EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division
Veterinary Medicines Division

Practical guidance for procedures related to Brexit for medicinal products for human and veterinary use within the framework of the centralised procedure

On 2 May 2017, the European Commission and EMA published a **Notice** to marketing authorisation holders (MAHs) of centrally authorised medicines products for human and veterinary use, stating: "*The United Kingdom submitted on 29 March 2017 the notification of its intention to withdraw from the Union pursuant to Article 50 of the Treaty on European Union. This means that unless the withdrawal agreement establishes another date or the period is extended by the European Council in accordance with Article 50(3) of the Treaty on European Union, all Union primary and secondary law ceases to apply to the United Kingdom from 30 March 2019, 00:00h (CET). The United Kingdom will then become a 'third country'*."

In this regard, MAHs of centrally authorised medicinal products for human and veterinary use are reminded of certain legal consequences that need to be considered in a timely manner. Preparing for the consequences of the UK's withdrawal from the Union is a significant matter for European and national administrations, and also equally important for private parties.

In order to consider the necessary changes, a list of Questions and Answers (Q&As) 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 drafted jointly by the European Commission and EMA is available on the EMA website.

The below Practical Guidance has been developed taking into consideration that as of 30 March 2019 the United Kingdom will become a third country. As a result, MAHs and applicants of centrally authorised products for human or veterinary use need to ensure that the necessary changes are made by the 30 March 2019, unless indicated otherwise in the guidance below.

This document complements the EC-EMA Q&A to provide procedural and practical guidance regarding submission of changes and related fees.

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1. Can I group Brexit-related variations?

Brexit-related variations can be grouped, where the grouping does not delay implementation of changes which need to be in place by the time of UK's withdrawal from the EU.

General information on established procedural rules for grouping can be found in the relevant Q&A on the post-authorisation Guidance published on the Agency's website concerning medicines for human use or veterinary use.

For guidance on classification of changes please also check the relevant Guidance published on the Agency's website concerning medicines for human use or veterinary use, respectively.

MAHs are also reminded that a worksharing application can be used in case of identical changes that apply to several products with the same MAH. Further guidance on these procedures is published on the Agency's website concerning medicines for human use or veterinary use, respectively.

MAHs are advised to liaise with the Procedure Manager of their product in advance of submitting the variations for medicinal products for human use or, for veterinary medicines, to contact vet.applications@ema.europa.eu.

2. How to classify Brexit-related changes impacting on the manufacturing activities for my medicinal product?

Each batch of finished product must be certified by a Qualified Person within the EEA before being released for placing on the market in the EEA or for export. Certification can only be performed by a Qualified Person of the manufacturer and/or importer who is identified in the marketing authorisation and is located in the EEA (see EudraLex, Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Annex 16: Certification by a Qualified Person and Batch Release).

Also the site for batch control (where each batch undergoes full qualitative analysis, a quantitative analysis of at least all the active substances and other tests necessary to ensure the quality of the products in accordance with the requirements of the marketing authorisation) needs to be located in the EEA or a country covered by a mutual recognition agreement. For products manufactured outside the EEA, also an authorised importation site in the EEA is required.

Products that only have batch release and quality control testing sites for finished product in the UK will have to change the batch release and testing sites. For products that have other batch release and testing sites the MAH may choose to delete the site(s) or may choose to replace them. For finished products manufactured in the UK an importation site (in EEA) will need to be introduced.

In many cases, a single site can perform manufacturing, testing, importation and/or batch release activities. In case the MAH decides to move part or all of these activities, the following scenarios, although not exhaustive, may apply:

Manufacturing process	Non-biological/non-immunological product	Biological or immunological product
Addition or replacement of site		
The UK site is only a batch release site and/or importation site for the finished product	Type IA_{IN} (B.II.b.2.c.1)	Type IA_{IN} (B.II.b.2.c.1)
The UK site is a batch release and quality control site of the finished product	Type IA_{IN} (B.II.b.2.c.2)	Type IB (B.II.b.2.c.2) if the test methods performed at the site are not biological/immunological/immunochemical methods. Otherwise, it is Type II (B.II.b.2.c.3)
The UK site is only a quality control site of the finished product	Type IA (B.II.b.2.a)	Type IB (B.II.b.2.a) if the test methods performed at the site are not biological/immunological/immunochemical methods. Otherwise, it is Type II (B.II.b.2.b)
At the same UK batch release site, primary and/or secondary packaging also takes place[1]	Type IA_{IN} (B.II.b.1a and b)	Type IA_{IN} (B.II.b.1a) – secondary packaging Type II (B.II.b.1c) – primary packaging
The UK batch release site performs manufacturing activities beyond batch release[1]	Grouping: A single type II scope B.II.b.1 - Addition of a new finished product manufacturing site: changes to the manufacturing process, batch size and in-process controls to adapt to the new manufacturing site settings. And a type IA_{IN} (B.II.b.2) to add/ replace the batch release site	Grouping: A single type II scope B.II.b.1 - Addition of a new finished product manufacturing site: changes to the manufacturing process, batch size and in-process controls to adapt to the new manufacturing site settings. And a type IA_{IN} (B.II.b.2) to add/ replace the batch release site
Deletion of a manufacturing site		
Deletion of site(s) for batch release, packaging, batch control[2]	Type IA (A.7)	Type IA (A.7)

Concerning the rules for grouping of Brexit-related applications please see above Question 1 “Can I group Brexit-related variations?”

For information on the fees applicable to variation applications, please refer to fees payable to the European Medicines Agency.

[1] Only batch control and batch release testing need to take place in a site in EU/EEA, however, other activities can also be transferred between the same involved sites as part of the Brexit related applications, if desired.
[2] In case more than one manufacturer in one MA has to be deleted, a single variation of type IA under classification category A.7 to delete all manufacturing sites may be submitted.

3. Can I submit several changes relating to manufacturing of the active substance or finished product under a single Type II variation?

Introduction of a new manufacturing site for the active substance or for the finished product and their respective consequential changes can be submitted as a Type II variation separately for the active substance and for the finished product, thereby replacing a large grouping of Quality IB (and IA) variations for the consequential changes. Such an approach can be followed for changes of UK manufacturing sites which are related to the Brexit.

The principles for a single Type II variation have already been established and can be found in the respective human or veterinary EMA questions and answers, and should be applied as follows:

- The following complex, related changes could be considered for submission under a single Type II scope B.II.b.1 - Addition of a new finished product manufacturing site: changes to the manufacturing process, batch size and in-process controls to adapt to the new manufacturing site settings.
- The introduction of a new manufacturing site for an active substance supported by an ASMF should be submitted under a single Type II scope B.I.a.1.b. The introduction of a new manufacturer of the active substance not supported by an ASMF that requires significant updates to 3.2.S should be submitted under a single Type II scope B.I.a.1.g).
- In case the introduction of the new active substance manufacturer has an impact on the finished product manufacturer (e.g. changes to the active substance specifications or related analytical methods) separate variations have to be submitted under the corresponding B.I.b. categories and may be grouped together, if related to the introduction of the new active substance manufacturer.

In case there is also a change of the UK batch release site, its replacement requires a Type IA variation (B.II.b.2). If the site also performs Quality control activities please refer to Question 2 above. The variation(s) can be submitted as a grouping with the respective Type II variation.

Any pre-submission queries of any intended submission of complex related changes under one Type II variation scope should be addressed to the appointed Procedure Manager or, for veterinary medicinal products, to vet.applications@ema.europa.eu.

4. How can I submit an application for the transfer of a marketing authorisation for my products and what would the applicable fees be?

In preparation for the UK's withdrawal from the Union, a MAH currently established in the UK will need to be replaced with a MAH established in one of the remaining countries of the EEA. This change in MAH requires an application for a transfer of a marketing authorisation from the current UK-based MAH (the "Transferor") to a different legal entity established in the EEA. In this respect, a proof of establishment for the new MAH within the EEA (the "Transferee"), issued in accordance with national provisions, will need to be provided as one of the supporting documents for the transfer application. The implementation timelines for the transfer are to be agreed during the transfer procedure. Implementation periods exceeding 6 months will be accepted, but in any case the transfer of the marketing authorisation must be fully completed and implemented by the MAH before 30 March 2019.

One transfer application will need to be submitted for each marketing authorisation concerned in accordance with the current procedure provided for in Regulation (EC) No 2141/96 even in cases where several marketing authorisations are transferred from a UK-based MAH to the same Transferee. It is not possible to group several marketing authorisations under one single transfer application.

For information on the fees applicable to transfer applications, please refer to fees payable to the European Medicines Agency. Such fees cover all authorised presentations of a given medicinal product.

In case the transfer procedure concerns a medicinal product whose name is constructed as [international non-proprietary name (INN) / common name + name of the MAH], the name of the medicinal product may need to be changed to reflect the name of the Transferee. A Type IA variation will be required and should be submitted in advance of the transfer application to allow the new product name to be reflected in the Commission Decision on the transfer. Confirmation that the change of name has been requested should be reflected in the cover letter for the marketing authorisation transfer. For human medicinal products, the acceptance by the Name Review Group (NRG) of the new name has to be finalised, and for veterinary medicinal products the invented name check procedure must be completed, prior to the submission of the variation for changing the name of the medicinal product. Alternatively, in case the product name is constructed as [international non-proprietary name (INN) / common name + name of the MAH] but where the Transferee and Transferor have an agreement for the Transferee to continue using the MAH name of the Transferor as a trademark (i.e. name of product will be regarded as [international non-proprietary name (INN) / common name + Trademark]), only a proof of trademark authorisation is to be provided to the NRG Secretariat, but no formal NRG review will be required.

For further details on the procedural aspects of marketing authorisation transfer applications please also check the relevant Guidance published on the Agency's website concerning medicines for human use or veterinary use, respectively.

4a. How to handle planned or ongoing regulatory procedures during the transfer of marketing authorisation?

Regulatory procedures can run in parallel with the Brexit related marketing authorisation transfer application. However, in case the transfer has to be submitted while there are ongoing procedures requiring an immediate Commission Decision, MAHs should consider the timelines of the respective procedures and plan in order to avoid a situation where decision making processes of the procedures will overlap.

In all cases, MAHs are strongly advised to contact the Agency at matransferquery@ema.europa.eu in advance of the submission of the transfer application (copying the Procedure Manager), in order to discuss how to handle any planned/ongoing procedures for medicinal products for human use or, for veterinary medicines, to contact vet.applications@ema.europa.eu.

4b. Is it possible to submit a transfer of the orphan designation in parallel with a transfer of the marketing authorisation?

An application for transfer of orphan designation has to be submitted, preferably, in advance of or at the latest in parallel with the application for transfer of the marketing authorisation, since the opinion on the orphan designation transfer has to be reached before the opinion on the marketing authorisation transfer.

4c. Is there any possibility to simplify transfer applications when these are Brexit related?

The requirements for marketing authorisation transfers are embedded in Regulation (EC) No 2141/96 and cannot be waived.

In order to facilitate handling of a large volume of transfer applications from one UK-based MAH to the same legal entity (Transferee) in EEA, a combined version of each required supportive document (except product information and, when applicable, mock-ups) can be created covering all products affected. In such case these combined supportive documents should be submitted with each related transfer application (i.e. in dossiers of all affected products). A declaration should be included in the cover letter, listing the related parallel transfer applications and confirming that supportive documents are identical, with the exception of product information and, when applicable, mock-ups. When supportive documents differ between applications this also needs to be reflected in the statement in the cover letter.

In addition, the Agency is allowing a unique statement signed by the Transferee to cover requirements in annexes 6.2 to 6.4 in case the persons already nominated do not change (see attachment).

In all cases, applicants are strongly advised to contact EMA at matransferquery@ema.europa.eu (copying the Procedure Manager for the product) in order to discuss their marketing authorisation transfer submission plan for medicinal products for human use or, for veterinary medicines, to contact vet.applications@ema.europa.eu.

4d. Can requirement for mock-ups be waived for Transfers?

In accordance with the Annex to Regulation (EC) No 2141/96 and published guidance, mock-ups (English and worst-case multilingual) have to be submitted as part of the marketing authorisation transfer in Module 1.3.2.

In the exceptional case, where as a result of a Brexit related transfer, the only change in the artworks would be the name and/or address of the MAH, with all other elements remaining the same, a written confirmation could be accepted by the Agency that the mock-ups remain unchanged with the exception of the new name/address of the MAH.

5. How can I submit a transfer or change in the name/address of an orphan drug designation sponsor for my products? *(for medicines for human use)*

In preparation for the UK's withdrawal from the Union, a sponsor currently established in the UK will need to be replaced with a sponsor established in one of the remaining countries of the EEA, at the latest by the date on which the UK leaves the Union.

Such a change of sponsor will result in a transfer of the orphan medicinal product designation if it involves a change in legal entity. As part of the supporting documents, proof that the new sponsor is established in the European Economic Area (EEA) will need to be submitted. It can be a certificate of registration in the register of legal entities, a certificate of incorporation, or a copy of a passport or ID card in case of an individual. A change of name and/or address of the orphan designation holder procedure (which does not require a new legal act) may only be used, where the sponsor remains the same person (i.e. the sponsor is a physical person and changes the place of residence).

For further details, please see the Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another, the Checklist for sponsors applying for the transfer of Orphan Medicinal Product (OMP) designation, and the corresponding templates.

Transfers of orphan designations are free of charge. In case a transfer is sought for several orphan designations, an application must be submitted for each designation (i.e. one application per designation).

6. How do I submit changes to Qualified Person for Pharmacovigilance (QPPV) and/or changes in the Pharmacovigilance Master File (PSMF) location (*for medicines for human use*)

According to EU pharmaceutical legislation the QPPV must reside and carry out his/her tasks in an EEA Member State; and the PSMF also must be located within EEA.

For medicinal products for Human use, changes to the summary of the pharmacovigilance system i.e. changes in QPPV (including contact details) and/or changes in the Pharmacovigilance Master File (PSMF) location are to be notified to the authorities through the Article 57 database only without the need for a variation. MAHs are therefore not required to notify EMA of changes to the QPPV or PSMF location by submitting a variation.

Upon a change in the QPPV or location of the PMSF, the Article 57 database should be updated by the MAH immediately to allow continuous supervision by the Competent Authorities.

Please also refer to Question: How to inform the authorities of a change in the summary of the pharmacovigilance system? as published under the Pharmacovigilance system section of the Post-Authorisation Guidance.

Please also note that as part of a transfer application, an updated summary of the PSMF should be provided in Module 1.8.1.

There is no fee to be paid for updates in Article 57 database.

7. How do I submit changes to QPPV (*for veterinary medicines*)

According to EU pharmaceutical legislation the QPPV must reside and carry out his/her tasks in an EEA Member State.

For veterinary medicinal products, where a DDPS is authorised as part of the marketing authorisation (or a subsequent extension procedure), a change in QPPV should be submitted via a Type IA_{IN} variation application (classification C.I.9.a), provided that the pharmacovigilance system itself remains unchanged. In all other cases, the change in QPPV can be simply notified to the EMA exclusively in writing on company headed paper and sent to vet.applications@ema.europa.eu.

For information on the fees applicable to variation applications, please refer to fees payable to the European Medicines Agency.

8. How do I submit changes to the person responsible of scientific services and to the person responsible for batch recall and quality defects (*for medicines for human use*)

For medicinal products for Human use, changes to the person responsible of scientific services and to the person responsible for batch recall and quality defects should be notified exclusively in writing using this template on company headed paper by fax or letter (which can also be sent electronically) and should be addressed to Product and Application Business Support (PA-BUS) only. Further information, please refer to Post-authorisation guidance for users of the centralised procedure, section 'Other', Question 4. How do I notify the European Medicines Agency of changes to my Contact Persons specified in the application form?

There is no fee to be paid for these changes.

9. How do I submit changes to the person responsible for batch recall and quality defects (*for veterinary medicines*)

For veterinary medicinal products, changes to the person responsible for batch recall and quality defects should be notified exclusively in writing on company headed paper and sent to vet.applications@ema.europa.eu.

There is no fee to be paid for these changes.