

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 29 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 essential that companies ensure continued communication with the HPRA for guidance and support as they prepare for Brexit.

The HPRA's aim is to continue 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. We are open to working together to address any areas of risk or difficulty and to support pragmatic solutions within the existing framework.

The HPRA works 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 wants 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 actively assuming a greater role in EU regulatory activities and has increased further 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 29 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. Therefore, the advice currently provided may require updating throughout the negotiations process and during the lead up to Brexit. In the event that a transition period is agreed, this guidance will be updated to reflect the terms of the transition.

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 actively working with companies to ensure 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 in managing any problems that might impact on the supply of medicines when responsibilities relating to marketing authorisations have to be transferred from the UK to other EU member states 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.
- Where feasible, we will work with companies to ensure that multilingual labels with other EU markets are developed or existing joint labels with the UK are maintained after Brexit.
- 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 continue to work with stakeholders on addressing company specific issues arising as a result of Brexit.
- Changes to the HPRA MAH transfer procedures to alleviate pressures on the supply chain following transfer of authorisations (see section 6.4 of this guidance document)

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. HPRA will continue to accept joint labelling with the UK after Brexit provided the labels meet the requirements of Title V of Directive 2004/83/EC and reflect the SMPC of the product authorised on the Irish market.

For human medicines, the HPRA will continue to accept joint labelling with the UK after Brexit and with 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.

To encourage the use of multilingual labelling the HPRA will proactively work with other European regulators to help optimise opportunities for multilingual labelling. The HPRA [‘Guide to labels and leaflets of Human Medicines’](#) has been updated (Oct 2018) to give specific guidance on the development of 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 is also commonly used for veterinary medicinal products and we will continue to work with other European regulators to help facilitate additional opportunities for multilingual labelling.

Information on labelling issues for both human and veterinary medicines are available at the links below:

[Human](#)

[Veterinary](#)

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 RMS is available on the Heads of Medicines Agencies (HMA) website:

[Human Medicines: Procedural Advice on Changing the Reference Member State \(Updated July 2018\)](#)

[Veterinary Medicines: Best Practice Guide for Changing the Reference Member State \(2017\)](#)

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 \(Updated](#)

June 2018) with regard to national authorised medicinal products for human use as well as a notice to MAHs (Updated June 2018).

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 (Updated June 2018) 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 together with the European Commission have developed a Q&A related to centrally authorised products and a notice to MAHs both of which are available via their website.

The EMA have also updated their post authorisation procedural advice for users of centralised procedure (August 2018).

The CMDh/CMDv Q&As were updated in June 2018 and 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 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.

6.2 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 continued supply of product 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 29 March 2019.

6.3 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

6.4 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. It is possible to transfer the MAH while there are ongoing/open variations. If the transfer is processed/issued, the new MA holder details will transfer onto the open/ongoing variations.

NOTE: Important changes to the HPRA transfer procedure:

HPRA transfer procedures have recently been changed to allow MAHs up to 6 months to implement packaging changes following issue of the transferred authorisation, for Brexit related transfers. In addition the HPRA no longer requires stock to be recalled from wholesaler level six months following the issue of the transferred authorisation/licence/registration.

6.4.1 Bulk MAH Transfers

Bulk transfers are accepted by the HPRA and reduced fees apply. Please contact submissions@hpra.ie prior to submission to discuss dates and timelines.

If transfers need to be processed on a particular date please highlight this in the cover letter accompanying the applications. Note that transfer applications are generally listed for

approval within the HPRA on a Friday. Please bear this in mind when proposing your preferred transfer date.

For bulk transfer applications, only one application form is required. Please include an annex listing of the product authorisation numbers, full product names and strengths with all applications.

6.4.2 Issuing of PA numbers

To facilitate the preparation of your application the HPRA Receipts and Validation section can provide you with the new PA numbers in advance of your application. Requests for PA numbers should be sent to submissions@hpra.ie. Typically, each request takes ten working days to process. When requesting new PA numbers please specify the existing product name and PA number as well as the current and new MAH.

6.4.3 Art work requirement with transfer application (Human Medicines Only)

An updated package leaflet is required to be submitted with a transfer application so that this can be displayed on the HPRA website. The package leaflet should reflect the new MAH details. A word version of the package leaflet is acceptable.

If the only changes proposed relate to MAH details and a new PA number, an Article 61(3) application is not required. However, if there are additional changes to the labels and package leaflet an Article 61(3) application must be submitted. This can be submitted in parallel to the transfer.

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 have been 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 29 March 2019, will continue to be valid authorisations notwithstanding that a reference medicinal product (RefMP) may no longer be an EU authorised product.

Further guidance regarding generic/hybrid Mas is available in Q10 and Q13 of the EC Q&A

6.7 Medical devices containing an ancillary medicinal substance

Manufacturers of medical devices containing an ancillary medicinal substance wishing to transfer an existing competent authority consultation to the HPRA are advised to contact the HPRA to discuss the transfer.

Transfers of medical devices containing a medicinal ancillary substance with a valid CE certificate are considered administrative only. Transfers typically take less than 30 days from validation of the submission to be completed. No fees will apply to this transfer process.

All queries in relation to IE acting as a consulting authority should be sent to the following e-mail address: article50changes@HPRA.ie

6.8 Parallel Product Authorisations

Parallel product authorisations (PPAs) can only be granted for medicines imported from an EU Member State or a country within the EEA. Therefore, PPAs issued for products imported from the UK will cease to be valid post 29 March 2019.

If the UK is listed as one of a number of source countries on a PPA, this will need to be removed by way of a type IA variation (category 4).

A PPA holder must be located within the EEA. Therefore, where the holder of PPA is located within the UK, the authorisation will need to be transferred to holder located within the EEA. This transfer can be conducted using the transfer procedure as outlined in section 6.4 above.

Qualified person certification of repackaging activity must take place within the EEA. Variations to change the site of batch certification/release from the UK to the EEA should be completed prior to the 29 March 2019. Variations to change the site of batch certification can be submitted using the PPA variation category No 9a and 9b.

All repackaging of parallel imported products must take place within the EEA as of the 29 March 2019. The European system is predicated on the products being sourced in one member state and remaining within the EEA throughout repackaging, certification/release and placing on the market

6.9 Variations to Marketing Authorisations to change Qualified Person Responsible for Pharmacovigilance (QPPV), manufacturing site or/and batch release sites.

Any variations required for a marketing authorisation (MA), e.g change in location of QPPV or site of batch release, 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.

Further guidance on QPPV and Batch Release scenarios is available in the CMD(h) guidance [‘Questions and Answers related to the United Kingdom's withdrawal from the European Union with regard to national authorised medicinal products for human use’](#)

Practical guidance on the type of variations required can be found in the CMD(h) guidance document entitled [‘Practical guidance for procedures related to Brexit for medicinal products for human use approved via MRP/DCP’](#).

7 CLINICAL TRIALS FOR HUMAN MEDICINES

The European clinical trial regulation EU No. 536/2014 is due to come into force in 2020. 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.

Further guidance on well-established clinical trial applications is available in Q14 of the EC Q&A

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. There is no legal impediment to having other pharmacovigilance activities located in the UK.

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.

Further guidance on QPPV scenarios is available in Q4 and Q25 of the EC Q&A

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.

Further guidance on QPPV scenarios in Q4 and Q25 of the EC Q&A

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 29 March 2019, 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.

9.1 Finished product and active substances coming from the UK; Importation Controls

Any Irish company that receives finished medicinal product from the UK, will be required to hold a manufacturer's/importer's authorisation. In addition the batches must be tested and certified in the EU/EEA after importation.

Sourcing of exempt/unlicensed medicines from the UK must be carried out under an MIA.

In the event that the UK remains within the common transit convention, medicines can be transported from a manufacturer in the EEA, over land through the UK, to Ireland, under the Customs' transit code. Under this provision medicines would not be considered as exported and re-imported and therefore a wholesaler can receive the goods and retesting and QP certification would not be required in Ireland.

Similarly, Irish manufacturers can use the transit code to transport batches of medicines from Ireland across the UK to other EEA markets without the batches undergoing importation controls on re-entry into the EU/EEA.

9.2 Active substances

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 active substances importer. An Irish dosage form manufacturer receiving active substance from a UK source will also need to register with the HPRA as an active substance importer.

In order to import active substances manufactured in the UK, under the Falsified Medicines Directive, a written confirmation issued by the UK regulatory authority for the manufacturing site will need to be provided for each imported consignment.

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.

9.3 Product testing for QP certification/release

Each batch of product which is manufactured in 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 after importation. Reliance on results from UK testing laboratories for batch release would not satisfy current legislative requirements.

9.4 Qualified person (QP) certification/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) in the EEA. If product has been QP certified in the UK and shipped to Ireland before March 29th 2019, it can continue to be used/sold until the stock is exhausted.

9.5 Process for changing the site of batch release

A company should apply to the HPRA for a manufacturer's/importer's authorisation (MIA) for batch certification/release within the Republic of Ireland. A GMP inspection will be conducted on receipt of an application. The batch certification activities must take place at the authorised address. [All necessary documentation can be found on the HPRA website](#). Queries relating to MIA applications should be directed to compliance@hpra.ie

9.6 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 products 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.