Brexit Guidance for Stakeholders

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1.0 Introduction

On 29 March 2017, the European Council received the notification by the United Kingdom (UK) of its intention to withdraw from the European Union. This allows for the opening of negotiations as foreseen by the Treaty.

The United Kingdom's decision to leave the Union creates significant uncertainties that have the potential to cause disruption, in particular in the United Kingdom but also, to a lesser extent, in other Member States. National authorities, businesses and other stakeholders should take all necessary steps to prepare for the consequences of the United Kingdom's withdrawal.

2.0 Impact of Brexit on the EU Regulatory Network

The Malta Medicines Authority's (MMA) main priority is the protection of public health and ensuring continuity of supply of medicinal products for the patients. To be able to achieve this, the Medicines Authority will provide any support necessary to its stakeholders. It is therefore important that all companies who require guidance and support to maintain their medicinal products on the market contact the MMA as soon as possible to effectively plan and prepare for the UK's exit from the EU/European Economic Area (EEA).

It is the aim of the MMA to support all stakeholders already present on the Maltese market or stakeholders who need to relocate to an EU/EEA country as a result of Brexit. Where feasible, we hope to provide pragmatic solutions to the anticipated challenges arising from the UK's exit from the EU/EEA.

The MMA would like to assure stakeholders that it is our intention to continue working closely with the UK to ensure continued product supply to the Maltese market. Malta is fully preparing to assume a greater role in EU regulatory activities and to increase our already significant contribution to the EU regulatory networks. In light of the pending withdrawal of the UK from the EU, information which may be useful to stakeholders is provided in this guidance document.

3.0 Key information to stakeholders

There are a wide range of potential scenarios arising from Brexit which could impact on the manufacturing, licensing and distribution of health products between Malta and the UK. While there have been discussions at EU level on the introduction of transitional arrangements, the implementation and details of any transitional period will depend on the outcome of the Brexit

negotiations. The guidance provided in this document on the key issues facing the MMA and our stakeholders is based on the premise that there will be a hard Brexit and the UK will become a third country after Brexit date. It is also based on our current understanding of the potential legal impact of an exit by the UK. However, it is important to note that guidance is still being developed and therefore the advice currently provided may require updating throughout the negotiations process and the during the lead up to Brexit.

4.0 Medicinal products Availability

A key priority in the protection of public health is the availability of medicinal products. This is reflected in our Strategic Plan for 2016-2020, which includes access to health products as a key strategic goal. The MMA is committed to ensuring that the impact of Brexit on medicinal product availability is assessed and proactively addressed by all relevant stakeholders and that, where necessary, timely actions are taken to ensure continuity of supply.

The MMA is offering support to companies when managing any supply problems that might arise when marketing authorisations have to be transferred from the UK to other EU markets as a result of Brexit.

The MMA is willing to act as RMS (Reference Member State) for all medicinal products where Malta is currently the only CMS and a change of RMS (UK) is required. Until Brexit date, a waiver of the fee for RMS transfer will apply when the MMA takes over RMSship from the UK. We will support companies both to simplify the transfer of RMS and to minimise the administrative burden of changing RMS.

The MMA will work with companies to ensure that existing joint labels with the UK are maintained and that multi-lingual labels with other EU markets are developed.

Regulatory issues which may arise for critical medicinal products should be highlighted as soon as possible so that pragmatic solutions will be sought for critical medicinal products to remain on the Maltese market.

The MMA will support stakeholders on addressing company specific issues related to Brexit.

5.0 Joint/Multi-lingual labelling

The MMA recognises that the maintenance of joint/multi-lingual labelling with other markets can be key to companies retaining medicinal products on the Maltese market. The MMA has facilitated, where possible, joint/multi-lingual labelling with the UK and other markets. This

approach will continue as the establishment of joint/multi-lingual labelling with other suitable markets is considered an important mechanism for maintaining products on the Maltese market. Through collaborations with other European competent authorities, the MMA is seeking support to facilitate additional opportunities for multi-lingual labelling.

6.0 Licensing Scenarios for Marketing Authorisation Holders

The implications of Brexit with regard to the UK's role in the licensing of medicinal products will be determined by the terms of the ongoing exit negotiations. The Marketing Authorisation Holder (MAH) must be located within the EU/EEA. In addition, for marketing authorisations issued through the mutual recognition procedure (MRP) or decentralised procedure (DCP), the RMS must be based in the EU/EEA.

The MMA is recommending that MAHs plan for a situation where the UK becomes a third country which involves selecting a RMS based in the EU/EEA and ensuring that the MAH is also based in the EU/EEA.

Guidance documents on the effect of post-Brexit on licensing procedures have been issued by the European Medicines Agency (EMA) and the Coordination Group for Mutual Recognition and Decentralised procedures – human (CMDh). Further information can be found in the hereunder section 9.0 Reference for more information.

6.1 Procedures for MAHs to change RMS

The following guidance, as agreed by CMDh applies when changing the RMS:

- Where the UK is RMS and there is only one concerned member state (CMS), then that CMS will automatically become the new RMS. In instances where Malta is that CMS, the MMA will become the RMS.

- Where there are two or more CMSs, it is the responsibility of the MAH to secure a new RMS based in the EU/EEA.

- The choice of a new RMS will be the decision for the MAH subject to agreement with the relevant national competent authority. MAHs are advised to communicate, as soon as possible, with their preferred new RMS and the UK to submit the official notification of change in a timely manner in order to facilitate completion of the change of RMS before the UK exits the EU.

6.2 Why select Malta as your RMS?

The MMA is willing to accept RMShips for medicinal products where the UK is RMS and Malta is CMS. Competent technical personnel have been recruited for the technical assessment of dossiers for such procedures to ensure adequate capacity to handle more procedures. All queries in relation to Malta acting as RMS should be sent to the following e-mail address: mrp-dcp.adm@gov.mt.

The MMA commits to an efficient and simple process for handling these requests and for taking on the role of RMS. The fees for RMSship transfer from the UK to Malta will be waived.

6.3 What is the timeline for changing RMS?

The procedure itself is a straightforward administrative procedure which can be completed within a matter of days. In order to ensure the successful change of RMS to Malta, MAHs are requested to contact the MMA as soon as possible to plan work volumes and to ensure continuation of product supply on the EU market prior to the UK's exit from the EU.

The critical issue will be the timing of when the change in RMS should occur as it is required to occur when there are no open regulatory activities for a product. It is therefore advisable that all planned regulatory activity with products requiring a change in RMS takes into account the expected duration of the procedures to ensure the RMS change is completed prior to Brexit.

6.4 National marketing authorisations, Article 126(a) authorisations and parallel import authorisations

National Marketing Authorisations

For national authorisations which are authorised in UK and Malta only, the marketing authorisation in Malta will remain valid subject to MAH transfer to Malta or another EU member state. The responsibilities for post-authorisation regulatory procedures must be carried out by the new MAH (refer to Section 7 for pharmacovigilance).

Authorisations in accordance with article 126(a) of Directive 2001/83/EC

Authorisation holders of Article 126(a) authorisations or parallel import authorisations with UK as the country of source should identify alternative source countries in the EU. Repackaging of the medicinal product should be performed if the pack is not available in English/Maltese

language. Please refer to the Guidelines on Repackaging found on the Medicines Authority website.

Authorisation holders of Article 126(a) which are the Marketing Authorisation Holders of the medicinal product are wherever possible, requested to use the 'MRP day zero or day 30 procedure' also referred to as the 'simplified procedure'. The MMA agrees to accept the assessment of the RMS, without any comments or questions. The approved product information will also be accepted without any comments. The MMA will not request any update of the assessment report or the dossier, nor will there be any changes related to such procedure, except that in this simple way Malta joins an MRP. These procedures can be finalised once the application has been accepted by the RMS and MMA, hence a "MRP day zero procedure".

Procedures have already been finalised successfully using these procedures with a number of RMS countries.

The Medicines Authority is also discussing the possibilities of reduced fees by the RMS countries to enable companies to seek registration using European procedures, especially in small countries. Some countries already have reduced fees for these procedures – if you require more information about this please send an email to mrp-dcp.adm@gov.mt.

More information on the Day 0 or Day 30 MRP (Simplified Procedure)

Applicants should inform the Medicines Authority of their intention to submit such an application to the RMS.

A request is then sent to the RMS requesting the use of this simplified procedure.

The RMS requests confirmation from the CMS regarding the criticality of the product applied for.

The CMS confirms the need for the product and guarantees that:

a. There will be no need for the RMS to update the assessment report since these will be accepted from the RMS without any comments
b. No day 50 comments will be sent by MT as CMS to the RMS thus enabling the application to be approved immediately
c. The addition of MT will not change the renewal cycle or PSUR submission timelines

d. The product information specifically the SmPC, package leaflet and labelling will be accepted as authorised in the RMS

An application form is then sent to MT as CMS and to the RMS. This submission should include:

a. A cover letter clearly stating that the submitted dossier is identical to the one currently approved in the RMS
b. The dossier preferably in eCTD format, together with any subsequent approved variations and a confirmation of their approval
c. Latest approved PI by the RMS

MT as CMS validates the application form within a 14 day validation period

- RMS then sets a Day 0

- A Day 0 procedure is concluded on the same day it started (i.e. following validation) by the RMS and a Day 30 procedure is concluded 30 days after it started by the RMS
- The End Of Procedure documents are sent by the RMS to the CMS
- Following this, the applicant submits the MT specific product information.
- The Medicines Authority then issues the MA during the 30 days national phase of the procedure.

6.5 Procedures for MAHs to transfer MAH to EU/EEA based MAH

A marketing authorisation may be transferred from the existing authorisation holder to another holder using a transfer procedure. The transfer procedure must be used where the legal entity of an authorisation/licence holder is changed as marketing authorisations are transferred to a new company number.

6.6 Authorised generic medicinal products which refer to an UK reference product

Marketing authorisations for generic/hybrids granted in accordance with Directives 2001/82/EC and 2001/83/EU granted before Brexit date, will continue to be valid authorisations notwithstanding that a reference product may no longer be an EU authorised product.

6.7 Variations to Marketing Authorisations to change Qualified Person Responsible for Pharmacovigilance (QPPV), manufacturing sites and sites of batch release

Any variations required for a marketing authorisation (MA), for example, a change to site of batch release or change in location of QPPV, should be completed prior to the date of the UK's departure from the EU. It is recommended that MAHs prepare and proactively screen authorisations they hold for any required changes. Variation applications should be submitted in sufficient time to ensure they are completed prior to Brexit.

7.0 Pharmacovigilance Operations

MAHs will need to ensure that their EU QPPV and their pharmacovigilance system master file (PSMF) are located within the EU/EEA. This is necessary to remain in compliance with the requirements outlined in article 104 of Directive 2001/83/EC, as amended, and in Article 7 of Commission Implementing Regulation No. 520/2012. Requirements for coordination of pharmacovigilance inspections undertaken by Member States, including the sharing of information on inspections planned and conducted inspections are provided for in EU legislation (Article 111 of Directive 2001/83/EC, Article 19 of Regulation No 726/2004) and associated Union procedures.

8.0 Changes to Import and Export Requirements

The following advice regarding the importation, export, storage and distribution of medicinal products are based on the assumption that the UK will become a third country after Brexit, leaving the European single market and customs union. It does not take into account however any possible future mutual recognition agreement (MRA) on good manufacturing practice (GMP) Inspection between the EU and the UK. Therefore, this advice may be subject to change in the future as the Brexit negotiations progress.

8.1 Finished product and active substances coming from the UK

Any companies that receive finished medicine sourced from the UK, including exempt/unlicensed medicinal products, will be required to hold a manufacturing importation authorisation (MIA). If a medicinal product is being procured, held, supplied or exported by a UK entity, then that entity will require a wholesale authorisation which the UK will employ post-Brexit. For products transiting through the UK only, it is not envisaged that there will be any additional requirements other than potential additional customs clearance/checks e.g. from a French distribution entity transiting via the UK to Malta. With respect to active substances for use in human medicinal products sourced from companies in the UK, an active substance distributor will also be required to register as an importer of active substances. In order to import active substances manufactured in the UK, under the Falsified Medicines Directive, the UK will need to be listed by the EU Commission as having a supervisory system for active pharmaceutical ingredients equivalent to that of the EU. There is no provision for an MRA on GMP inspection between the EU and UK at this time.

8.2 Qualified person (QP) release

For EU markets, all products that originate from the UK, or those imported via the UK, must be imported by a manufacturer/importer located within the EU/EEA and certified after being batch released by a Qualified Person (QP) at that site. No changes are anticipated to Annex 16 of the EU Guide to GMP as result of Brexit as certification must take place within the EU/EEA in accordance with current legislation and guidance.

8.3 Product testing

In the absence of an MRA on GMP inspection, each batch of product which is manufactured within the UK, or imported to the UK with the intention of being distributed within the EU, will be required to undergo testing within the EU/EEA. Reliance on results from UK testing laboratories would not satisfy current legislative requirements.

8.4 GMP certification

To date, there has not been any decision regarding the mutual recognition of GMP certificates issued by the UK/competent authorities post Brexit. As the MHRA is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and PIC/S GMP standards are largely aligned with EU GMP, with the exception of the requirement for a qualified person, significant divergence in this area is not expected. However it would not be possible to rely on GMP certificates issued by MHRA in the absence of an MRA between the UK and the EU or some other form of agreement with regards to mutual GMP recognition.

9.0 References for more information

- Heads of Medicines Agencies (HMA). Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh) - Procedural Advice on Changing the Reference Member State. Introduction/Overview/Mandate. Available from: URL: http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/01_General_Info/CMDh_039_2002-Rev5-2017_03-Clean.pdf

- Heads of Medicines Agencies (HMA). Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh) - Notice to marketing authorisation holders of national authorised medicinal products for human use. Available from: URL: http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/BREXIT/CMDh_360_2017.pdf

- Heads of Medicines Agencies (HMA). Co-ordination Group for Mutual Recognition and Decentralised Procedures (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. Available from: URL: http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/BREXIT/CMDh_361_2017_clean.pdf

- European Commission, European Medicines Agency. Questions and Answers related to the United Kingdom's withdrawal from the European Union with regard to the medicinal products for human and veterinary use within the framework of the Centralised Procedure. Available from: URL: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228739.pdf

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