regulatory changes both for marketing authorisation holders in the UK and in the EU27/EEA. In particular, companies will have to adapt their procedures or relocate some of their processes to comply with the new legal UK and EU27/EEA requirements for the authorisation and supervision of medicines for human use (for example recruitment of new QPs, relocation of the testing and batch release facilities, modification of the management of the supply chain of the medicines, management of parallel regulatory submissions). A transition period that gives sufficient time for companies to adapt to these important changes is important to avoid aggravating the public health impact of the withdrawal of the UK from the EU. If comprehensive agreements (FTA and MRA) cannot be negotiated, the public health impacts will be felt in terms of reduced availability of medicines in the UK; delays of two to three months or more for marketing authorisation applications to be submitted in the UK; delays of up to five months in signal detection and management for pharmacovigilance; delays in the management of crises and public health threats in the UK and the EU27/EEA, and shortages of medicines in both jurisdictions

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