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BREXIT: IMPLICATIONS FOR LIFE SCIENCES REGULATIONS AND INFRASTRUCTURES

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This article considers the legal implications of Brexit for the life sciences sector.

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Although we do not yet know the timing for the formal exit negotiations under Article 50 of the Lisbon Treaty, companies in this sector should nevertheless begin to consider the potential implications of Brexit for their operations in the UK and elsewhere in the EU. This article discusses the possible impact on pharmaceutical and medical device regulations and associated infrastructures in the context of three possible post-Brexit models (*see box, Post-Brexit models*).

EU/EEA PHARMACEUTICALS REGIME

Pharmaceutical companies must hold a marketing authorisation before they can place a medicinal product on the European Economic Area (EEA) market. Applicants for, and holders of, marketing authorisations must be established in the EEA. The EU operates a range of review and approval procedures for companies wishing to place a medicinal product on the market in more than one EEA member state. These include the centralised procedure, where the European Commission (the Commission) grants a single marketing authorisation valid throughout the EU (and by extension in the three EEA member states), following review by the Committee for Medicinal Products for Human Use (CHMP) within the European Medicines Agency (EMA). There are also the mutual recognition and decentralised procedures in accordance with which one member state, known as the reference member state (RMS), takes the lead in the review of applications, and other so-called concerned member states (CMSs) are expected to recognise the RMS determination.

EU law also regulates the pharmaceutical supply chain by requiring that all importers and manufacturers of medicinal products in the EEA must have an appropriate authorisation granted by the relevant national competent authority. Distributors of medicines must also hold equivalent authorisations.

Finally, the holder of a clinical trial authorisation must either be established in the EEA or have designated a legal representative there, and sponsors of orphan drug designations must also be established in the EEA.

General implications of Brexit on pharmaceuticals

Whatever the post-Brexit arrangements, the UK will lose influence in EU legislative, policy and regulatory spheres. It is also almost inevitable that the EMA will leave London and a number of member states have already expressed an interest in hosting the EMA.

The best that the UK Medicines and Healthcare Products Regulatory Agency (MHRA) can realistically hope for is to participate as an observer in key EU regulatory committees and procedures, in which it will most likely lose the ability to vote. While the UK may continue to act as an RMS in the mutual recognition and decentralised procedures, there will inevitably be a reduction in its prestige and influence.

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POST-BREXIT MODELS

The European Economic Area model

Norway, Iceland and Liechtenstein have all signed the EEA Agreement with the EU and operate as EEA member states. They can participate fully in the EU internal market because the EEA Agreement requires that they implement the bulk of EU free movement laws. However, they must accept free movement of goods, services, capital and persons and contribute financially to the EU. A downside is that EEA member states lack influence when compared with the EU equivalents. The current EEA member states only have "observer status" in EU regulatory committees and procedures; they do not have Members of the European Parliament and have no vote in the Council of the European Union.

The European Free Trade Association model

Switzerland is the only EFTA member state that is not also in the EEA. The lack of the wide-ranging EEA Agreement means that the Swiss government must enter into bilateral free trade relations with the EU and EEA on a case-by-case basis. This gives Switzerland some flexibility to cherry pick policies, but some issues, for example, in relation to border control, have proven to be controversial.

The World Trade Organisation model

The UK's relationships with the WTO are all currently via the EU, which negotiates international trade relationships on behalf of the member states. If the UK wished to negotiate ad hoc trade agreements with the EU, EEA and other jurisdictions within the WTO framework, it would first need to enter into a multilateral trade relationship with the WTO and then proceed to negotiate separate bilateral trade agreements with countries of its choosing. There are many possible options including negotiation of a comprehensive economic trade agreements (CETA), such as the CETA between Canada and the EU, or more standard free trade agreements, such as that between the EU and Turkey.

The UK is also likely to lose access to a significant amount of EU funding that is an important contributor to academic and other research in the UK. Any attempt by the UK to limit cross-border movement will make collaborative research more challenging.

One area in which we do not expect to see significant change is the pricing and reimbursement of pharmaceuticals in the UK. This is because the EU lacks competence to regulate the structure and delivery of health care at the member state level.

Below are more detailed implications for the industry in the context of three different possible post-Brexit outcomes which we have selected because they have features that make them particularly relevant to pharmaceuticals and medical devices (*see box, Post-Brexit models*).

EEA model. Under the EEA Agreement, the UK would be required to implement all current and future EU pharmaceutical laws. As a result, UK companies would continue to be able to apply for and hold marketing authorisations, clinical trial authorisations and orphan designations. They would also have full access to EU regulatory procedures, such as the centralised procedure. Key individuals with residency requirements, such as the qualified person for pharmacovigilance (QPPV), would be able to remain in the UK.

The supply chain would also be unaffected, as UK importers, manufacturers and distributors would still be able to supply products throughout the EEA.

There would, however, be a technical change to the way in which centralised marketing authorisations take effect in the UK. Rather than the Commission decision granting the EU marketing authorisation automatically applying in the UK, the UK would have to take steps to give effect to it, for example, by granting a national marketing authorisation to mirror the EU approval.

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European Free Trade Association (EFTA) model. The EU pharmaceutical rules would no longer apply unless there is a bilateral treaty to that effect. UK companies would no longer be able to apply for or hold EEA marketing authorisations, clinical trial authorisations or orphan designations, or participate in EU regulatory procedures.

The outcome would be similar for importers, manufacturers and distributors in the UK, which would not automatically be able to supply products into the EEA. Although Switzerland has a mutual recognition agreement with the EU under which the EU recognises the quality and compliance of products manufactured in Swiss facilities and vice versa, they must still be imported into the EU by an authorised importer and released by an appropriate qualified person (QP).

Subject to a bilateral treaty to the contrary, individuals with EU residency requirements, such as the QPPV, could not be based in the UK. The arrangements for the pharmacovigilance database and pharmacovigilance system master file may also need to be adjusted so that they are accessible in the EEA.

World Trade Organisation (WTO) model. This model would lead to even greater separation from the EU pharmaceutical regulatory scheme. Subject to any bilateral trade agreements, UK regulators would approve and supervise products for the UK to standards that the UK would define, taking into account key existing global standards. There are some bilateral agreements governing aspects of pharmaceutical regulation, including the CETA with Canada under which the EU and Canada will reciprocally recognise the results of Good Manufacturing Practice inspections and certificates of compliance.

Next steps

While we wait for the proposals for the Brexit negotiations, companies in this sector should carry out an initial regulatory mapping exercise, including asking the following questions:

- Do UK entities hold marketing authorisations or are they applicants for marketing authorisations? Do UK entities hold clinical trial authorisations or are they legal representatives of non-EEA sponsors?
- Are UK entities participants in the company's EEA supply chain?
- Do UK entities sponsor orphan drug designations?
- Do UK entities house key individuals such as the QPPV?
- Do UK entities support key functions, such as pharmacovigilance and regulatory?

EU MEDICAL DEVICE REGULATION AND INFRASTRUCTURES

The nature of the EU medical device CE-marking regime mean that Brexit will most likely have less impact on medical devices than pharmaceuticals because there is no government pre-market review and approval of devices. Manufacturers either self-assess and declare conformity of their products with the medical device rules or rely on notified bodies to conduct conformity assessment and issue certificates of conformity.

There is no requirement that the manufacturer responsible for CE-marking a medical device and placing it on the market or putting it into service in the EEA must be established in the EEA. Non-EEA manufacturers need only designate an EEA authorised representative. Manufacturers are however, required to maintain a technical file for their products within the EEA and make it available to the authorities on request.

Manufacturers conducting clinical investigations of medical devices also do not need to be established in the EEA to submit appropriate notifications. In addition, there is no EU regulation of the medical device supply chain, and manufacturers have flexibility to define and operate quality systems appropriate for their devices.

The medical device regulations that the EU recently agreed will not affect these fundamental principles.

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General implications of Brexit on medical devices

Whatever the post-Brexit arrangements, the UK will lose some influence over EU legislative, policy and regulatory procedures. However, this and its impact on MHRA prestige and influence will be lower than in the pharmaceutical context because there is little multi-jurisdictional review and oversight of medical devices. Rather, national competent authorities focus on post-market surveillance of devices marketed in their jurisdictions.

As above, there may be a loss of EU funding for research, but pricing, reimbursement and the delivery of healthcare will most likely be unaffected.

EEA model. Since signing the EEA Agreement would require that the UK implements all current and future EU device laws, this model for Brexit would have very little impact on the operations of device companies in the UK. They would still be able to participate in the EU medical device regime and act as manufacturers or authorised representatives. UK notified bodies would be able to continue to certify the conformity of medical devices and device quality systems. The new "person responsible for regulatory compliance" required by the forthcoming regulations could also remain in the UK.

EFTA model. Without the extremely broad EEA Agreement, EU medical device rules would no longer apply unless there is a bilateral treaty between the UK and the EU/EEA to that effect. Switzerland has entered into such a mutual recognition agreement for medical devices under which it has implemented all the EU medical device directives and recognises conformity assessment and CE-marking of medical devices in the EEA.

The result is that medical devices lawfully sold in the EEA may also be sold in Switzerland and vice versa. If the UK adopts a similar approach the outcome would be very similar to the analysis under the EEA model. UK manufacturers would not need to designate an authorised representative in the EEA and could supply lawfully CE-marked devices into the EEA. The UK might also enter into similar separate agreements with Switzerland.

WTO model. Unless the UK agrees a free trade agreement to the contrary, the MHRA would regulate medical devices for the UK alone to UK standards, again subject to international standards adopted by the UK. UK manufacturers would need to comply separately with EU device rules, including designation of an authorised representative (and responsible person when the regulations take effect) and maintain technical documentation in the EEA.

We consider it unlikely that the UK would disengage fully from the EU regulatory scheme, however, and we may see some mutual recognition of conformity assessments conducted by notified bodies, as is the case with the EU-Turkey free trade agreement.

Next steps

Companies in this sector need not take action at this stage but they should carry out an initial mapping exercise to assess whether:

- UK entities act as the legal manufacturer of the company's medical devices and, consequentially, apply the CE-mark to the products.
- UK entities act as the authorised representatives of non-EEA manufacturers of medical devices.
- UK entities hold the technical documentation supporting the CE-marking of the company's medical devices.
- UK entities have made pre-launch registrations of devices, either as manufacturers or authorised representatives of non-EEA manufacturers.
- UK-based notified bodies have been involved in the CE-marking process of the company's medical devices.

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For more Brexit-related coverage on Practical Law please see Brexit: the legal implications (http://uk.practicallaw.com/country/eu-referendum).

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