Brexit at Halfway: Pharma and Medical Devices

APRIL 5, 2018

The object of this Alert is to highlight some practical implications of Brexit for the supply of pharmaceutical products and medical devices in the European Union (EU) and related action items which companies should be considering if they have not done so before.

I. Overall Timing

The United Kingdom (UK) notified its intention to withdraw from the EU pursuant to Article 50 of the Treaty on the Functioning of the European Union on 29 March 2017. Subject to finalisation of the Withdrawal Agreement, under Article 50, the UK's membership of the EU should therefore terminate on 30 March 2019.

On 19 March 2018, the EU and the UK reached an agreement on a transitional arrangement. According to this agreement, the UK commits to remain in the EU Customs Union and retains access to the EU Single Market until 31 December 2020, provided that it abides by EU law.[1]

This should have the effect of deferring the impact of the changes outlined in this Alert from 30 March 2019 to 31 December 2020.

However, the agreement on the transitional period is still subject to ratification. As a result, pharmaceutical and medical devices companies should treat this development cautiously, and already be addressing their post-Brexit solutions.

For the purposes of this Alert, “EU27” refers to the EU without the UK and, by virtue of various measures under the European Economic Area (EEA) Agreement, includes Iceland, Liechtenstein and Norway.

II. Pharmaceutical Products

(a) UK Participation in the EMA

On 2 March 2018, the UK Prime Minister, Theresa May, delivered a speech on the future of the UK's relationship with the EU, calling for the UK to become an associate member of the European Medicines Agency (EMA). Mrs. May stated that the UK would commit to abiding by the rules of the EMA as well as make appropriate financial contributions to the Medicines Agency.

The European Council, however, quickly appeared to reject the possibility of the UK's participation in the EMA by stating that *'the Union will preserve its autonomy as regards its decision-making, which excludes participation of the United Kingdom as a third-country to EU Institutions, agencies or bodies'*.[2] As regards the EMA, this statement is in line with the EU regulation on authorisation and supervision of medicinal products, which does not contain a provision for third states to become members or observers of the EMA.[3]

We will have to see what happens in the future negotiations on the Free Trade Agreement (FTA) on this issue.

In January 2018, the UK Medicines and Healthcare Products Regulatory Agency published an update to pharmaceutical companies on Brexit preparation. The update aims at reassuring pharmaceutical companies that there should be no sudden change to the UK regulatory framework and that pragmatic solutions will be put in place to accommodate companies in implementing any changed requirements.[4]

In any event, despite the transitional period, the EMA will be relocated from London to Amsterdam, the Netherlands on 30 March 2019 at the latest, in line with the timeline of Article 50.

(b) Current To-Dos and Brexit Related Guidance of EMA and CMDh

The EU rules in the field of medicinal products for human and veterinary use will no longer apply to the UK after 30 March 2019. This has, in particular, the following consequences in the different areas of EU law on medicinal products:

- *EU law requires that marketing authorisation (MA) holders are established in the EU. Consequently, MAs for the EU which are currently held by UK entities have to be transferred to EU27 entities.*
- *In addition, a number of activities related to pharmacovigilance or batch release can no longer be performed in the UK, but have to be transferred to entities/persons in the EU27.*

The EMA and the relevant Coordination Groups of national medicines agencies of EU Member States (the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) and the Coordination Group for Mutual Recognition and Decentralised Procedures – Veterinary (CMDv)) have issued several guidance documents on the formal steps that may have to be implemented to avoid any disruptions of supply and sale of medicinal products in the EU.

These guidance documents[5] are updated on a continuous basis and reflect the questions raised by pharmaceutical companies in stakeholder meetings with the EMA. The guidance documents cover a number of possible issues relating to existing MAs, ongoing MA procedures, pharmacovigilance obligations and the supply chain (production, batch release) as a consequence of Brexit.

Generally, the required modifications on the regulatory files/authorisations have to be implemented by 30 March 2019.

Pharmaceutical companies should therefore check whether:

- *UK entities are currently MA holders for products sold in the EU.*
- *Any relevant tasks relating to pharmacovigilance are performed by Qualified Persons for Pharmacovigilance[6] (QPPV) in the UK.*
- *Any relevant tasks related to the supply chain (such as batch release) are performed by Qualified Persons[7] (QP) in the UK.*

If that is the case, companies should implement the required changes in accordance with the EMA/CMDh Guidance. These issues are covered in the sections below.

(c) Centralised Marketing Authorisations

The MA issued under the 'centralised procedure' by the European Commission (EC), following the assessment of the application carried out by the EMA, allows the MA holder to offer its medicinal products throughout the EU on the basis of a single MA. According to Article 2 of Regulation 726/2004[8], the MA holder must be established in the EU.

- *MA holders established in the UK therefore have to transfer their centrally authorised MAs to a legal entity based in the EU27 in order to maintain the validity of such MAs.*

Currently, around 2,400 central MAs and 400 centrally authorised products are held by UK legal entities (multiple MAs can be held per product). These figures account respectively for 17% of all central MAs and 45% of all centrally authorised products in the EU.[9]

According to the EMA Guidance, the transfer of the MA must be fully completed and implemented before 30 March 2019. The EMA expects that implementation periods will exceed six months.[10] A separate transfer application has to be lodged with the EMA for each MA. However, for the purpose of facilitating the large number of transfer applications, the EMA agreed that a combined version of each required supportive document (except product information and, when applicable, mock-ups) can be created, covering all products affected.[11]

- *Similarly, for ongoing MA procedures with the EMA or the filing of new MA applications with the EMA, the applicant has to be changed to an entity based in the EU27 if the applicant is currently a UK entity.*

(d) National Marketing Authorisations

For National Marketing Authorisations (NMA) for medicinal products granted in one, or a number of EU Member States under the so-called Mutual Recognition Procedure (MRP) and/or Decentralised Procedure (DCP), EU law requires that these NMAs must be held by EU-based legal entities.[12]

- *All non-UK NMAs currently held by marketing authorisation holders established in the UK therefore have to be transferred to companies in the EU27 by 30 March 2019.[13]*

For ongoing procedures/applications for NMA, EU law provides that marketing authorisation applicants must be established in the EU.

- *Therefore, for marketing authorisation applications that are expected to receive an NMA in an EU Member State after 30 March 2019, applicants established in the UK will need to*

change to a non-UK applicant established in the EU27.

- *In addition, if the Reference Member State (RMS) in an ongoing DCP or MRP is the UK, applicants need to change the task of the RMS to an agency of a Member State of the EU27. The same applies for already authorised products in which the UK acted as the RMS.*[14]

(e) Pharmacovigilance

According to EU pharmaceutical legislation, the QPPV for authorised medicinal products must reside and carry out his/her tasks in an EU Member State, and the Pharmacovigilance Master File (PSMF) also must be located within the EU.[15]

- *If these tasks are currently fulfilled in the UK, the respective changes on the QPPV and the location of the PSMF have to be notified to the authorities.*

(f) Supply chain, including batch release/control

Brexit may also impact the supply chain. EU law requires that all batch release/control activities have to be performed by a QP within the EU.[16] Furthermore, active substances or finished products manufactured in the UK will be considered imported medical products under EU law as of the withdrawal date.

Each batch of a finished product manufactured in the EU must be certified by a QP within the EU before being placed on the market. For products imported into the EU from the UK, MA holders therefore have to specify an authorised importer established in the EU, must obtain an import authorisation.[17] Furthermore, such imported products manufactured in the UK have to undergo batch control at a site in the EU.

- *If the QP and/or the site for batch release/control is currently located in the UK, this has to be changed to a location established in the EU27 by submitting corresponding variations of the MA documents to the EMA (in case of centrally authorised products) or the respective national authorities in EU27 Member States (in case of national marketing authorisations).*

III. Medical Devices

(a) Current To-Dos–Authorised Representatives

Under EU law, medical devices manufacturers offering their devices in the EU must either (a) have a physical location in the EU, or (b) appoint an Authorised Representative (AR) established within the EU. As of 30 March 2019, unless something more specific is agreed in the FTA, it appears that all the ARs established in the UK will no longer be operative.

If that is the case, the medical devices companies will no longer be able to rely on their ARs established in the UK and, as a result, must implement certain measures to continue selling their medical devices in the EU27 after Brexit:

- *UK medical devices manufacturers have to appoint an AR established in one of the EU27 Member States.*

- *Medical devices manufacturers from 'third countries' that currently use an AR established in the UK also have to appoint a new AR established in one of the EU27 Member States.*
- *Should the UK and the EU27 both require their own ARs, non-UK-based manufacturers would have to appoint an AR in the UK also.*

(b) Current To-Dos–Notified Bodies and CE Markings

As of 30 March 2019, unless the future FTA provides otherwise, the "notified bodies"[18] located in the UK will cease to be authorised to conduct conformity assessments and to affix CE markings. As a consequence, all the CE markings affixed by the UK notified bodies for medical devices would become void.

Companies that currently hold such certificates or that are planning to apply for a new certification have to take the necessary steps to ensure that they can continue selling their products within the EU27:

- Medical devices manufacturers working with UK notified bodies have to:

(i) either appoint a new notified body established in one of the EU27 Member States, which would require a new conformity assessment to permit the continued CE marking of their medical devices in the EU27; or

(ii) if possible, transfer the CE marking from a UK notified body to an EU27 subsidiary through the same standards body, as this should be a less burdensome alternative and would not require the applicant company to undergo the same full certification process a second time.

- Medical devices manufacturers looking to obtain an EU certification for a new product have to:

(i) if possible, use one of the EU27 subsidiaries of the UK parent notified body, because, in principle, it should be simpler to apply for a second certification in the UK by using the same standards body; or

(ii) use any EU27 notified body and appoint a new notified body within the UK for a second certification to cover the UK market.

Medical devices manufacturers already certified by an EU27 notified body will have to apply for a second certification in the UK.

(c) Status of the UK Notified Bodies

In the UK, there are currently five notified bodies.[19] It is reported that these bodies together perform more than half of all conformity assessments for medical devices in the EU market.[20]

Most of the UK's notified bodies are already implementing various strategies to accommodate medical devices manufacturers in this transition, for example, by formally applying for designation as medical devices notified bodies in the EU27, or negotiating a retention of their capabilities and capacities as medical devices notified bodies in the UK after Brexit.

Some designated organisations, even outside the EU, are recognised as notified bodies for the purposes of medical devices certification (e.g. in Iceland, Liechtenstein and Norway, under the EEA agreement; in Switzerland and Australia through Mutual Recognition Agreements).

It is too early yet to predict with certainty what the UK's position will be, but the EC's Notice to Stakeholders of 22 January 2018 presents a scenario whereby if no action is taken to ensure continuation for conformity assessment procedures and notified bodies in the UK, the UK notified bodies would lose their status as EU notified bodies and would be removed from the EC's information system on notified organisations.[21]

In addition, the draft Withdrawal Agreement between the EU and the UK requires both the UK and the EU to ensure that, upon request by the certificate holders, their respective notified bodies will provide information about the holder's certification activities to another notified body without undue delay. This requirement also points to the scenario in which the companies will be required to have separate conformity certificates in the UK and the EU27.

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[1] Article 122 of 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 of 19 March 2018.

[2] European Council (Art. 50) guidelines on the framework for the future EU-UK relationship, 23 March 2018, para. 7.

[3] Under Article 77 of Regulation (EC) No 726/2004, only the representatives of international organisation may participate as observers in the work of the EMA if conditions determined by the European Commission are met.

[4] MHRA update to pharmaceutical companies on exit preparations, 16 January 2018.

[5] European Commission/EMA, Practical guidance for procedures related to Brexit for medicinal products for human and veterinary use within the framework of the centralised procedure, EMA/478309/2017 Rev. 1, 29 January 2018 (“EMA Guidance”) and CMDh, Questions and answers related to the United Kingdom's withdrawal from the European Union with regard to national authorised medicinal products for human use, CMDh/361/2017, Rev.1, 1 December 2017 (“CMDh Guidance”).

[6] A Qualified Person for Pharmacovigilance is an individual, usually an employee of a pharmaceutical company, who is personally responsible for the safety of the human pharmaceutical products marketed by that company in the EU for pharmacovigilance or batch release/control.

[7] A Qualified Person is responsible for compliance with pharmaceutical regulations regarding manufacturing, testing and release.

[8] Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

[9] BREXIT EFPIA survey results of 8 November 2017, European Federation of Pharmaceutical Industries and Associations.

[10] No. 4 of EMA Guidance.

[11] No. 4c of EMA Guidance.

[12] Article 8(2) of Directive 2001/83/EC.

[13] No. 1 of CMDh Guidance.

[14] No. 1b of CMDh Guidance.

[15] Article 8 of Directive 2001/83/EC (QPPV) and Commission Implementing Regulation (EU) No 520/2012.

[16] Articles 51(1) (batch release) and 51(1)(b) (batch control after importation of products into the EEA) of Directive 2001/83/EC.

[17] Articles 40(3), 41 and 42 of Directive 2001/83/EC.

[18] In EU law, a “notified body” is an organisation designated by an EU country to assess the conformity of medical devices before being placed on the market. These bodies carry out tasks related to conformity assessment procedures set out in the applicable legislation, when a third party is required.

[19] British Standards Institution, SGS United Kingdom Ltd., Lloyd's Register Quality Assurance Ltd., AMTAC Certification Services Ltd. and UL International (UK) Ltd.

[20] Brexit and the impact on patient access to medicines and medical technologies, Brexit Health Alliance, Briefing of January 2018.

[21] European Commission Notice to Stakeholders Withdrawal of the United Kingdom and EU Rules in the Field of Industrial Products, DG for Internal Market, Industry, Entrepreneurship and SMEs, 22 January 2018.

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