Hogan Lovells

Brexit: first aid for Pharma

Brexit, if and when it happens, may have a substantial impact on the UK pharmaceutical industry. Although related issues will also have an impact upon many aspects of that industry, this note focuses on the key regulatory implications.

"First Aid for Pharma" focuses on UK pharmaceutical companies that wish to continue to operate within the EU structure in a post-Brexit world. It examines the potential impact of Brexit, if and when it happens, on the following areas:

1. Marketing Authorization
2. Clinical Trials
3. Data Privacy

1. Marketing Authorization

Will EU marketing authorizations held by UK pharmaceutical companies continue to be valid? What steps need to be taken to ensure their on-going validity?

1.1. Establishment in the EU

Article 8(2) of Directive 2001/83/EC on the community code relating to medicinal products for human use (the "Community Code") provides that:

"*a marketing authorization may only be granted to an applicant established in the Community*".

If and when the UK leaves the EU, and depending upon the exact terms of the UK's withdrawal, UK pharmaceutical companies are likely to no longer have an establishment within the EU at which a valid marketing authorization can be held. This raises the possibility that UK companies may no longer be permitted to continue to market their medicinal products in the EU, post-Brexit. It would, in such circumstances, be necessary for these companies to seek a valid EU marketing authorization.

Two alternatives may be available to allow UK pharmaceutical companies to continue to market their medicinal products in the EU, post-Brexit:

- Establishment of an entity in another EU Member State, to which the marketing authorization is transferred; or
- Entry into a licensing agreement with a third party that is established in another EU Member State, to which the marketing authorization would be transferred.

The transfer of centralized marketing authorizations is governed by the provisions of Commission Regulation (EC) No 1234/2008. A related application for transfer is submitted to the European Medicines Agency (EMA). This must be accompanied by a number of documents specified in the Regulation, including:

- proof of establishment of the transferee in the EEA;
- the related agreement between the parties;
- identification of the Qualified Person for Pharmacovigilance (QPPV) and the Qualified Person (QP) for batch control; and
- the Summary of Product Characteristics (SmPC) for the product.

A final decision on the request for transfer will be made by the European Commission.

National marketing authorizations granted via the decentralized procedure or mutual recognition procedure must be transferred in

accordance with the national laws of the EU Member States.

1.2. Marketing authorizations granted by the MHRA

During the 2014/2015 period, the UK (acting through the Medicines & Healthcare Products Regulatory Agency - MHRA) was the preferred Reference Member State responsible for 45% of all decentralized procedures in which the UK was involved. If and when the UK leaves the EU, it is unlikely that the MHRA will still be a recognized authority competent to grant marketing authorizations within the decentralized and mutual recognition procedures. This may give rise to questions concerning the on-going validity of both the marketing authorization granted by the MHRA pre-Brexit and the related authorizations and mutual recognitions by other EU Member States.

The MHRA also had the highest number of Rapporteur/Co-Rapporteur appointments for the scientific evaluation of marketing authorizations granted via the centralized procedure during the 2014/15 reporting period. The Rapporteur remains actively involved in post-authorization activities, including the processing of extensions, variations and pharmacovigilance. Departure by the UK from the EU may give rise to, at least, confusion. This confusion could arise particularly concerning post-marketing elements of centralized marketing authorizations granted on the basis of an evaluation by the MHRA, and for which the MHRA remains the Rapporteur.

Finally, marketing authorizations granted either through the centralized procedure or by the competent authorities of other EU Member States, might not be recognized by the UK, post-Brexit. This would mean that pharmaceutical companies may be required to obtain marketing authorizations from both the UK and the EU, if they wish to continue to market medicinal products in both territories.

1.3. Renewals

Marketing authorizations are valid for five years, after which an application for renewal for an unlimited period can be made. When considering an application for renewal under the centralized procedure, the EMA will liaise with the Rapporteur. Similarly, the Reference Member State, acting through its competent authority, plays an active role in the renewal process under the decentralized and mutual recognition procedures.

It, therefore, remains to be seen whether the MHRA will have the power to renew or vary existing EU marketing authorizations, post-Brexit, and to what effect. This concern may not just be limited to renewals occurring after the UK leaves the EU. Marketing authorizations held by UK companies that come up for renewal in the period between initiation of the Article 50 process and the departure by the UK from the EU should in principle be renewed indefinitely. There is nothing in the existing legislation permitting limited term renewals.

1.4. Manufacturing authorizations

Article 40 of the Community Code requires EU Member States to ensure that the manufacture of medicinal products within their territory, and imports of medicinal products from third countries is subject to the holding of a manufacturing authorization by the manufacturer. These authorizations are a prerequisite to obtaining marketing authorizations.

Manufacturing certificates are granted by the competent authorities of the EU Member States, on the basis of their national rules. These are, however, an important element of an application for marketing authorization, whether through the centralized procedure, the decentralized procedure or through the mutual recognition. If and when the UK decides to leave the EU, marketing authorization holders with manufacturing sites that have been certified by the MHRA in the UK, or in third countries, may

be required to undergo new Good Manufacturing Practice (GMP) inspections and related manufacturing certificates issued by another competent authority in the EU.

1.5. Pharmacovigilance

Marketing authorization holders for medicinal products in the EU are required to appoint at least one qualified person responsible for pharmacovigilance. This person must reside and operate in the EU, and must be available to the marketing authorization holder on a permanent and continuous basis. UK pharmaceutical companies that choose to transfer their marketing authorization to an entity established in the EU must, therefore, ensure that such a person is permanently based at the EU establishment at all times in order to fulfil this role.

Marketing authorization holders are required to conduct pharmacovigilance activities to ensure the continued safety of medicinal products and efficient detection of new and emerging safety concerns. Pharmaceutical companies established in the UK that are no longer holders of valid EU marketing authorizations will no longer be required to comply with such pharmacovigilance obligations. This raises questions as to who will be responsible for the pharmacovigilance obligations related to products still in circulation in the EU or with a remaining shelf life after the UK has left the EU.

UK regulations relating to pharmacovigilance will apply to medicinal products marketed in the UK. It cannot be assured that the pharmacovigilance obligations imposed on pharmaceutical companies marketing medicinal products in both the EU and the UK will not, in the future, significantly diverge.

2. Clinical Trials

2.1. Validity of UK clinical trial data

Applications for marketing authorization for medicinal products must be supported by clinical trials that have been carried out in accordance with EU provisions governing the protection of clinical trial subjects, such as the requirement to obtain written informed consent from trial subjects (or their legal representative), as well as minimum requirements to ensure patient safety.

Data from clinical trials conducted in third countries submitted in support of applications for marketing authorization in the EU must be accompanied by a statement that they were carried out in compliance with EU requirements related to the protection and safety of trial subjects. If and when the UK leaves the EU, clinical trials carried out in the UK might no longer be regulated by EU provisions relating to the clinical trial conduct.

This raises questions concerning the validity of clinical data generated in clinical trials conducted in the UK, both pre and post the UK departure from the EU to support applications for marketing authorization for a medicinal product, whether through the centralized procedure, the decentralized procedure or through the mutual recognition.

For clinical trials that are currently on-going in the UK, and which will terminate before the UK leaves the EU (if, indeed, the UK does leave the EU), it would appear likely (although not certain) that such clinical trial data will continue to be valid for the purposes of applying for EU marketing authorizations in the future. This is because they will have been conducted in accordance with EU law applicable at the time.

For UK trials that begin before the UK leaves the EU (if, indeed, the UK does leave the EU) but continue after this period, as well as trials conducted post-Brexit in accordance with UK law, it is not known whether these will be valid and accepted by the authorities in the EU in support of an application for marketing authorization. Similarly, the informed consent provided by clinical trial subjects under EU provisions may not continue to be valid once the

clinical trial is effectively no longer being carried out on the basis of EU law.

Sponsors of trials conducted in the EU that are established in the UK will, following the departure of the UK from the EU, also need to appoint a legal representative in the EU in accordance with Article 19 of the Clinical Trials Directive (2001/20/EC).

2.2. New Clinical Trials Regulation

A new Clinical Trials Regulation entered into force on 16 June 2014, and is due to apply across the EU in the near future. It is uncertain whether the provisions of this new Regulation will be applied in the UK. Sponsors will be required to ensure that clinical trials conducted in the UK which are intended to support an application for marketing authorization in the EU comply with the EU provisions in force, at least when the trial was conducted and potentially, at the time that the application for marketing authorization is submitted.

The new Clinical Trials Regulation is intended to streamline applications for authorization of clinical trials conducted in the EU through the introduction of a single, harmonized initial assessment procedure. This procedure will permit sponsors of clinical trials to submit a single application to a reporting EU Member State through an online EU Portal. This authorization will be recognized by the Competent Authorities of all other EU Member States in which the clinical trials will be conducted. If the UK leaves the EU, UK clinical trial sites may no longer benefit from this multi-center approval process. UK sponsors may need to submit authorizations for approval through both the UK clinical trial authorization system and that in the EU.

3. Data privacy

3.1. Clinical trials conducted in the EU: validity of the informed consent provided by study subjects

3.1.1. Transfer of study subject data to the UK

Article 2 of the Clinical Trials Directive (2001/20/EC) provides that the informed consent to participation in a clinical trial must be given by the study subject after being duly informed of the implications of such participation. The information to be provided to the study subject includes information concerning the processing and transfer of their personal data.

In the context of clinical trials conducted in the EU that are on-going if and when the UK leaves the EU, the informed consent already signed by the study subject may need to be revised for the purposes of permitting the transfer of the study subject's personal data to the UK.

If and when the UK leaves the EU, the UK will become a "third-country" for the purposes of the application of the Data Protection Directive. Article 25.1 of the Data Protection Directive prohibits the transfer of personal data outside the EU to countries that do not ensure an adequate level of data protection.

It may be anticipated that the UK will be required to undergo an "adequacy assessment" carried out by the European Commission, for the purposes of the application of the Data Protection Directive. The result of the European Commission assessment may depend on the nature of the data protection legislation that will be in force in the UK at that time and on whether the UK chooses to implement the new EU General Data Protection Regulation, which will enter into force on 25 May 2018. Pending the related decision of the European Commission, or in the case of a negative decision by the European Commission, UK pharmaceutical companies will be required to

comply with the requirements provided by EU law for the transfer of personal data to third countries.

3.1.2. Options for transferring personal data to third countries

Article 26 of the Data Protection Directive establishes exceptions to the prohibition on transfer of personal data to third countries which are considered by the European Commission not to ensure an adequate level of protection. The following alternatives are possible:

- the individual's unambiguous prior written consent to the transfer of their personal data to the third country;
- data transfer agreements, based on the standard contractual clauses adopted by the European Commission; and
- Binding Corporate Rules concluded between the EU and UK entities transferring the data. These binding corporate rules are internal codes of conduct, defining a company's global policy with regard to the international transfer of personal data between entities within the same corporate group. Binding Corporate Rules should comply with the EU General Data Protection Regulation because the UK entities of companies will need to meet EU standards in order to receive data originating from the EU.

Given the options described above, the informed consent given by study subjects, particularly in clinical trials that are on-going if and when the UK leaves the EU, may not be adequate if this does not include their unambiguous prior written consent to the transfer of personal data to the UK or if, in the alternative, the transfer is not based on standard contractual clauses or Binding Corporate Rules.

3.2. Clinical trials conducted in the EU: designation of a Data Protection Representative

Article 4.2 of the Data Protection Directive provides that when a data controller is not established within the territory of the EU, it must designate a Data Protection Representative established in the territory of each EU Member State in which data processing activities are carried out.

The sponsor of a clinical trial determines the purposes for which the study subjects' data are processed and is commonly considered the data controller.

If a UK pharmaceutical company is the sponsor of a clinical trial conducted in the EU, it will be required to designate a Data Protection Representative in each EU Member State where there is a clinical trial site and where the personal data of the patients are processed.

This essentially means that UK companies would be required to appoint a Data Protection Representative in each EU Member State in which a trial site is established.

3.3. Clinical trials conducted with study subject in the UK

If and when the UK leaves the EU, trial subjects in the UK will be subject to a new set of data protection laws. These may, particularly in on-going clinical trials, differ from those referred to in the informed consent signed by the study subjects at the beginning of the trial.

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