HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Brexit Guidance for Stakeholders
Human and veterinary medicines

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1 BACKGROUND

Following the outcome of the 2016 referendum vote for the United Kingdom (UK) to leave the European Union (EU) and the triggering of Article 50 in March 2017, the HPRA along with other colleagues within the EU regulatory network is making preparations to ensure that we continue to deliver on our patient and animal health remit. Although the eventual outcome of the ongoing discussions in relation to the UK's withdrawal from the EU is unknown, the HPRA, European agencies and all other stakeholders in the health products supply chain must plan for all eventualities including that the UK will fully exit the current regulatory system on 30 March 2019.

2 IMPACT OF BREXIT ON EU/EEA REGULATORY NETWORK

The HPRA's priority, working with all relevant stakeholders, is to ensure continuity in the supply of health products and continued access for patients. It is therefore essential that all companies who require guidance and support to maintain their products on the market, contact the HPRA as soon as possible to effectively plan and prepare for the UK's exit from the EU/European Economic Area (EEA).

It is the HPRA's aim to support all stakeholders already present on the Irish 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 HPRA works together with the UK's Medicines and Healthcare products Regulatory Agency (MHRA) and Veterinary Medicines Directorate (VMD) on many regulatory issues both bilaterally and at EU level. The HPRA would like to assure stakeholders that it is our intention to continue working closely with the UK to ensure continued product supply to the Irish market. Ireland is fully prepared 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 below.

3 KEY INFORMATION FOR HPRA 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 Ireland 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 HPRA and our stakeholders is based on the premise that there will be a hard Brexit and the UK will become a third country by 30 March 2019. 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 must be agreed in respect of so-called 'grey' areas and therefore the advice currently provided may require updating throughout the negotiations process and the during the lead up to Brexit.

4 MEDICINES AVAILABILITY

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

The HPRA 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. Actions under this initiative include:

- Willingness to act as RMS for all products where Ireland (IE) is currently CMS and a change of RMS is required. No fees will apply to the process for changing RMS to IE. In addition, where at all possible we will work with companies both to simplify the transfer of RMS and to minimise the administrative burden of changing RMS.
- Where feasible, we will work with companies to ensure that existing joint labels with the UK are maintained and that multilingual labels with other EU markets are developed.
- We will look at regulatory issues which may arise for critical products and seek, where possible, pragmatic solutions to allow the products remain on the Irish market.
- We will work with stakeholders on addressing company specific issues arising out of Brexit.

5 JOINT LABELLING

The HPRA recognises that the maintenance of joint labelling with other markets can be key to companies retaining medicines on the Irish market. We are committed to facilitate such joint labelling while remaining compliant with regulatory requirements and thereby safeguarding continued patient access.

For human medicines, the HPRA has facilitated, where possible, joint labelling with the UK and other markets. This approach will continue as the establishment of joint labelling with other suitable markets is considered an important mechanism for maintaining products on the Irish market. Multilingual labelling can also be used and we will continue to work with other European regulators to help facilitate additional opportunities for multilingual labelling.

For veterinary medicines, the HPRA and the VMD have enjoyed a close working relationship and have successfully operated a bilateral joint labelling procedure for in excess of 10 years. It is the intention of the HPRA to maintain a close working relationship with the VMD and that

this procedure will continue after the UK leaves the EU. Multilingual labelling can also be used and we will continue to work with other European regulators to help facilitate additional opportunities for multilingual labelling.

6 POST BREXIT LICENSING SCENARIOS FOR MARKETING AUTHORISATION HOLDERS

The implications of Brexit with regard to the UK's role in the licensing of medicines will be determined by the terms of the ongoing exit negotiations. However, in accordance with Directives 2001/82/EC and 2001/83/EC, 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 Reference Member State (RMS) must be based in the EU/EEA. Guidance on changing of RMS is available on the Heads of Medicines Agencies (HMA) website:

Human Medicines: Procedural Advice on Changing the Reference Member State

Veterinary Medicines: Best Practice Guide for Changing the Reference Member State

The HPRA 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.

The Coordination Group for Mutual Recognition and Decentralised procedures – human (CMDh) has issued a Q&A related to the UK's withdrawal from the European Union with regard to national authorised medicinal products for human use as well as a notice to MAHs.

The Coordination Group for Mutual Recognition and Decentralised procedures – veterinary (CMDv) has also issued a Q&A related to the UK's withdrawal from the European Union with regard to national authorised medicinal products for veterinary use in addition to a notice to MAHs.

The issue of centrally authorised products is being coordinated by the European Medicines Agency (EMA). The EMA has developed a Q&A related to centrally authorised products and a notice to MAHs both of which are available via their website.

The CMDh/CMDv Q&As will be updated periodically with further questions and answers. These lists of Q&As have been drafted by the CMDs taking into account the European Commission's and EMA's Question and Answers on the same issue within the framework of the centralised procedure.

6.1 Procedures for MAHs to change RMS

For both human and veterinary medicines, when making a change to the RMS the following guidance, as agreed by CMDh and CMDv applies:

- 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 IE is that CMS, the HPRA 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 a decision for the MAH subject to agreement with the relevant national competent authority. MAHs are advised to communicate 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. IE is very willing to become the RMS for any product where the UK is RMS and IE is CMS.

For human medicinal products, all queries in relation to IE acting as RMS should be sent to the following e-mail address: article50changes@HPRA.ie

For veterinary medicinal products, all queries in relation to IE acting as RMS should be sent to the following e-mail address: vetinfo@hpra.ie

6.2 Why select Ireland as your RMS?

The HPRA has a proven track record of conducting high quality and timely assessments, and will be happy to receive requests to act as RMS for all product types including all products for which the UK is currently the RMS and IE is a CMS. There will be no fees charged for switching the RMS from the UK to IE. The HPRA commits to an efficient and simple process for handling these requests (for example allowing the inclusion of multiple products in one request where applicable) and for taking on the role of RMS.

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 IE, MAHs are requested to contact the HPRA 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 30 March 2019.

The following guidance documents are available on the HMA website www.hma.eu:

CMDh procedural advice for changing reference member state

http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/01_General_Info/CMDh_039_2002-Rev5-2017_03-Clean.pdf

CMDv/BPG/021 Best Practise Guide for changing reference member state
http://www.hma.eu/fileadmin/dateien/Veterinary_medicines/CMDv_Website/Procedural_guidance/General_info_on_applications/BPG-021_Changing_RMS.pdf

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

A marketing authorisation or parallel product 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 (parallel or product authorisation) are transferred to a new company number.

Bulk transfers are accepted by the HPRA and reduced fees apply. Please contact submissions@hpra.ie prior to submission to discuss dates and timelines. Also, for bulk transfer applications, only one application form is required. If necessary, please provide an annex listing of the product authorisation numbers, full product names and strengths.

Further information on transfers can be found on our website:
Human Medicines
Veterinary Medicines

6.5 Meeting licensing requirements for products under development

A series of questions and answers will be developed at a European level to manage specific scenarios for products, including those under development. Examples of these include queries relating to reference products for generic/hybrid or biosimilar applications, the well-established use legal basis and traditional use registrations for herbal products. For products under development for which data has already been generated, it is recommended that all data are screened to ensure that these will comply with EU requirements following the UK's exit from the EU.

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 prior to 30 March 2019, 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 CLINICAL TRIALS FOR HUMAN MEDICINES

The European clinical trial regulation EU No. 536/2014 is due to come into force in 2019. Key features of this Regulation will include:

- Identical rules for conducting clinical trials throughout the EU.
- Increase in the efficiency of the approval process for clinical trials.
- Single submission & approval of multinational clinical trial applications through an EU 'Clinical Trial portal and database'.
- A harmonised procedure for assessment by member states, divided in two parts.
- Strictly defined deadlines for assessment.
- Involvement of the ethics committees in the assessment procedure.

It is recognised that the UK is involved in many European clinical trials and it is hoped that the UK will fully adopt the new Regulation, which aims to increase the number of clinical trials conducted in Europe.

7.1 UK based sponsor or legal representative listed on clinical trial application

Under the current clinical trial directive, Article 19 of Directive 2001/20/EC requires that the sponsor or a legal representative of the sponsor is established in the EU/EEA. This does not exclude the possibility that this establishment is a branch or subsidiary of a legal person having its principal seat outside the EU. This establishment could be the sponsor or act as legal representative of the sponsor established outside the EU.

In the new clinical trial regulation (article 74, paragraph 1), where the sponsor of a clinical trial is not established in the EU, that sponsor is required to ensure that a natural or legal person is established in the EU as its legal representative. Member States may choose not to implement paragraph 1 for clinical trials to be conducted solely on their territory, or on their territory and the territory of a third country, provided that they ensure that the sponsor establishes at least a contact person on their territory in respect of that clinical trial, who shall be the addressee for all communications with the sponsor provided for in this regulation.
As regards clinical trials to be conducted in more than one Member State, all those Member States may choose not to apply paragraph 1 provided that they ensure that the sponsor establishes at least a contact person in the EU in respect of that clinical trial who shall be the addressee for all communications with the sponsor provided for in this Regulation.
While the full impact of Brexit is still unclear, the HPRA remains committed to supporting sponsors during this period of change.

7.2 Implications for Ireland as a site for clinical trials

Clinical trials are central to the development of new treatments for patients. The HPRA acknowledges the importance of ensuring that Ireland is recognised as an attractive country in which to conduct clinical trials. Ireland will continue to conduct clinical trials in line with EU legislation and within the new clinical trial regulation when it comes into force. The majority of clinical trials conducted here are multinational and international trials. The HPRA will continue to support both commercial and non-commercial sponsors in the conduct of clinical trials in Ireland.

8 PHARMACOVIGILANCE OPERATIONS

8.1 Human medicines

MAHs will need to ensure that their EU qualified person responsible for pharmacovigilance (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.

8.2 Veterinary medicines

Article 74 of Directive 2001/82/EC states that the EU QPPV shall reside and operate in the EU/EEA. Therefore, there will be a requirement for MAHs to relocate their EU QPPV to another EU member state if it is currently located in the UK. There is no legal impediment to having other pharmacovigilance activities located in the UK.

The regulation of pharmacovigilance within Ireland will continue in line with EU legislation.

9 CHANGES TO IMPORT AND EXPORT REQUIREMENTS

The following advice regarding the importation, export, storage and distribution of medicines are based on the assumption that the UK will become a third country from 30 March 2019, leaving the European single market and customs union. It does not take into account however any possible future m 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.

9.1 Finished product and active substances coming from the UK

Any Irish company that receives finished medicinal product sourced from the UK, including exempt/unlicensed medicines, will be required to hold a manufacturing authorisation.
If a medicinal product is being procured, held, supplied or exported by a UK entity, then that entity will require whatever wholesale authorisation 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 Ireland.

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.

With respect to active substances for use in veterinary medicinal products sourced from companies in the UK, there is no requirement for a supervisory system for active pharmaceutical ingredients and there are, therefore, no additional requirements for active substance arising from the decision of the UK to leave the EU.

9.2 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 located within the EU/EEA and certified 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.

9.3 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. Pre-shipment samples would be allowed under Annex 16 for marketed products.

9.4 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 and VMD are members 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.

9.5 Finished product supplied from Ireland to the UK

An Irish wholesale entity supplying the UK market will need to vary its authorisation to include the activity 'export' to continue this supply.

Irish manufacturers of medicinal that are supplied to the UK market will need to comply with any additional requirements that may be put in place by the UK competent authorities.