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How A No-Deal Brexit Would Affect Life Sciences Cos.

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There are now fewer than three months to go until the United Kingdom's exit from the European Union on March 29, 2019. On Jan. 15, 2019, the U.K. government rejected the provisional deal proposed by the prime minister and accepted by the EU which would have offered terms for Brexit and future interactions between the U.K. and the EU following the withdrawal date. Unless the EU and the U.K. agree to an alternative deal, the withdrawal date is delayed or Article 50 is revoked, all EU primary and secondary law will cease to apply to the U.K. with effect from the withdrawal date, and the U.K. will become a "third country" for the purposes of EU legislation. Under this no-deal Brexit scenario, all provisions of EU law relating to EU member states will no longer apply to the U.K., with potentially chaotic results for the life sciences industry.

In particular, the impact on marketing authorizations could be highly disruptive. The marketing authorization holder, or MAH, of a marketing authorization approved via the European Medicines Agency's centralized approval procedure (each a CMA) must be established in the European Economic Area. Following the withdrawal date, the U.K. will no longer be part of the EEA, so any CMA held by a U.K. MAH will need to be transferred to an entity within the EEA prior to the withdrawal date. If not, it will be unlawful for the relevant CMA-approved product to be placed on the market in the EU. The EMA follows a 30-day timeline from submission of a CMA transfer application to finalization of the EMA's transfer opinion. However, after the transfer opinion is issued, the European Commission must deliver its decision on the transfer before it becomes effective, a process which generally takes between two and three months, following which product labeling must be updated and implemented. To the extent that a CMA transfer application is not already underway, it will be too late to transfer such CMA to an EU MAH before the withdrawal date and avoid disruption to supply, even where bridging stock will be used to build supply in markets as a contingency measure.

In the EMA's "Report on EMA industry survey on Brexit Preparedness" published in July 2018 in response to a survey of more than 180 MAHs of 694 human and veterinary CMA-approved products with connections to the U.K., the EMA reported that 400 medicines required a transfer of CMA from a U.K. MAH to an EU MAH. The EMA further reported that 6 percent of respondents to its survey indicated that they expected to miss the withdrawal date deadline for submission of CMA transfer applications. Notably, a large

number of submissions are expected in Q1 2019. The centralized approval procedure is compulsory for: (a) products derived from biotechnology, (b) orphan medicinal products, (c) advance-therapy medicines, and (d) medicines containing a new active substance intended for the treatment of AIDS or HIV, cancer, neurodegenerative disorders, diabetes, auto-immune and other immune dysfunctions and viral diseases, and is optional for all other products containing a new active substance that are a significant therapeutic, scientific or technical innovation and whose authorization would be in the interest of public health at EU level. Given the large number of products subject to the centralized marketing authorization procedure, the failure to transfer CMAs in advance of the withdrawal date is likely to significantly adversely affect patients in the U.K. and the EU for a period of time following the withdrawal date.

Valid CMAs (i.e. held by an EU MAH on the withdrawal date) will be automatically converted into national U.K. marketing authorizations, or U.K. MAs, on the withdrawal date, so CMA-approved medicines will still be lawfully capable of sale in the U.K. following the withdrawal date, unless the relevant MAH has opted out of such conversion. However, given that a CMA will cease to be valid if the transfer of the CMA from a U.K. MAH to an EU MAH is not completed prior to the withdrawal date, this conversion process will not permit sale in the U.K. if the MAH transfer is not completed on time.

What Does a No-Deal Brexit Mean?

In terms of U.K. rules, the U.K.'s European Union (Withdrawal) Act 2018 converts all EU laws that apply to the U.K. at the withdrawal date into U.K. national law, with such amendments as are necessary to make the rules work when applied to the U.K. only.

While U.K. national law will mirror existing EU laws, the EU is not required to comply with its obligations under those existing EU laws as applied to the U.K. if reflected only under U.K. national law. In addition, the EU (Withdrawal) Act will mirror only EU laws in existence at the withdrawal date — not future EU laws. The U.K. government has confirmed that it will comply with all key elements of the Medical Devices Regulation and the In-Vitro Diagnostic Regulations (which will apply in the EU from May 2020 and 2022, respectively), though which elements the U.K. government considers "key" remain unclear. The U.K. government has also indicated its intention to align with the new EU Clinical Trials Regulation, which will replace the existing EU clinical trials regime will not be in force on the withdrawal date and will not therefore be incorporated automatically into U.K. law. However, the relevant legislation and approvals for the CTR have not yet been drafted, so it is unclear what the U.K. government's intentions will mean in practice.

In addition, the EMA will cease to have jurisdiction with respect to medicines for the U.K. market following the withdrawal date. Therefore the U.K. Medicines and Healthcare Products Regulatory Agency will take on the activities currently handled by the EMA with respect to medicines for the U.K. market.

Below are additional key disruptions that life sciences companies may face following a no-deal Brexit, depending on the status of their contingency planning.

Importation of U.K.-Manufactured Products Into the EEA

In the event of a no-deal Brexit, all finished products, active substances and investigational medicinal products manufactured in the U.K. will be considered imports from a third country into the EU. Third

countries that import products into the EU must comply with a number of additional regulatory hurdles over and above those an EEA manufacturer faces. In relation to finished products, these hurdles include:

- Obtaining additional importation authorizations;
- Appointing an authorized importer;
- Setting up EEA-based batch control and batch release sites;
- Undertaking a full qualitative and quantitative analysis of each production batch upon importation into the EEA.

Similar requirements apply in respect of active substances and investigational medicinal products, all of which potentially add cost, time and complexity to the supply chain for products offered for sale in the EU.

Changes to EU and U.K. Approvals

In addition to CMAs, other specific EU rights/authorizations need to be transferred prior to the withdrawal date or obtained following the withdrawal date so that they continue to be held by entities established in the EEA. These rights/authorizations include:

Applications for CMAs

In order for a CMA to be granted after the withdrawal date, the applicant must be established in the EEA, so any pending CMA applications will need to be transferred to an applicant established in a member state. The applicant of a pending marketing authorization may be changed provided that the change is made prior to day 181 of the CMA application review process. The same timeline applies to the transfer of a CMA application as for an application for the transfer of a granted CMA, meaning to the extent that a CMA application transfer is not already well underway, it likely will be too late to transfer such CMA application to an EU MAH before the withdrawal date.

Orphan Designation

The sponsor of an orphan medicinal product designation must be established in the EEA (Art. 2 Regulation 141/2000), so any orphan medicinal product designations held by a U.K. entity will need to be transferred to an entity within the EEA. The same timeline applies to the transfer of an orphan designation as for an application for the transfer of a granted CMA, meaning to the extent that a CMA application transfer is not already underway, it likely will be too late to transfer such orphan designation to an EU MAH before the withdrawal date

Applications for U.K. MAs

As a CMA granted after the withdrawal date will not apply to the placing of the relevant product on the market in the U.K., an initial U.K. MA application will also need to be submitted and approved by the MHRA, if the MAH intends to place the product on the market in the U.K. after the withdrawal date. The MHRA has indicated that it intends to “take account” of EMA decisions whenever possible in determining future U.K. MA applications, though it is not clear what that will mean in practice until the MHRA starts making decisions or issues more guidance.

Applications for U.K. MAs for Generic Medicinal Products

For a U.K. MA to be granted after the withdrawal date for a generic medicinal product, such application must be based on reference products with U.K. MAs, as the MHRA will cease to have access to the dossiers and data supplied in support of EU marketing authorizations, increasing the barrier to obtaining U.K. MAs for generic products based on a reference product with an EU marketing authorization. Note that if an existing U.K. MA has been granted for a generic product based on a reference product with an EU marketing authorization, such U.K. MA will remain valid.

Transfer of Roles and Activities

Specific roles and activities need to be moved prior to the withdrawal date so that they continue to be performed in the EEA. Depending on the status of existing preparations, it may still be possible to complete some of these activities prior to the withdrawal date. These activities include:

Clinical Trial Representative

The sponsor of a clinical trial conducted in the EEA must either be based in the EEA or a legal representative based in the EEA must be appointed. Sponsors based in the U.K. or based outside of the EEA with a legal representative based in the U.K. need to appoint a new legal representative in the EEA prior to the withdrawal date. Such change will constitute a substantial amendment requiring notification — for CMA-approved products sites typically have 35 days following validation of the amendment notice to raise objections to the amendment. Assuming no objections are raised, the amendment may then be implemented after 35 days have elapsed. For products other than MA-approved products, timelines may differ from member state to member state.

Qualified Person for Pharmacovigilance (QPPV)

A QPPV for EU medicinal products must reside in and carry out their tasks in the EEA. A U.K.-based EU QPPV will therefore need to move its place of residence and employment to the EEA, or the manufacturer will need to notify the EMA of a new EU QPPV, residing and employed in the EEA, prior to the withdrawal date. The pharmacovigilance system master file, or PSMF, will also need to be updated to reflect such change. In addition, from the withdrawal date, for the sale of medicines in the U.K., a U.K.-based U.K. QPPV will be required. The U.K. government plans to offer a transition period to the end of 2020 to allow U.K. MAHs who do not currently have a U.K. QPPV to appoint one. However during such transition period, the U.K. MAH will be required to provide the MHRA with access to safety data relevant to its U.K. MAs at any time.

Pharmacovigilance System Master File

The PSMF must be located within the EEA (Commission Implementing Regulation 520/2012). Any U.K.-located PSMF will need to be transferred to the supervisory authority for pharmacovigilance of an EEA member state prior to the withdrawal date.

Data Protection

In addition to these industry-specific issues, from a data protection perspective, under the General Data Protection Regulation certain changes will also need to be made. For example:

- An EEA-based legal representative for data protection purposes will need to be appointed from the withdrawal date for companies subject to the GDPR but without a presence in the EEA; and

- Transfers of personal data from the EEA to the U.K. from the withdrawal date will constitute transfers to a third country, and adequate protections will need to be put in place in respect of such transfers in order for them to continue to be lawful — for example, by entering into appropriate model clauses.

The U.K. and EMA have issued practical guidance on these issues.[1][2][3]

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[1] https://www.gov.uk/government/publications/how-medicines-medical-devices-and-clinical-trials-would-be-regulated-if-theres-no-brexit-deal/how-medicines-medical-devices-and-clinical-trials-would-be-regulated-if-theres-no-brexit-dea

[2] https://www.ema.europa.eu/en/about-us/uks-withdrawal-eu/brexit-related-guidance-companies

[3] https://www.ema.europa.eu/documents/report/report-ema-industry-survey-brexit-preparedness_en.pdf